

# We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

**4,800**

Open access books available

**122,000**

International authors and editors

**135M**

Downloads

Our authors are among the

**154**

Countries delivered to

**TOP 1%**

most cited scientists

**12.2%**

Contributors from top 500 universities



**WEB OF SCIENCE™**

Selection of our books indexed in the Book Citation Index  
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?  
Contact [book.department@intechopen.com](mailto:book.department@intechopen.com)

Numbers displayed above are based on latest data collected.

For more information visit [www.intechopen.com](http://www.intechopen.com)



# Carbohydrate Derivatives and Glycomimetic Compounds in Established and Investigational Therapies of Type 2 Diabetes Mellitus

László Somsák, Éva Bokor, Katalin Czifrák,  
László Juhász and Marietta Tóth  
*Department of Organic Chemistry, University of Debrecen  
Hungary*

## 1. Introduction

Diabetes mellitus is characterized by chronically elevated serum glucose levels resulting in damage of several tissues (e. g. retina, kidney, nerves) due to higher protein glycation, retardation of wound healing, impaired insulin secretion, enhanced insulin resistance, cell apoptosis, and increased oxidative stress. Type 2 diabetes (T2DM), representing 90-95 % of all diabetic cases, is a multifactorial disease where impaired insulin secretion and the development of insulin resistance ultimately leads to hyperglycemia (Hengesh, 1995). The end of the 20th century has witnessed a dramatic increase in the number of patients diagnosed with diabetes worldwide. The predicted number for the year 2025 is well over 300 million representing a 4-5 % yearly increase of the population above 20 years of age (Treadway et al., 2001). This striking prevalence can even be an underestimate due to methodological uncertainties as well as undiagnosed cases (Green et al., 2003). The highest increases are expected in the developing countries of Africa, Asia, and South America, while European populations seem to be less affected (Diamond, 2003). T2DM has been considered as the adult- or late-onset variant, however, the recent decade has seen the appearance and spreading of the disease among young people including children: this forecasts severe economic and health service burdens in the near future (Alberti et al., 2004; Ehtisham & Barrett, 2004).

The epidemic of T2DM is in conjunction with genetic susceptibility: evidence for a genetic component to the disease are accumulating, and the potential of these factors in the treatment and prevention of diabetes has been reviewed (Barroso, 2005; Bonnefond et al., 2010; Sladek et al., 2007; Toye & Gauguier, 2003). A similarly high contribution to this epidemic may originate from behavioral factors such as sedentary lifestyle, overly rich nutrition, and obesity (Bloomgarden, 2004).

Especially due to its long term complications (Brownlee, 2001) like retinopathy, neuropathy, nephropathy, and in particular cardiovascular diseases, as well as significantly higher risk of myocardial infarction, stroke, gangrene, and limb amputation diabetes has become one of the largest contributors to disability and mortality. Although several pathomechanisms (Lowell & Shulman, 2005; Panunti et al., 2004; Stumvoll et al., 2005) are under investigation, no firm understanding of the molecular origins (Ross et al., 2004) of the disease exists.

Thereby, all available and investigational treatments are symptomatic. As the complications can first of all be attributed to the high blood glucose levels, current antidiabetic therapies (Table 1) aim at reaching normoglycemia. However, most of the applied oral hypoglycemic agents (Cheng & Fantus, 2005; Krentz & Bailey, 2005; Mizuno et al., 2008; Padwal et al., 2005; Rendell, 2004; Uwaifo & Ratner, 2005) have several side effects and are inadequate for 30-40 % of the patients (Wagman & Nuss, 2001). On the other hand, their efficacy is lost over the time, and several concerns exist regarding their safety (Israili, 2011).

Drug type	Molecular target	Site of action	Adverse effects
<i>Insulin sensitizers</i>			
Metformin (biguanides)	Unknown	Liver, intestine, pancreas	Gastrointestinal intolerance (diarrhea, nausea), lactic acidosis, decreased vitamin B <sub>12</sub> level
Thiazolidinediones (glitazones)	PPAR $\gamma$	Liver, adipose tissue, skeletal muscle	Weight gain, ankle edema, sodium and fluid retention, possible bone loss
<i>Insulin secretagogues</i>			
Sulfonylureas	Sulfonylurea receptor	Pancreas	Weight gain, hypoglycemia, hyperinsulinemia, hypoglycemia-provoked ischemia and arrhythmia, progressive decline in $\beta$ -cell function
Meglitinides	K-ATP channel	Pancreas	Weight gain, hypoglycemia, hypoglycemia-provoked ischemia and arrhythmia
GLP-1 analogues and mimetics	GLP-1 receptor	Pancreas	Nausea, vomiting, diarrhea
DPP-4 inhibitors (glinides)	DPP-4	Intestine, pancreas	Gastrointestinal intolerance, nasopharyngitis, upper respiratory infection, urinary tract infection
<i>Others</i>			
$\alpha$ -Glucosidase inhibitors	$\alpha$ -Glucosidases	Pancreas, small intestine	Gastrointestinal intolerance (flatulence, bloating)
SGLT2-inhibitors (gliflozins)	SGLT2	Kidney	Gastrointestinal intolerance (nausea), urinary tract infection
Insulin	Insulin receptor	Liver, muscles	Weight gain, hypoglycemia

Table 1. Main types of current therapeutic agents for T2DM and their major side effects (Israili, 2011; Moller, 2001)

The complexity of T2DM offers many potential points of intervention for pharmacotherapy for which the main molecular targets and strategies such as insulin secretagogues, insulin sensitizers, hormones, inhibitors of PTP-1B, GSK3, and hepatic glucose production, methods for altering lipid metabolism, combination therapies, etc. have been reviewed in details (Israili, 2011; Morral, 2003; Nourparvar et al., 2004; Wagman et al., 2004).

Among the numerous methods used to treat type 2 diabetes and investigated to find new therapeutic possibilities there are several approaches which apply carbohydrate (especially glucose) derivatives as well as compounds mimicking the properties of sugars. Based on our

experience in the chemistry of carbohydrates and glycomimetics, in this survey we summarize the roles of such compounds in combatting type 2 diabetes relying on the review literature and very recent primary scientific papers.

## 2. Inhibitors of $\alpha$ -glucosidase enzymes

Starch and sucrose are the most important dietary carbohydrates but they are not directly available for the cells. They are digested in the gastrointestinal tract to monosaccharides which can be absorbed to the circulation to raise the serum concentration (Hanhineva et al., 2010). The normal blood glucose level (3.6–5.8 mM) fluctuates throughout the day, is usually lowest in the morning, before the first meal of the day, and rises after meals for an hour or two.

A medically applied treatment of diabetes is to retard the absorption of glucose by inhibition of the carbohydrate hydrolyzing enzymes  $\alpha$ -amylase and  $\alpha$ -glucosidase in the digestive tract. In humans the digestion of starch, maltodextrins, and maltooligosaccharides includes several stages: degradation of the polymeric substrates results in shorter oligomers which are then cleaved by  $\alpha$ -amylase into smaller oligosaccharides. This mixture is broken down to monosaccharides by  $\alpha$ -glucosidase from the non-reducing end of the oligosaccharides. By inhibition of these enzymes the rate of glucose production can be reduced that contributes to diminishing the blood glucose levels, too (Tundis et al., 2010). Such inhibitors decrease postprandial hyperglycaemia and hyperinsulinaemia, thereby may improve sensitivity to insulin and release the stress on  $\beta$ -cells (Scheen, 2003).

Glycosidases are a long known and studied class of glycoenzymes for which an enormous number of compounds have been tested as inhibitors (El Ashry et al., 2000a; El Ashry et al., 2000b; El Ashry et al., 2000c; Lillelund et al., 2002). Analogues of monosaccharides in which the ring oxygen is replaced by a nitrogen atom are known as iminosugars (or less properly azasugars) comprising both natural and synthetic molecules (Table 2) which, as the most potent inhibitors of glycosidases, have high pharmacological potential not only in the context of T2DM (Asano, 2009; Compain & Martin, 2007).

The naturally occurring salacinol and analogous sugar mimics with a 4-thiofuranoid type ring (Table 2) belong to a growing class of zwitterionic glycosidase inhibitors, which attract great interest both as synthetic targets and applications for  $\alpha$ -glucosidase inhibition (Praly & Vidal, 2010).

The positive charge on the sulfur atom in the thiosugar derivatives and in the iminosugar-based glycosidase inhibitors at physiological pH is facilitating the binding in the active sites of glycosidase enzymes as a mimicry of the charge of the oxocarbeniumion-like transition state formed during hydrolysis of the natural enzyme substrate (Zechel & Withers, 2000). The stabilizing electrostatic interactions between the ammonium (protonated nitrogen) or sulfonium (positively charged sulfur) moieties and an active-site carboxylate residue are considered to be a possible mechanism of action of these inhibitors (Mohan & Pinto, 2007).

Three competitive inhibitors of  $\alpha$ -glucosidases: acarbose, miglitol, and voglibose (de Melo et al., 2006) (Table 3) are used as drugs in the treatment of T2DM under various brand names. These compounds are known to inhibit a wide range of glycosidases. In the absence of specificity and because of the known serious side effects, the applications of these first generation iminosugar drugs are limited. Current investigations aim at discovering safer, more specific, and effective iminosugar based derivatives not only as hypoglycemic agents but for several other purposes among others in oncology, as antivirals, and against cystic fibrosis as reviewed in (Home et al., 2011).

	Pyrrolidine type				Piperidine type			
	DAB	Deoxy-nojirimycin	Nojirimycin	$\alpha$ -Homonojirimycin	DAB	Deoxy-nojirimycin	Nojirimycin	$\alpha$ -Homonojirimycin
$IC_{50}/K_i^*$ [ $\mu$ M] (Compain et al., 2007)								
<i>Rat intestinal sucrase</i>	0.01	16	0.21	0.17	0.56	(de Melo et al., 2006)	0.17	(de Melo et al., 2006)
<i>Rat intestinal maltase</i>	1.4	55	0.36	0.34*	1.7	(de Melo et al., 2006)	0.34*	(de Melo et al., 2006)
<i>Rat intestinal isomaltase</i>	0.05	5.8	0.03	0.70	0.25	(de Melo et al., 2006)	0.70	(de Melo et al., 2006)
<i>Rat intestinal lactase</i>	-	260	26	-	-		-	
	Pyrrolizidine type				Thiosugar type			
	Australine	Indolizidine type	Nortropane type	Calistegin derivative	Salacinol	Neosalacinol		
$IC_{50}/K_i^*$ [ $\mu$ M] (Compain et al., 2007)								
<i>Rat intestinal sucrase</i>	4.6	0.00055 (de Melo et al., 2006)	160	190	1.3	(Muraoka et al., 2011)	2.5	(Muraoka et al., 2011)
<i>Rat intestinal maltase</i>	24	-	190	190	1.5	(Xie et al., 2011)	1.3	
<i>Rat intestinal isomaltase</i>	97	-	-	-	6.0	(Muraoka et al., 2011)	22.2	(Muraoka et al., 2011)
<i>Rat intestinal lactase</i>	-	-	0.38	0.38	5.2	(Xie et al., 2011)	8.0	(Xie et al., 2011)
<i>Rat intestinal glucoamylase</i> (de Melo et al., 2006)	5.8	-	-	-	1.3	(Muraoka et al., 2011)	0.68	(Muraoka et al., 2011)
					1.5	(Xie et al., 2011)	0.3	(Xie et al., 2011)

Table 2. Select iminosugar and thiosugar type inhibitors and their effect against  $\alpha$ -glucosidases originating from mammalian gastrointestinal tract

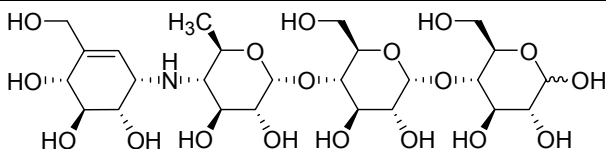
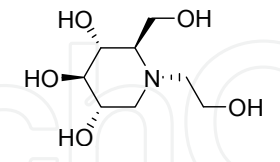
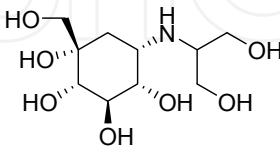
Name	Structure	Side-effect
<b>Acarbose</b> Approved in 1995		Flatulence (78% of the patients) Diarrhea (14% of the patients)
<b>Miglitol</b> Approved in 1996		Diarrhea, gas, soft stools, stomach pain
<b>Voglibose</b> Approved in 1997		Diarrhea, stool loss, meteorism, upset stomach

Table 3.  $\alpha$ -Glucosidase inhibitors in the clinical practice against T2DM

### 3. Inhibitors of renal sodium-glucose cotransporters

The mammalian kidney plays an important role in the maintenance of energy balance of the organism. In healthy individuals 180 g/day of D-glucose is filtered from plasma through the glomerulus, which is completely reabsorbed in the renal proximal tubules to the bloodstream, thereby preventing the loss of glucose in the urine (Wright, 2001). This reabsorption process is mediated by two sodium dependent glucose cotransporters (SGLTs). SGLT1 is a high-affinity, low-capacity glucose/galactose transporter located predominantly in the small intestine, but is also present in the S3 segment of the proximal tubule in the kidney, as well as in the heart. The primary function of SGLT1 is the absorption of dietary glucose in the intestine, however it shares in the renal glucose transport in the kidney and regulates cardiac glucose transport in the heart, as well. SGLT2 is a low affinity, high capacity glucose transporter specifically expressed in the S1 segment of the proximal convoluted tubule. SGLT2 is responsible for ~90 % of renal glucose reabsorption, while SGLT1 plays only an auxiliary role in this process (Boldys & Okopien, 2009; Idris & Donnelly, 2009; Washburn, 2009b). Genetic studies demonstrated that defects of SGLT2 but in a lesser extent of SGLT1 genes had neither adverse effects on kidney function as well as carbohydrate metabolism, nor hypoglycaemia (Handlon, 2005; Santer & Calado, 2010; Wright, 2001).

Nowadays sodium-glucose cotransporters have received remarkable attention as new drug targets for the treatment of diabetes (Bailey, 2011). Considering the exclusive expression of SGLT2 in the kidney and its predominant role in renal glucose recovery, most pharmaceutical investigations have focused primarily on selective SGLT2 inhibition to facilitate benign glucosuria (Santer & Calado, 2010; Washburn, 2009b). In contrast to the currently applied diabetic therapies most of which aim at insulin resistance and insulin deficiency, targeting SGLT2 is an insulin-independent strategy based on enhanced renal glucose excretion and, consequently, lowering plasma glucose levels without severe side effects (Isaji, 2007).

In recent years aromatic, heteroaromatic, and fused aromatic O- and N-glucopyranosides, C-glucopyranosyl derivatives, anomeric spirocycles, as well as their congeners with modified sugar rings have been developed as SGLT2 inhibitors (Handlon, 2005; Idris & Donnelly, 2009; Isaji, 2007; Nomura, 2010; Vaidya & Goyal, 2010; Washburn, 2009a; Washburn, 2009b).

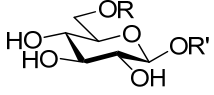
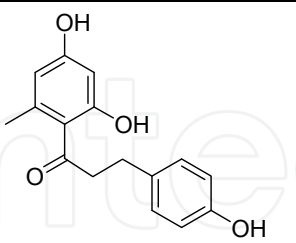
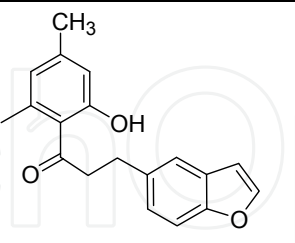
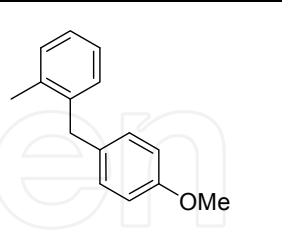
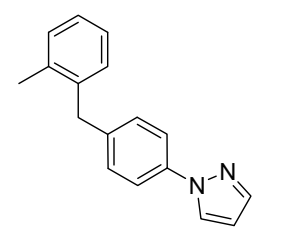
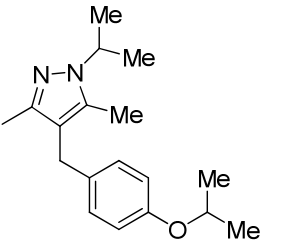
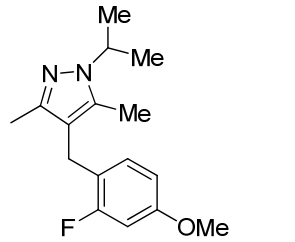
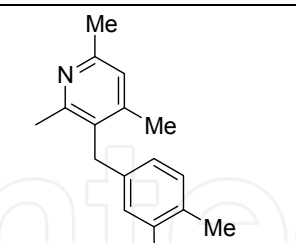
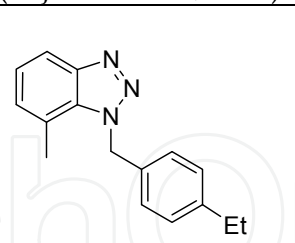
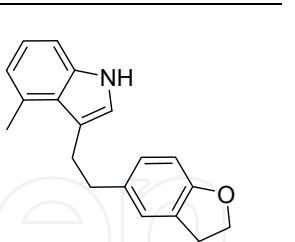
Entry	R'	Entry	R'	Entry	R'
 R = H unless indicated otherwise					
1.		2.		3.	
	<b>Phlorizin</b> 35.6* (Meng et al., 2008) 18.6** (Katsuno et al., 2007)		<b>T-1095</b> R = COOMe (prodrug form) <b>T-1095A</b> R = H (active form) 50 (Handlon, 2005) 6.6* (Meng et al., 2008)		<b>Sergliflozin</b> R = COOEt (prodrug form) <b>Sergliflozin-A</b> R = H (active form) 9.2* (Meng et al., 2008) 2.39** (Katsuno et al., 2007)
4.		5.		6.	
	0.1 (Handlon, 2005)		<b>Remogliflozin etabonate</b> R = COOEt (prodrug form) <b>Remogliflozin</b> R = H (active form) 12.4** (Fujimori et al., 2008)		<b>BI 44847</b> (Washburn, 2009b)
7.		8.		9.	
	3 (Handlon, 2005)		8 (Handlon, 2005)		20 (Handlon, 2005)

Table 4. Selected *O*-glucopyranoside type inhibitors of SGLT2 ( $IC_{50}$ ,  $EC_{50}$ \*,  $K_i$ \*\* values [nM])

The first class of potential SGLT2 inhibitors to be explored was the *O*-glucosides derived from the structure of phlorizin (Table 4, Entry 1) of natural origin isolated from the root bark of the apple tree (Ehrenkranz et al., 2005). Phlorizin lowers plasma glucose levels and improves insulin resistance by increasing renal glucose excretion (Isaji, 2007). However, it is not considered as an antidiabetic drug because of its nonselective inhibition against SGLTs as well as its metabolic instability due to hydrolysis by glucosidase enzymes in the intestinal tract that prevented oral administration (Washburn, 2009a). In addition, enzymatic release of the aglycone phloretin, a micromolar inhibitor of sodium-independent facilitative glucose

transporters (GLUTs), could potentially inhibit GLUT-mediated cellular uptake of glucose (Ehrenkranz et al., 2005; Washburn, 2009a). Because of the poor bioavailability and the aforementioned undesirable effects of phlorizin, initial efforts entailed exploring more stable and selective *O*-glucoside analogues of this compound.

T-1095 (Table 4, Entry 2) is a methyl carbonate prodrug which, after oral administration, is rapidly converted to an active metabolite, T-1095A showing high affinity and plausible selectivity against human SGLT2 (Handlon, 2005). Development of T-1095 reached phase II clinical trials but was subsequently discontinued (Isaji, 2007).

The  $\beta$ -D-glucosides in which the aglycone moiety is a phenyl ring substituted in ortho position by a benzyl group represent a promising type of *O*-glucoside candidates (Entries 3 and 4). Sergliflozin (Entry 3), an ethyl carbonate prodrug, emerged from this series to enter clinical trials (Isaji, 2007). According to the *in vitro* assay, its active form is a highly potent and 296-fold more selective inhibitor for human SGLT2 over SGLT1 (Katsuno et al., 2007).

Heteroaromatic *O*-glucosides are the next potent series of SGLT2 inhibitors. Among pyrazole derivatives remogliflozin (Entry 5) showed a reassuring 365-fold selectivity for SGLT2 versus SGLT1 *in vitro* (Fujimori et al., 2008), and reached clinical developments (Isaji, 2007). In addition, an analogue of remogliflozin (Entry 6) presumably entered clinical trials as BI 44847 (Washburn, 2009b). 2-Pyridyl-*O*-glucoside (Entry 7) with a potency of 3 nM against human SGLT2 represent an additional highly active compound of this class (Handlon, 2005).

Efficacy of a series of benzofused heterocyclic derivatives was also investigated and, for example, benzotriazole and indole *O*-glucosides (Entries 8 and 9, respectively) were found to strongly inhibit human SGLT2 (Handlon, 2005).

Susceptibility of *O*-glucosides to enzymatic degradation by glucosidases impacted bioavailability and duration of action (Washburn, 2009b). Therefore, remarkable attention has been paid to metabolically more stable C-glucoopyranosyl derivatives.

Compounds containing a diarylmethane aglycone represent the first type of this class (Table 5). According to the SAR the benzyl substituent in meta position of the central aryl ring is more favourable compared to the ortho attached derivatives of high activity in case of *O*-glucosides (Washburn, 2009a; Washburn, 2009b). At present, dapagliflozin (Entry 1) with considerable *in vitro* as well as *in vivo* activity is the most advanced SGLT2 inhibitor in phase III clinical trials and has become a leading structure for further inhibitor design (Washburn, 2009a; Washburn, 2009b).

Additional SAR exploration revealed that introduction of an appropriate ortho substituent at the proximal phenyl ring adjacent to the glycosidic bond is beneficial in respect of inhibitory efficiency (Entry 2) (Washburn, 2009a). For example, propargyl ether derivative (Entry 3) exhibited sub-nanomolar activity and a more than 3300-fold selectivity for SGLT2 (Xu et al., 2010).

Replacement of the distal phenyl group with fused rings resulted in a new potent inhibitor type. For example, 1:1 choline complex of azulene (Entry 4) as well as 1:1 L-proline complex of benzothiophene (Entry 5) derivatives appeared as clinical candidates (Washburn, 2009b).

Modification of dapagliflozin by replacing the distal aryl ring by heterocycles led to the discovery of canagliflozin (Entry 6) which obtained the second highest interest in clinical developments (Nomura et al., 2010).

Recently, along this line, the structure of dapagliflozin was modified by other heterocycles such as thiazole (Song et al., 2011), 1,3,4-thiadiazole (Lee et al., 2010b), pyridazine (Kim et al., 2010), and pyrimidine (Lee et al., 2010a) moieties. Among them, the thiazole derivative



Entry	R	Entry	R	Entry	R
1.		2.		3.	
	<p><b>Dapagliflozin</b>  <b>BMS-512148</b>            1.1* (Meng et al., 2008)            0.49 (Song et al., 2011)            6.7 (Xu et al., 2010)            1.4 (Robinson et al., 2010)</p>		<p>1.3* (Nomura, 2010)</p>		<p>0.3 (Xu et al., 2010)</p>
4.		5.		6.	
	<p><b>YM-543</b> = 1:1 complex            with choline            8.9 (Washburn, 2009b)</p>		<p><b>ASP1941</b> = 1:1 complex            with L-proline            8.4 (Washburn, 2009b)</p>		<p><b>Canagliflozin</b>  <b>TA-7284</b>            2.2 (Nomura et al., 2010)</p>
7.		8.		9.	
	<p>0.72 (Song et al., 2011)</p>		<p>6.5 (Handlon, 2005)</p>		<p>6 (Washburn, 2009b)</p>
10.		11.		12.	
	<p>10 (Zhou et al., 2010)</p>		<p>1.4 (Washburn, 2009b)</p>		<p>2 (Washburn, 2009b)</p>

Table 5. C-glucopyranosyl compounds as SGLT2 inhibitors (IC<sub>50</sub>, EC<sub>50</sub>\* values [nM])

(Entry 7) displayed the best result, however, according to its *in vitro* ( $IC_{50} = 0.72$  nM) as well as *in vivo* activity, it was less potent than dapagliflozin ( $IC_{50} = 0.49$  nM) (Song et al., 2011). From C-glucosyl hetarenes containing a central heterocyclic ring such as pyrazine, indole, benzisothiazole, and benzothiophenes (Entries 8-12, respectively) the latter two proved most efficient (Washburn, 2009b).

N-Glucopyranosides represent an other series of SGLT2 inhibitors with probably higher metabolic stability as compared to O-glucopyranosides. Among these derivatives benzylated aniline-, pyrrole-, and indole N-glucosides (Table 6, Entries 1-4, respectively) are potent orally active SGLT2 inhibitors (Washburn, 2009b).

O-Spiroketal C-arylglucosides (Entries 5 and 6) which combine the character of both O-glucosides and C-glucosyl derivatives, show good inhibitory activity (Lv et al., 2009) and high selectivity (Washburn, 2009b) for SGLT2 which can be attributed, in part, to a greater conformational constraint imposed by the spiro-annulated ring system.

In the quest of new candidates for SGLT2 inhibition the modification of the sugar part of the molecules is a further possibility. Replacement of the ring oxygen by a sulfur atom provided new potent 1,5-anhydro-1-thio-D-glucitol derivatives (Table 7, Entries 1-3) (Washburn, 2009b). TS-071 (Entry 1) showed excellent urinary glucose excretion in dogs and is currently undergoing phase II clinical trials (Kakinuma et al., 2010). Modification of the glucose moiety by substituting the hydroxyl groups attached to either C-4 or C-6 with fluorine (Entries 4 and 5) also resulted in effective molecules (Washburn, 2009b). Replacement of the hydroxymethyl side chain of the glucose part with a methyl- or methylsulfanyl group (Entries 6 and 7, respectively) provided molecules with good inhibitory effect, from which LX4211 (Entry 7) is a clinical candidate (Washburn, 2009b). Further transformation of the

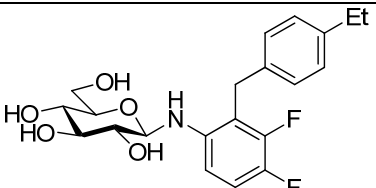
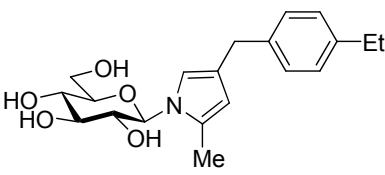
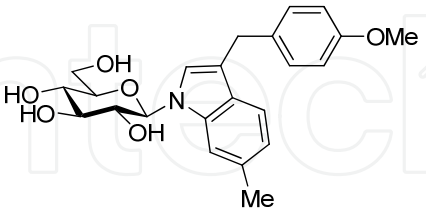
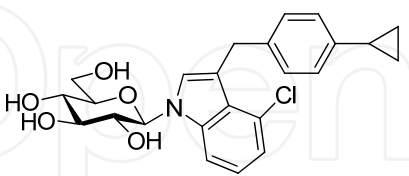
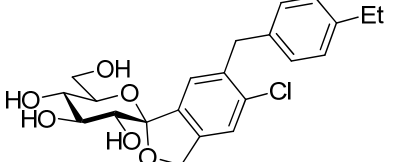
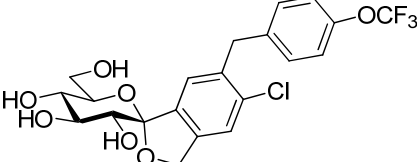
Entry	Entry
1.  2.9 (Washburn, 2009b)	2.  1.1 (Washburn, 2009b)
3.  0.9 (Washburn, 2009b)	4.  2.3 (Washburn, 2009b)
5.  1.5 (Washburn, 2009b)	6.  0.3 (Lv et al., 2009)

Table 6. Select compounds of N-glucopyranosides, N-glucopyranosyl heterocycles, and anomeric spirocycles ( $IC_{50}$  [nM])

side chain of the sugar moiety as in the C-5-spirocyclic analogues (Entries 8 and 9) as well as removal of the 4-OH from the glucose ring (Entry 10) furnished compounds exhibiting SGLT2 inhibitory effect in the low nanomolar range (Robinson et al., 2010).

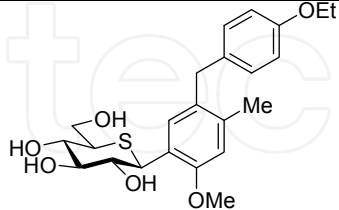
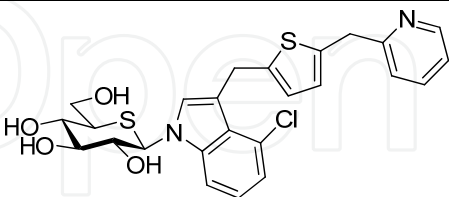
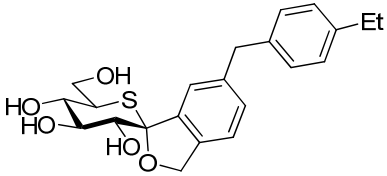
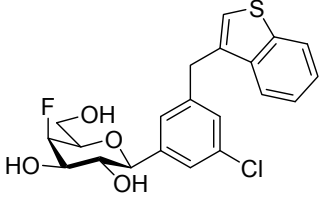
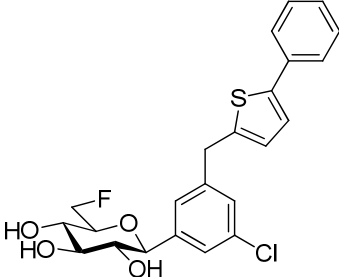
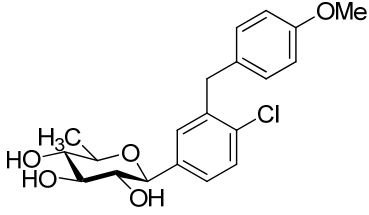
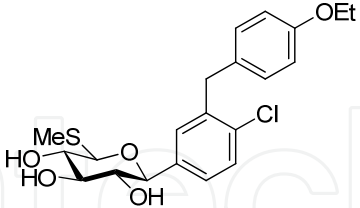
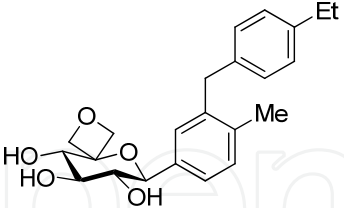
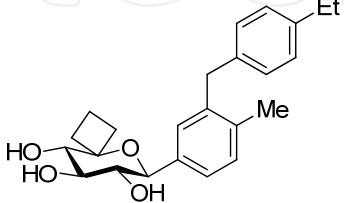
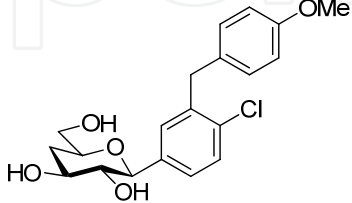
Entry	Entry
1.  <b>TS-071</b> 2.26 (Kakinuma et al., 2010)	2.  10 (Washburn, 2009b)
3.  12 (Washburn, 2009b)	4.  5 (Washburn, 2009b)
5.  31 (Washburn, 2009b)	6.  2.4 (Robinson et al., 2010)
7.  <b>LX4211</b> (Washburn, 2009b)	8.  3.4 (Robinson et al., 2010)
9.  3.0 (Robinson et al., 2010)	10.  21 (Robinson et al., 2010)

Table 7. Miscellaneous compounds with modifications in the glucose unit as inhibitors of SGLT2 ( $IC_{50}$ , [nM])

#### 4. Glucose analogue inhibitors of glycogen phosphorylase

The liver accounts for ~90 % of the body's endogenous glucose production. Hepatic glucose is formed via two pathways: glycogenolysis (release of monomeric glucose from the glycogen polymer storage form) and gluconeogenesis (*de novo* synthesis of glucose from C-3 precursors). Hepatic glucose output is elevated in type 2 diabetic patients, therefore, modulation (mostly inhibition) of one or more of the respective biochemical pathways may contribute to diminishing blood sugar levels. Targets for this can be the glucagon receptor (enhances hepatic glucose output), GCK (catalyzes the first step of glycolysis), 6PF-2-K/F-2,6-P2ase (regulator of glycolytic and gluconeogenic rates through production of F-2,6-P2), G-6-Pase (catalyzes the last step of gluconeogenesis), F-1,6-P2ase (regulates gluconeogenic rates), GSK3 (inhibits glycogen synthase), and glycogen phosphorylase (GP, catalyzes the conversion of glycogen to glucose-1-phosphate monomers) (Morral, 2003). Current evidence indicates that glycogenolysis is an important contributor (~75 %) to the production of glucose by the liver. Furthermore, a substantial portion of glucose formed by gluconeogenesis is cycled through the glycogen pool prior to efflux from the liver cells (Andersen et al., 1999). As GP is the rate determining enzyme of glycogen breakdown (Kurukulasuriya et al., 2003; Ross et al., 2004) its pharmacological inhibition has been regarded as an effective therapeutic approach to treating diseases caused by abnormalities in glycogen metabolism, such as type 2 diabetes (Oikonomakos, 2002; Somsák et al., 2003; Somsák et al., 2005), myocardial ischemia (Tracey, W. et al., 2003; Tracey, W. R. et al., 2004), cerebral ischemia (Sun & Xu, 2010), and tumors (Geschwind et al., 2004; Schnier et al., 2003). Glycogen phosphorylases (existing as 'muscle', 'brain', or 'liver' isoforms) are allosterically regulated enzymes consisting of a dimeric arrangement of two identical subunits related to each other by a C2 symmetry. Protein crystallographic studies (Chrysin, 2010; Oikonomakos, 2002) revealed the existence of six binding sites in GP (Fig. 1): the catalytic, the inhibitor, the allosteric, the glycogen storage, and the new allosteric sites, as well as the newly discovered benzimidazole site (Chrysin et al., 2005). Each binding site can be targeted by small molecules, and a large variety of inhibitors were tested as described in recent reviews (Loughlin, 2010; Oikonomakos & Somsák, 2008; Somsák et al., 2008).

Physiological investigations with glycogen phosphorylase inhibitors in the context of T2DM have recently been reviewed (Agius, 2010).

Under physiological conditions glucose (Fig. 2) serves as a regulator of GP since the less active T state of the enzyme is stabilized (Board et al., 1995) by its weak binding to the catalytic centre. This has raised the possibility to search for glucose derivatives with much higher affinity to the active site. A large variety of glucose based compounds were synthesized and tested mainly against the prototype of the GP enzymes, the best available rabbit muscle GP (Chrysin, 2010).

For the inhibitory glucose derivatives (Gimisis, 2010; Praly & Vidal, 2010; Somsák, 2011; Somsák et al., 2003; Somsák et al., 2005) protein crystallography showed primary binding to the catalytic site of the enzyme. Some glucose analogues can also occupy the new allosteric site (Oikonomakos et al., 2002), and the benzimidazole-site was evidenced by a 2-( $\beta$ -D-glucopyranosyl)-benzimidazole (Chrysin et al., 2005).

The studied *O*-, and *S*-glucopyranosides proved very weak inhibitors with  $K_i$  values in the 2000-25000  $\mu$ M and 650-21100  $\mu$ M, respectively (Somsák et al., 2003; Somsák et al., 2005).

Extensive investigation of *N*-glucopyranosylamide type compounds (Table 8, Entries 1-4) revealed that a) the NHCONHCO linker between the sugar and the aromatic part of the

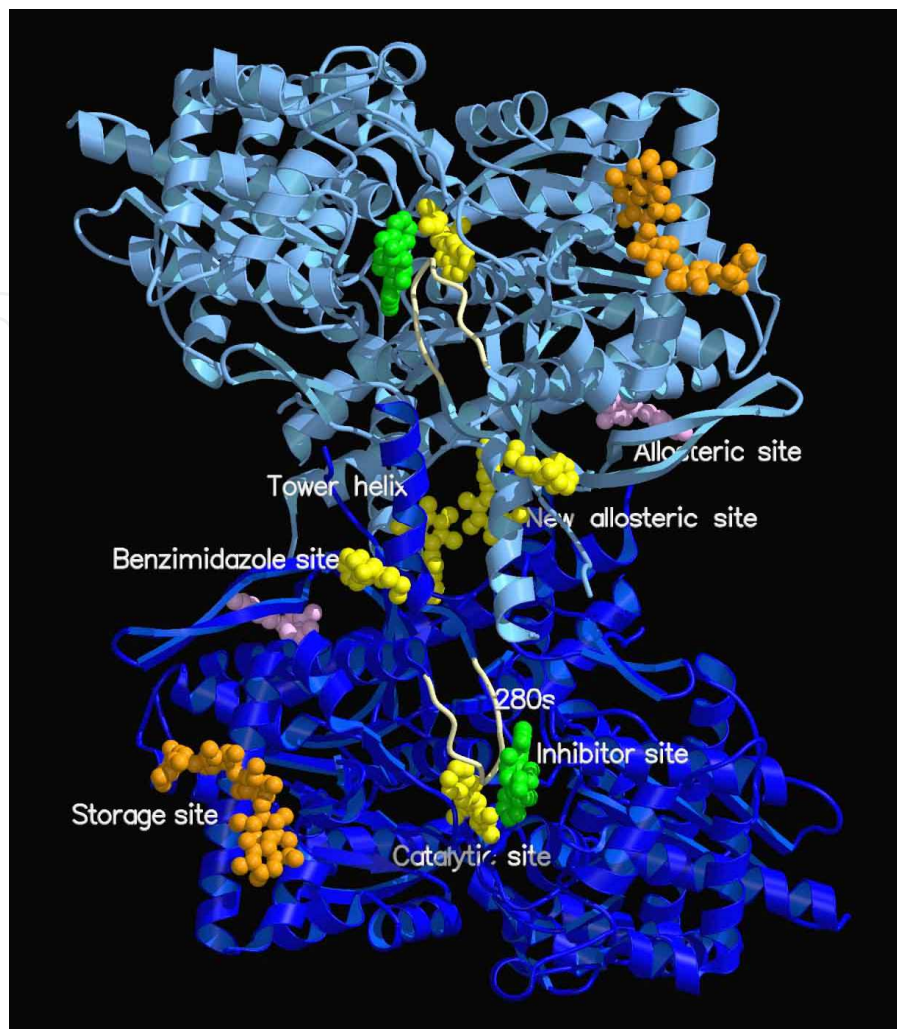
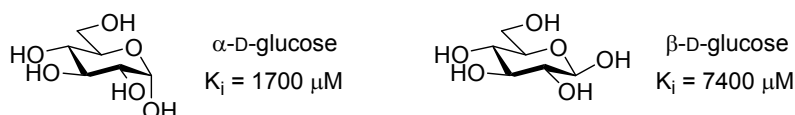


Fig. 1. A schematic diagram of the muscle GPb dimeric molecule viewed down the molecular dyad. (The positions are shown for the catalytic, allosteric, glycogen storage, inhibitor, new allosteric, and benzimidazole sites. The catalytic site, marked by 2- $\beta$ -D-glucopyranosyl benzimidazole, is buried at the center of the subunit and is accessible to the bulk solvent through a 15 Å-long channel. Binding of the competitive inhibitor benzimidazole promotes the less active T state through stabilization of the closed position of the 280s loop (shown in white). The allosteric site, which binds the activator AMP (indicated in the figure), is situated at the subunit-subunit interface some 30 Å from the catalytic site. The inhibitor site or caffeine binding site, which binds purine compounds such as caffeine and flavopiridol (indicated) is located on the surface of the enzyme some 12 Å from the catalytic site and, in the T state, obstructs the entrance to the catalytic site tunnel. The glycogen storage site (with bound maltopentaose) is on the surface of the molecule some 30 Å from the catalytic site, 40 Å from the allosteric site and 50 Å from the new allosteric inhibitor site. The new allosteric or indole binding site, located inside the central cavity, formed on association of the two subunits, binds indole-2 carboxamide analogs, *N*-benzoyl-*N'*- $\beta$ -D-glucopyranosyl urea, and benzimidazole (indicated). The novel binding site with bound benzimidazole, also located on the surface of the molecule, is some 31 Å from the catalytic site, 32 Å from the allosteric site, and 32 Å from the indole site. (Figure by courtesy of N. G. Oikonomakos and E. D. Chrysina.)

Fig. 2. Structure of  $\alpha$ - and  $\beta$ -D-glucose and their inhibition constants with RMGPb.

Entry	Compound	R		
		A	B	C
(Somsák, 2011; Somsák et al., 2008)				
1.		CH <sub>3</sub> 32	81	10
2.		H 140	18	5.2
3.		-	4.6	0.35
4.		-	21	-
(Gimisis, 2010)				
5.		-CH <sub>3</sub> 510	-(CH <sub>2</sub> ) <sub>2</sub> SCH <sub>3</sub> 1200	350
(Alexacou et al., 2010; Deleanu et al., 2008)				
6.		33	5.7	28

Table 8. Inhibition of RMGPb by *N*-glucopyranosidic derivatives ( $K_i$  [ $\mu\text{M}$ ])

compounds and b) a large hydrophobic substituent (compare columns B and C) make the best inhibitor (Entry 3C), actually the first glucose analogue in the nanomolar inhibition range. Other structures, e. g. those in Entries 1-2A, are much less efficient. For further detailed analysis of structure-activity relationships of analogous compounds see (Somsák et al., 2008). *N*-Glucopyranosylamides incorporating natural L-amino acids (Entry 5) proved weaker inhibitors (Gimisis, 2010), although the hydrophobicity of the appendage seems to play an important role in this series, as well (compare Entries 5A and 5B to 5C). Very recently thiosemicarbazone type inhibitors (Entry 6) have been published with inhibitory efficiency in the low micromolar range (Alexacou et al., 2010; Deleanu et al., 2008).

Among 1-glucopyranosyl-1,2,3-triazoles (Table 9, Entries 1-3), which can be regarded as non-classical bioisosteres of *N*-glucopyranosylamides (Table 8, Entry 1), some low micromolar inhibitors were found (Somsák, 2011) which again show the preference for a

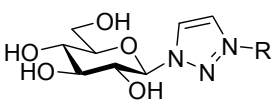

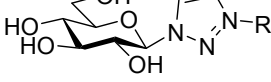
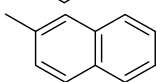
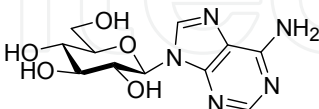
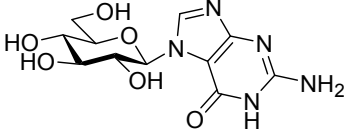
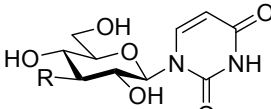
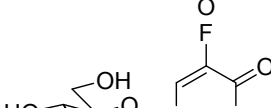
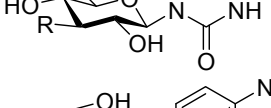
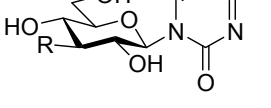
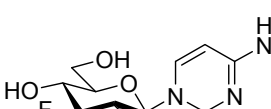
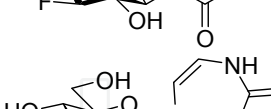
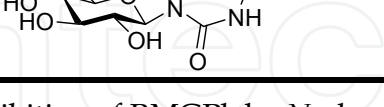
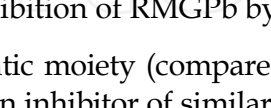
Entry	Compound	R	K <sub>i</sub> [μM]
(Somsák, 2011)			
1.			151
2.			16
3.		-CH <sub>2</sub> OH	14
(Gimisis, 2010; Praly & Vidal, 2010)			
4.			310
5.			170
6.		OH	6.1
7.		F	3460
8.		OH	5.5
9.		F	3670
10.		OH	7.7
11.		F	4010
12.			46
13.			76

Table 9. Inhibition of RMGPb by *N*-glucopyranosyl heterocycles

large aromatic moiety (compare Entries 1 and 2 in Table 9). Interestingly, a polar appendage also led to an inhibitor of similar efficiency (Entry 3). *N*-Glucopyranosyl derivatives of the well known nucleobases were also tested towards GP (Gimisis, 2010): while the purine derivatives (Entries 4 and 5) proved modest inhibitors, pyrimidines in Entries 6, 8, and 10 showed binding in the low micromolar range. Modification of the glucose moiety by replacing the 3-OH of these compounds by fluorine (Entries 7, 9, and 11) weakened the inhibition by a factor of ~600 on an average. On the other hand, introduction of a hydrophobic group (compare Entries 11 and 12) was beneficial in this series, as well, resulting in an almost 100-fold stronger inhibitor. Enlarging the heterocyclic ring to a seven-membered one (Entry 13) gave a weaker inhibitor in comparison to the six-membered pyrimidine derivatives.

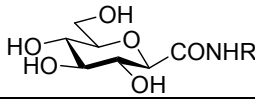
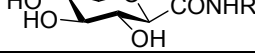
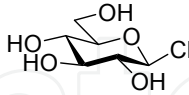
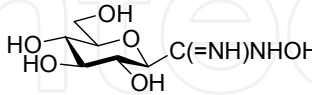
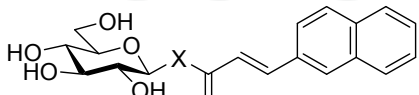
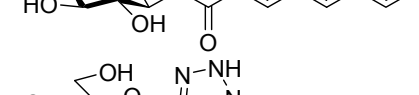
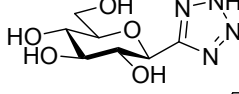
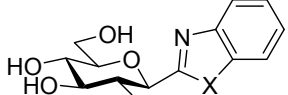
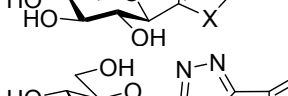
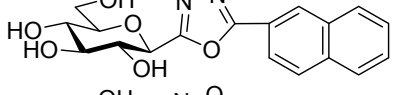
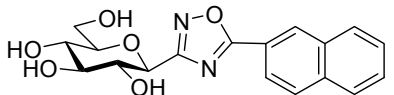
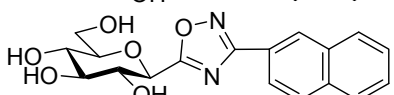
Entry	Compound	$K_i$ [ $\mu\text{M}$ ]
(Somsák et al., 2003)		
1.		R = H 440
2.		R = CH <sub>3</sub> 160
(Somsák, 2011)		
3.		130
4.		No inhibition
5.		X = CH <sub>2</sub> 52 % at 100 $\mu\text{M}$
6.		X = NH 3.5
7.		No inhibition
8.		X = S 76
9.		X = NH 9
10.		10 % at 625 $\mu\text{M}$
11.		38
12.		2.4

Table 10. Inhibition of RMGPb by C-glucopyranosyl compounds

Glucose derivatives with a substituent attached by a carbon-carbon bond (Table 10, Entries 1-4) showed weak or no inhibition. A comparison of the C-glucosyl compound in Entry 5 to the analogous N-glucosyl derivative in Entry 6 demonstrates that the more rigid amide type structure binds stronger to GP than its counterpart with the CH<sub>2</sub>-group lending more flexibility to the molecule. In a series of C-glucopyranosyl heterocycles (Entries 7-12) the size and nature of the heterorings proved very important showing stronger inhibition for the larger ones (compare Entries 7-9), and especially for the benzimidazole in Entry 9. Among oxadiazole derivatives of equal size (Entries 10-12) the constitution of the heterocycle proved decisive to give the low micromolar inhibitor of Entry 12.

The anomeric spiro-hydantoin and -thiohydantoin (Table 11, Entries 1 and 2, respectively) belong to the first efficient compounds of early GP inhibitor design. Changing the sugar part from glucose to xylose (by removal of the CH<sub>2</sub>OH substituent, Entries 3 and 4) resulted in complete loss of inhibition. Reversal of the spiro-configuration (compare Entries 1 and 5) as well as spiro-annulation of a six-membered ring (Entry 6) gave compounds with significantly weaker binding (Somsák et al., 2003). Extension of the anomeric spirocycles by further ring-condensations as in Entries 7 and 8 produced practically inefficient structures (Gimisis, 2010). Substitution by aromatic groups in the spiro-isoxazolines (Entries 9 and 11)



and spiro-oxathiazoles (Entries 10 and 12) gave good inhibitors and the naphthyl derivatives (Entries 11 and 12) are among the best known glucose derived compounds (Somsák, 2011). Contrary to  $\alpha$ -glucosidases, iminosugar type compounds with 5-7 membered rings do not show significant inhibition against GP enzymes: e. g. nojirimicin has no effect, for 1-deoxy-nojirimicin  $K_i = 55000 \mu\text{M}$  (for the structures see Table 2) (Compain et al., 2007). There are a few exceptions to this such as DAB and isofagomine derivatives (Fig. 3) (Praly & Vidal, 2010; Somsák et al., 2008; Somsák et al., 2003). A comprehensive tabulation of glycogen phosphorylase inhibition studies with iminosugars can be found in (Compain et al., 2007).

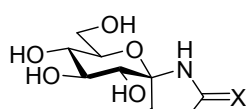
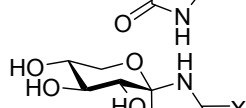
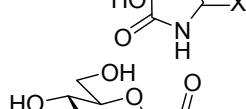
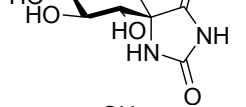
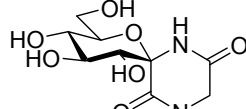
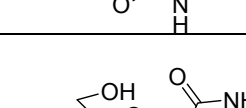
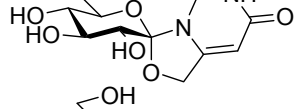
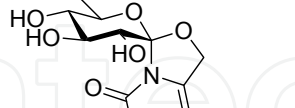
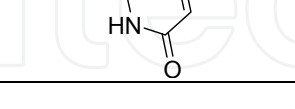
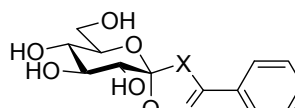
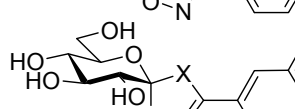
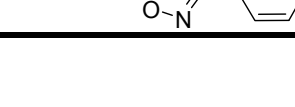
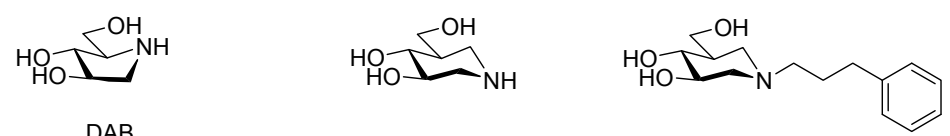
Entry	Compound	X	$K_i$ [ $\mu\text{M}$ ]
(Somsák et al., 2003)			
1.		O	3.1
2.		S	5.1
3.		O	No inhibition
4.		S	No inhibition
5.			320
6.			59
(Gimisis, 2010)			
7.			~2100
8.			~1700
(Somsák, 2011)			
9.		$\text{CH}_2$	19.6
10.		S	26
11.		$\text{CH}_2$	0.63
12.		S	0.16

Table 11. Inhibition of RMGPb by anomeric spirocycles



	DAB 1,4-dideoxy-1,4-imino-D-arabinitol	isofagomine	N-(3-phenylpropyl)-isofagomine
	IC <sub>50</sub> [μM]		
RMGPb	0.39	1.21	0.84
RLGPa	0.37	0.68	1.22
PLGPa	0.49	0.67	0.85

Fig. 3. Iminosugar type inhibitors of various GP enzymes

Miscellaneous sugar derivatives including further *O*-, *S*-, and *N*-glucopyranosides, *C*-glucopyranosyl compounds, *S*-glucopyranosyl sulfonamide, homo- and heteromultivalent glucose derivatives, as well as other sugar type compounds with significantly lower efficiency as compared to the above listed ones were also reviewed (Praly & Vidal, 2010; Somsák, 2011; Somsák et al., 2008; Somsák et al., 2003).

While no physiological investigations with glucose analogue inhibitors of GP can be found in the literature, very recently it has been demonstrated that glucopyranosylidene-spirothiohydantoin (Table 11, Entry 2) is effective in lowering blood glucose levels and restoring hepatic glycogen content in streptozotocin-induced diabetic rats (Docsa et al., 2011).

## 5. Conclusion

This survey provided an overview of carbohydrate derivatives and sugar like compounds (glycomimetics) which are employed in current therapies or investigated as potential future medications for type 2 diabetes mellitus. Although these applications and explorations do not exceed the symptomatic level of treatments characteristic of present curing, they promise the possibility of broadening the arsenal of the physician. Together with several other carbohydrate-based therapeutics these drugs and studied molecules pave the way for a more extensive use of saccharides in medicine.

## 6. Acknowledgment

This work was supported by the Hungarian Scientific Research Fund (OTKA CK 77712) and by the TÁMOP 4.2.1/B-09/1/KONV-2010-0007 project co-financed by the European Union and the European Social Fund.

## 7. Abbreviations

DPP-4	dipeptidyl-peptidase-4	6PF-2-K	6-phosphofructo-2-kinase
F-1,6-P2ase	fructose-1,6-bisphosphatase	PLGP	pig liver glycogen phosphorylase
F-2,6-P2	fructose-2,6-bisphosphate	PPAR $\gamma$	peroxisome proliferator-activated receptor $\gamma$
G-6-Pase	glucose-6-phosphatase	PTP-1B	protein tyrosin phosphatase-1B
GCK	glucokinase	RLGP	rat liver glycogen phosphorylase
GLP-1	glucagon-like peptide-1	RMGP	rabbit muscle glycogen phosphorylase
GLUT	glucose transporter	SAR	structure-activity relationship
GP	glycogen phosphorylase	SGLT	sodium dependent glucose transporter
GPI	glycogen phosphorylase inhibitor	T2DM	type 2 diabetes mellitus
GSK3	glycogen synthase kinase-3		

## 8. References

- Agius, L. (2010). Physiological control of liver glycogen metabolism: Lessons from novel glycogen phosphorylase inhibitors. *Mini-Reviews in Medicinal Chemistry*, Vol. 10, pp. 1175-1187.
- Alberti, G., Zimmet, P., Shaw, J., Bloomgarden, Z., Kaufman, F. & Silink, M. (2004). Type 2 diabetes in the young: The evolving epidemic - The International Diabetes Federation Consensus Workshop. *Diabetes Care*, Vol. 27, pp. 1798-1811.
- Alexacou, K. M., Tenchiu, A. C., Chrysina, E. D., Charavgi, M. D., Kostas, I. D., Zographos, S. E., Oikonomakos, N. G. & Leonidas, D. D. (2010). The binding of  $\beta$ -D-glucopyranosyl-thiosemicarbazone derivatives to glycogen phosphorylase: A new class of inhibitors. *Bioorganic & Medicinal Chemistry*, Vol. 18, pp. 7911-7922.
- Andersen, B., Rassov, A., Westergaard, N. & Lundgren, K. (1999). Inhibition of glycogenolysis in primary rat hepatocytes by 1,4-dideoxy-1,4-imino-arabinitol. *Biochemical Journal*, Vol. 342, pp. 545-550.
- Asano, N. (2009). Sugar-mimicking glycosidase inhibitors: bioactivity and application. *Cellular and Molecular Life Sciences*, Vol. 66, pp. 1479-1492.
- Bailey, C. J. (2011). Renal glucose reabsorption inhibitors to treat diabetes. *Trends in Pharmacological Sciences*, Vol. 32, pp. 63-71.
- Barroso, I. (2005). Genetics of type 2 diabetes. *Diabetic Medicine*, Vol. 22, pp. 517-535.
- Bloomgarden, Z. T. (2004). Type 2 diabetes in the young - The evolving epidemic. *Diabetes Care*, Vol. 27, pp. 998-1010.
- Board, M., Hadwen, M. & Johnson, L. N. (1995). Effects of novel analogs of D-glucose on glycogen-phosphorylase activities in crude extracts of liver and skeletal-muscle. *European Journal of Biochemistry*, Vol. 228, pp. 753-761.
- Boldys, A. & Okopien, B. (2009). Inhibitors of type 2 sodium glucose co-transporters - a new strategy for diabetes treatment. *Pharmacological Reports*, Vol. 61, pp. 778-784.
- Bonnefond, A., Froguel, P. & Vaxillaire, M. (2010). The emerging genetics of type 2 diabetes. *Trends in Molecular Medicine*, Vol. 16, pp. 407-416.
- Brownlee, M. (2001). Biochemistry and molecular cell biology of diabetic complications. *Nature*, Vol. 414, pp. 813-820.
- Cheng, A. Y. Y. & Fantus, I. G. (2005). Oral antihyperglycemic therapy for type 2 diabetes mellitus. *Canadian Medical Association Journal*, Vol. 172, pp. 213-226.
- Chrysina, E. D. (2010). The prototype of glycogen phosphorylase. *Mini-Reviews in Medicinal Chemistry*, Vol. 10, pp. 1093-1101.
- Chrysina, E. D., Kosmopolou, M. N., Tiraidis, C., Kardarakis, R., Bischler, N., Leonidas, D. D., Hadady, Z., Somsák, L., Docsa, T., Gergely, P. & Oikonomakos, N. G. (2005). Kinetic and crystallographic studies on 2-( $\beta$ -D-glucopyranosyl)-5-methyl-1,3,4-oxadiazole, -benzothiazole, and -benzimidazole, inhibitors of muscle glycogen phosphorylase *b*. Evidence for a new binding site. *Protein Science*, Vol. 14, pp. 873-888.
- Compain, P., Desvergnés, V., Liautard, V., Pillard, C. & Toumieux, S. (2007). Tables of iminosugars, their biological activities and their potential as therapeutic agents. In: *Iminosugars: From synthesis to therapeutic applications*. Compain, P. & Martin, O. R. (Ed(s)). Chichester, John Wiley & Sons Ltd. pp. 327-455.
- Compain, P. & Martin, O. R., Eds. (2007). *Iminosugars: From synthesis to therapeutic applications*. Chichester, John Wiley & Sons Ltd.

- de Melo, E. B., Gomes, A. D. & Carvalho, I. (2006).  $\alpha$ - and  $\beta$ -Glucosidase inhibitors: chemical structure and biological activity. *Tetrahedron*, Vol. 62, pp. 10277-10302.
- Deleanu, A. C., Kostas, I. D., Liratzis, I., Alexacou, K.-M., Leonidas, D. D., Zographos, S. E. & Oikonomakos, N. G. (2008).  $\beta$ -D-Glucopyranosyl-modified thiosemicarbazones as inhibitors of glycogen phosphorylase. *4<sup>th</sup> Central European Conference Chemistry towards Biology*. Dobogókő, Hungary, September 8-11, 2008. Book of Abstracts p. 80.
- Diamond, J. (2003). The double puzzle of diabetes. *Nature*, Vol. 423, pp. 599-602.
- Docsa, T., Czifrák, K., Hüse, C., Somsák, L. & Gergely, P. (2011). The effect of glucopyranosylidene-spiro-thiohydantoin on the glycogen metabolism in liver tissues of streptozotocin-induced and obese diabetic rats. *Molecular Medicine Reports*, Vol. 4, pp. 477-481.
- Ehrenkranz, J. R. L., Lewis, N. G., Kahn, C. R. & Roth, J. (2005). Phlorizin: a review. *Diabetes-Metabolism Research and Reviews*, Vol. 21, pp. 31-38.
- Ehtisham, S. & Barrett, T. G. (2004). The emergence of type 2 diabetes in childhood. *Annals of Clinical Biochemistry*, Vol. 41, pp. 10-16.
- El Ashry, E. S. H., Rashed, N. & Shobier, A. H. S. (2000a). Glycosidase inhibitors and their chemotherapeutic value, part 1. *Pharmazie*, Vol. 55, pp. 251-262.
- El Ashry, E. S. H., Rashed, N. & Shobier, A. H. S. (2000b). Glycosidase inhibitors and their chemotherapeutic value, part 2. *Pharmazie*, Vol. 55, pp. 331-348.
- El Ashry, E. S. H., Rashed, N. & Shobier, A. H. S. (2000c). Glycosidase inhibitors and their chemotherapeutic value, part 3. *Pharmazie*, Vol. 55, pp. 403-415.
- Fujimori, Y., Katsuno, K., Nakashima, I., Ishikawa-Takemura, Y., Fujikura, H. & Isaji, M. (2008). Remogliflozin etabonate, in a novel category of selective low-affinity sodium glucose cotransporter (SGLT2) inhibitors, exhibits antidiabetic efficacy in rodent models. *Journal of Pharmacology and Experimental Therapeutics*, Vol. 327, pp. 268-276.
- Geschwind, J.-F., Georgiades, C. S., Ko, Y. H. & Pedersen, P. L. (2004). Recently elucidated energy catabolism pathways provide opportunities for novel treatments in hepatocellular carcinoma. *Expert Review of Anticancer Therapy*, Vol. 4, pp. 449-457.
- Gimisis, T. (2010). Synthesis of *N*-glucopyranosidic derivatives as potential inhibitors that bind at the catalytic site of glycogen phosphorylase. *Mini-Reviews in Medicinal Chemistry*, Vol. 10, pp. 1127-1138.
- Green, A., Hirsch, N. C. & Pramming, S. K. (2003). The changing world demography of type 2 diabetes. *Diabetes-Metabolism Research and Reviews*, Vol. 19, pp. 3-7.
- Handlon, A. L. (2005). Sodium glucose co-transporter 2 (SGLT2) inhibitors as potential antidiabetic agents. *Expert Opinion on Therapeutic Patents*, Vol. 15, pp. 1531-1540.
- Hanhineva, K., Torronen, R., Bondia-Pons, I., Pekkinen, J., Kolehmainen, M., Mykkanen, H. & Poutanen, K. (2010). Impact of dietary polyphenols on carbohydrate metabolism. *International Journal of Molecular Sciences*, Vol. 11, pp. 1365-1402.
- Hengesh, E. J. (1995). Drugs affecting sugar metabolism. In: *Principles of Medicinal Chemistry*. Foye, W. O., Lemke, T. L. & Williams, D. A. (Ed(s)). Baltimore, Williams & Wilkins. pp. 581-600.
- Home, G., Wilson, F. X., Tinsley, J., Williams, D. H. & Storer, R. (2011). Iminosugars past, present and future: medicines for tomorrow. *Drug Discovery Today*, Vol. 16, pp. 107-118.

- Idris, I. & Donnelly, R. (2009). Sodium-glucose co-transporter-2 inhibitors: an emerging new class of oral antidiabetic drug. *Diabetes Obesity & Metabolism*, Vol. 11, pp. 79-88.
- Isaji, M. (2007). Sodium-glucose cotransporter inhibitors for diabetes. *Current Opinion in Investigational Drugs*, Vol. 8, pp. 285-292.
- Israili, Z. H. (2011). Advances in the treatment of type 2 diabetes mellitus. *American Journal of Therapeutics*, Vol. 18, pp. 117-152.
- Kakinuma, H., Oi, T., Hashimoto-Tsuchiya, Y., Arai, M., Kawakita, Y., Fukasawa, Y., Iida, I., Hagima, N., Takeuchi, H., Chino, Y., Asami, J., Okumura-Kitajima, L., Io, F., Yamamoto, D., Miyata, N., Takahashi, T., Uchida, S. & Yamamoto, K. (2010). (1S)-1,5-Anhydro-1-[5-(4-ethoxybenzyl)-2-methoxy-4-methylphenyl]-1-thio-D-glucitol (TS-071) is a potent, selective sodium-dependent glucose cotransporter 2 (SGLT2) inhibitor for type 2 diabetes treatment. *Journal of Medicinal Chemistry*, Vol. 53, pp. 3247-3261.
- Katsuno, K., Fujimori, Y., Takemura, Y., Hiratochi, M., Itoh, F., Komatsu, Y., Fujikura, H. & Isaji, M. (2007). Sertgliflozin, a novel selective inhibitor of low-affinity sodium glucose cotransporter (SGLT2), validates the critical role of SGLT2 in renal glucose reabsorption and modulates plasma glucose level. *Journal of Pharmacology and Experimental Therapeutics*, Vol. 320, pp. 323-330.
- Kim, M. J., Lee, J., Kang, S. Y., Lee, S. H., Son, E. J., Jung, M. E., Lee, S. H., Song, K. S., Lee, M., Han, H. K., Kim, J. & Lee, J. (2010). Novel C-aryl glucoside SGLT2 inhibitors as potential antidiabetic agents: pyridazinylmethylphenyl glucoside congeners. *Bioorganic & Medicinal Chemistry Letters*, Vol. 20, pp. 3420-3425.
- Krentz, A. J. & Bailey, C. J. (2005). Oral antidiabetic agents - current role in type 2 diabetes mellitus. *Drugs*, Vol. 65, pp. 385-411.
- Kurukulasuriya, R., Link, J. T., Madar, D. J., Pei, Z., Richards, S. J., Rohde, J. J., Souers, A. J. & Szczepankiewicz, B. G. (2003). Potential drug targets and progress towards pharmacologic inhibition of hepatic glucose production. *Current Medicinal Chemistry*, Vol. 10, pp. 123-153.
- Lee, J., Kim, J. Y., Choi, J., Lee, S. H., Kim, J. & Lee, J. (2010a). Pyrimidinylmethylphenyl glucoside as novel C-aryl glucoside SGLT2 inhibitors. *Bioorganic & Medicinal Chemistry Letters*, Vol. 20, pp. 7046-7049.
- Lee, J., Lee, S. H., Seo, H. J., Son, E. J., Lee, S. H., Jung, M. E., Lee, M., Han, H. K., Kim, J., Kang, J. & Lee, J. (2010b). Novel C-aryl glucoside SGLT2 inhibitors as potential antidiabetic agents: 1,3,4-thiadiazolylmethylphenyl glucoside congeners. *Bioorganic & Medicinal Chemistry*, Vol. 18, pp. 2178-2194.
- Lillelund, V. H., Jensen, H. H., Liang, X. & Bols, M. (2002). Recent developments of transition-state analogue glycosidase inhibitors of non-natural product origin. *Chemical Reviews*, Vol. 102, pp. 515-553.
- Loughlin, W. A. (2010). Recent advances in the allosteric inhibition of glycogen phosphorylase. *Mini-Reviews in Medicinal Chemistry*, Vol. 10, pp. 1139-1155.
- Lowell, B. B. & Shulman, G. I. (2005). Mitochondrial dysfunction and type 2 diabetes. *Science*, Vol. 307, pp. 384-387.
- Lv, B. H., Xu, B. H., Feng, Y., Peng, K., Xu, G., Du, J. Y., Zhang, L. L., Zhang, W. B., Zhang, T., Zhu, L. C., Ding, H. F., Sheng, Z. L., Welihinda, A., Seed, B. & Chen, Y. W. (2009). Exploration of O-spiroketal C-arylglucosides as novel and selective renal

- sodium-dependent glucose co-transporter 2 (SGLT2) inhibitors. *Bioorganic & Medicinal Chemistry Letters*, Vol. 19, pp. 6877-6881.
- Meng, W., Ellsworth, B. A., Nirschl, A. A., McCann, P. J., Patel, M., Girotra, R. N., Wu, G., Sher, P. M., Morrison, E. P., Biller, S. A., Zahler, R., Deshpande, P. P., Pullockaran, A., Hagan, D. L., Morgan, N., Taylor, J. R., Obermeier, M. T., Humphreys, W. G., Khanna, A., Discenza, L., Robertson, J. G., Wang, A., Hang, S., Wetterau, J. R., Janovitz, E. B., Flint, O. P., Whaley, J. M. & Washburn, W. N. (2008). Discovery of dapagliflozin: A potent, selective renal sodium-dependent glucose cotransporter 2 (SGLT2) inhibitor for the treatment of type 2 diabetes. *Journal of Medicinal Chemistry*, Vol. 51, pp. 1145-1149.
- Mizuno, C. S., Chittiboyina, A. G., Kurtz, T. W., Pershadsingh, H. A. & Avery, M. A. (2008). Type 2 diabetes and oral antihyperglycemic drugs. *Current Medicinal Chemistry*, Vol. 15, pp. 61-74.
- Mohan, S. & Pinto, B. M. (2007). Zwitterionic glycosidase inhibitors: salacinol and related analogues. *Carbohydrate Research*, Vol. 342, pp. 1551-1580.
- Moller, D. E. (2001). New drug targets for type 2 diabetes and the metabolic syndrome. *Nature*, Vol. 414, pp. 821-827.
- Morral, N. (2003). Novel targets and therapeutic strategies for type 2 diabetes. *Trends in Endocrinology and Metabolism*, Vol. 14, pp. 169-175.
- Muraoka, O., Morikawa, T., Miyake, S., Akaki, J., Ninomiya, K., Pongpiriyadacha, Y. & Yoshikawa, M. (2011). Quantitative analysis of neosalacinol and neokotalanol, another two potent alpha-glucosidase inhibitors from *Salacia* species, by LC-MS with ion pair chromatography. *Journal of Natural Medicines*, Vol. 65, pp. 142-148.
- Nomura, S. (2010). Renal sodium-dependent glucose cotransporter 2 (SGLT2) inhibitors for new anti-diabetic agent. *Current Topics in Medicinal Chemistry*, Vol. 10, pp. 411-418.
- Nomura, S., Sakamaki, S., Hongu, M., Kawanishi, E., Koga, Y., Sakamoto, T., Yamamoto, Y., Ueta, K., Kimata, H., Nakayama, K. & Tsuda-Tsukimoto, M. (2010). Discovery of canagliflozin, a novel C-glucoside with thiophene ring, as sodium-dependent glucose cotransporter 2 inhibitor for the treatment of type 2 diabetes mellitus. *Journal of Medicinal Chemistry*, Vol. 53, pp. 6355-6360.
- Nourparvar, A., Bulotta, A., Di Mario, U. & Perfetti, R. (2004). Novel strategies for the pharmacological management of type 2 diabetes. *Trends in Pharmacological Sciences*, Vol. 25, pp. 86-91.
- Oikonomakos, N. G. (2002). Glycogen phosphorylase as a molecular target for type 2 diabetes therapy. *Current Protein & Peptide Science*, Vol. 3, pp. 561-586.
- Oikonomakos, N. G., Kosmopolou, M., Zographos, S. E., Leonidas, D. D., Somsák, L., Nagy, V., Praly, J.-P., Docsa, T., Tóth, B. & Gergely, P. (2002). Binding of *N*-acetyl-*N'*- $\beta$ -D-glucopyranosyl urea and *N*-benzoyl-*N'*- $\beta$ -D-glucopyranosyl urea to glycogen phosphorylase *b*: Kinetic and crystallographic studies. *European Journal of Biochemistry*, Vol. 269, pp. 1684-1696.
- Oikonomakos, N. G. & Somsák, L. (2008). Recent advances in glycogen phosphorylase inhibitor design. *Current Opinion in Investigational Drugs*, Vol. 9, pp. 379-395.
- Padwal, R., Majumdar, S. R., Johnson, J. A., Varney, J. & McAlister, F. A. (2005). A systematic delay or pre review of drug therapy to delay or prevent type 2 diabetes. *Diabetes Care*, Vol. 28, pp. 736-744.

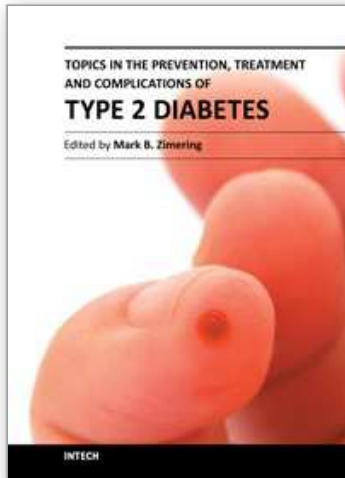
- Panunti, B., Jawa, A. A. & Fonseca, V. A. (2004). Mechanisms and therapeutic targets in type 2 diabetes mellitus. *Drug Discovery Today: Disease Mechanisms*, Vol. 1, pp. 151-157.
- Praly, J. P. & Vidal, S. (2010). Inhibition of glycogen phosphorylase in the context of type 2 diabetes, with focus on recent inhibitors bound at the active site. *Mini-Reviews in Medicinal Chemistry*, Vol. 10, pp. 1102-1126.
- Rendell, M. (2004). The role of sulphonylureas in the management of type 2 diabetes mellitus. *Drugs*, Vol. 64, pp. 1339-1358.
- Robinson, R. P., Mascitti, V., Boustany-Kari, C. M., Carr, C. L., Foley, P. M., Kimoto, E., Leininger, M. T., Lowe, A., Klenotic, M. K., MacDonald, J. I., Maguire, R. J., Masterson, V. M., Maurer, T. S., Miao, Z., Patel, J. D., Preville, C., Reese, M. R., She, L., Steppan, C. M., Thuma, B. A. & Zhu, T. (2010). C-Aryl glycoside inhibitors of SGLT2: exploration of sugar modifications including C-5 spirocyclization. *Bioorganic & Medicinal Chemistry Letters*, Vol. 20, pp. 1569-1572.
- Ross, S. A., Gulve, E. A. & Wang, M. H. (2004). Chemistry and biochemistry of type 2 diabetes. *Chemical Reviews*, Vol. 104, pp. 1255-1282.
- Santer, R. & Calado, J. (2010). Familial renal glucosuria and SGLT2: From a Mendelian trait to a therapeutic target. *Clinical Journal of the American Society of Nephrology*, Vol. 5, pp. 133-141.
- Scheen, A. J. (2003). Is there a role for  $\alpha$ -glucosidase inhibitors in the prevention of type 2 diabetes mellitus? *Drugs*, Vol. 63, pp. 933-951.
- Schnier, J. B., Nishi, K., Monks, A., Gorin, F. A. & Bradbury, E. M. (2003). Inhibition of glycogen phosphorylase (GP) by CP-91,149 induces growth inhibition correlating with brain GP expression. *Biochemical and Biophysical Research Communications*, Vol. 309, pp. 126-134.
- Sladek, R., Rocheleau, G., Rung, J., Dina, C., Lishuang, S., Serre, D., Boutin, P., Vincent, D., Belisle, A., Hadjadj, S., Balkau, B., Heude, B., Charpentier, G., Hudson, T. J., Montpetit, A., Pshezhetsky, A. V., Prentki, M., Posner, B. I., Balding, D. J., Meyre, D., Sladek, R., Rocheleau, G., Rung, J., Dina, C., Shen, L., Serre, D., Boutin, P., Vincent, D., Belisle, A., Hadjadj, S., Balkau, B., Heude, B., Charpentier, G., Hudson, T. J., Montpetit, A., Pshezhetsky, A. V., Prentki, M., Posner, B. I., Balding, D. J., Meyre, D., Polychronakos, C., Sladek, R., Rocheleau, G., Rung, J., Dina, C., Shen, L., Serre, D., Boutin, P., Vincent, D., Belisle, A., Hadjadj, S., Balkau, B., Heude, B., Charpentier, G., Hudson, T. J., Montpetit, A., Pshezhetsky, A. V., Prentki, M., Posner, B. I., Balding, D. J., Meyre, D., Polychronakos, C., Froguel, P., Sladek, R., Rocheleau, G., Rung, J., Dina, C., Shen, L., Serre, D., Boutin, P., Vincent, D., Belisle, A., Hadjadj, S., Balkau, B., Heude, B., Charpentier, G., Hudson, T. J., Montpetit, A., Pshezhetsky, A. V., Prentki, M., Posner, B. I., Balding, D. J., Meyre, D., Polychronakos, C. & Froguel, P. (2007). A genome-wide association study identifies novel risk loci for type 2 diabetes. *Nature*, Vol. 445, pp. 881-885.
- Somsák, L. (2011). Glucose derived inhibitors of glycogen phosphorylase. *Comptes Rendus Chimie*, Vol. 14, pp. 211-223.
- Somsák, L., Czifrák, K., Tóth, M., Bokor, É., Chrysina, E. D., Alexacou, K. M., Hayes, J. M., Tiraidis, C., Lazoura, E., Leonidas, D. D., Zographos, S. E. & Oikonomakos, N. G. (2008). New inhibitors of glycogen phosphorylase as potential antidiabetic agents. *Current Medicinal Chemistry*, Vol. 15, pp. 2933-2983.

- Somsák, L., Nagy, V., Hadady, Z., Docsa, T. & Gergely, P. (2003). Glucose analog inhibitors of glycogen phosphorylases as potential antidiabetic agents: recent developments. *Current Pharmaceutical Design*, Vol. 9, pp. 1177-1189.
- Somsák, L., Nagy, V., Hadady, Z., Felföldi, N., Docsa, T. & Gergely, P. (2005). Recent developments in the synthesis and evaluation of glucose analog inhibitors of glycogen phosphorylases as potential antidiabetic agents. In: *Frontiers in Medicinal Chemistry*. Reitz, A. B., Kordik, C. P., Choudhary, M. I. & Rahman, A. u. (Ed(s)). Bentham. pp. 253-272.
- Song, K. S., Lee, S. H., Kim, M. J., Seo, H. J., Lee, J., Lee, S. H., Jung, M. E., Son, E. J., Lee, M., Kim, J. & Lee, J. (2011). Synthesis and SAR of thiazolylmethylphenyl glucoside as novel C-aryl glucoside SGLT2 inhibitors. *ACS Medicinal Chemistry Letters*, Vol. 2, pp. 182-187.
- Stumvoll, M., Goldstein, B. J. & van Haeften, T. W. (2005). Type 2 diabetes: principles of pathogenesis and therapy. *Lancet*, Vol. 365, pp. 1333-1346.
- Sun, H. & Xu, L. (2010). Pharmacological manipulation of brain glycogenolysis as a therapeutic approach to cerebral ischemia. *Mini-Reviews in Medicinal Chemistry*, Vol. 10, pp. 1188-1193.
- Toye, A. & Gauguier, D. (2003). Genetics and functional genomics of type 2 diabetes mellitus. *Genome Biology*, Vol. 4, pp. 241.
- Tracey, W., Treadway, J., Magee, W., McPherson, R., Levy, C., Wilder, D., Li, Y., Yue, C., Zavadowski, W., Gibbs, E., Smith, A., Flynn, D. & Knight, D. (2003). A novel glycogen phosphorylase inhibitor, CP-368296, reduces myocardial ischemic injury. *Diabetes*, Vol. 52, pp. A135-A135.
- Tracey, W. R., Treadway, J. L., Magee, W. P., Sutt, J. C., McPherson, R. K., Levy, C. B., Wilder, D. E., Yu, L. J., Chen, Y., Shanker, R. M., Mutchler, A. K., Smith, A. H., Flynn, D. M. & Knight, D. R. (2004). Cardioprotective effects of ingliforib, a novel glycogen phosphorylase inhibitor. *American Journal of Physiology-Heart and Circulatory Physiology*, Vol. 286, pp. H1177-H1184.
- Treadway, J. L., Mendys, P. & Hoover, D. J. (2001). Glycogen phosphorylase inhibitors for treatment of type 2 diabetes mellitus. *Expert Opinion on Investigational Drugs*, Vol. 10, pp. 439-454.
- Tundis, R., Loizzo, M. R. & Menichini, F. (2010). Natural products as  $\alpha$ -amylase and  $\alpha$ -glycosidase inhibitors and their hypoglycaemic potential in the treatment of diabetes: An update. *Mini-Reviews in Medicinal Chemistry*, 2010, 10, 315, Vol. 10, pp. 315-331.
- Uwaifo, G. I. & Ratner, R. E. (2005). Novel pharmacologic agents for type 2 diabetes. *Endocrinology and Metabolism Clinics of North America*, Vol. 34, pp. 155-197.
- Vaidya, H. B. & Goyal, R. K. (2010). Exploring newer target sodium glucose transporter 2 for the treatment of diabetes mellitus. *Mini-Reviews in Medicinal Chemistry*, Vol. 10, pp. 905-913.
- Wagman, A. S., Johnson, K. W. & Bussiere, D. E. (2004). Discovery and development of GSK3 inhibitors for the treatment of type 2 diabetes. *Current Pharmaceutical Design*, Vol. 10, pp. 1105-1137.
- Wagman, A. S. & Nuss, J. M. (2001). Current therapies and emerging targets for the treatment of diabetes. *Current Pharmaceutical Design*, Vol. 7, pp. 417-450.



- Washburn, W. N. (2009a). Development of the renal glucose reabsorption inhibitors: A new mechanism for the pharmacotherapy of diabetes mellitus type 2. *Journal of Medicinal Chemistry*, Vol. 52, pp. 1785-1794.
- Washburn, W. N. (2009b). Evolution of sodium glucose co-transporter 2 inhibitors as anti-diabetic agents. *Expert Opinion on Therapeutic Patents*, Vol. 19, pp. 1485-1499.
- Wright, E. M. (2001). Renal Na<sup>+</sup>-glucose cotransporters. *American Journal of Physiology-Renal Physiology*, Vol. 280, pp. F10-F18.
- Xie, W., Tanabe, G., Akaki, J., Morikawa, T., Ninomiya, K., Minematsu, T., Yoshikawa, M., Wu, X. & Muraoka, O. (2011). Isolation, structure identification and SAR studies on thiosugar sulfonium salts, neosalaprinol and neoponkoranol, as potent [alpha]-glucosidase inhibitors. *Bioorganic & Medicinal Chemistry*, Vol. 19, pp. 2015-2022.
- Xu, B. H., Feng, Y., Lv, B. H., Xu, G., Zhang, L. L., Du, J. Y., Peng, K., Xub, M., Dong, J. J., Zhang, W. B., Zhang, T., Zhu, L. C., Ding, H. F., Sheng, Z. L., Welihinda, A., Seed, B. & Chen, Y. W. (2010). ortho-Substituted C-aryl glucosides as highly potent and selective renal sodium-dependent glucose co-transporter 2 (SGLT2) inhibitors. *Bioorganic & Medicinal Chemistry*, Vol. 18, pp. 4422-4432.
- Zechel, D. L. & Withers, S. G. (2000). Glycosidase mechanisms: Anatomy of a finely tuned catalyst. *Accounts of Chemical Research*, Vol. 33, pp. 11-18.
- Zhou, H. Q., Danger, D. P., Dock, S. T., Hawley, L., Roller, S. G., Smith, C. D. & Handlon, A. L. (2010). Synthesis and SAR of benzisothiazole- and indolizine-β-D-glucopyranoside inhibitors of SGLT2. *ACS Medicinal Chemistry Letters*, Vol. 1, pp. 19-23.

IntechOpen



## **Topics in the Prevention, Treatment and Complications of Type 2 Diabetes**

Edited by Prof. Mark Zimering

ISBN 978-953-307-590-7

Hard cover, 340 pages

**Publisher** InTech

**Published online** 04, November, 2011

**Published in print edition** November, 2011

Type 2 diabetes is estimated to affect 120 million people worldwide- and according to projections from the World Health Organization this number is expected to double over the next two decades. Novel, cost-effective strategies are needed to reverse the global epidemic of obesity which is driving the increased occurrence of type 2 diabetes and to less the burden of diabetic vascular complications. In the current volume, Topics in the Prevention, Treatment and Complications of Type 2 Diabetes, experts in biology and medicine from four different continents contribute important information and cutting-edge scientific knowledge on a variety of topics relevant to the management and prevention of diabetes and related illnesses.

### **How to reference**

In order to correctly reference this scholarly work, feel free to copy and paste the following:

László Somsák, Éva Bokor, Katalin Czifrák, László Juhász and Marietta Tóth (2011). Carbohydrate Derivatives and Glycomimetic Compounds in Established and Investigational Therapies of Type 2 Diabetes Mellitus, Topics in the Prevention, Treatment and Complications of Type 2 Diabetes, Prof. Mark Zimering (Ed.), ISBN: 978-953-307-590-7, InTech, Available from: <http://www.intechopen.com/books/topics-in-the-prevention-treatment-and-complications-of-type-2-diabetes/carbohydrate-derivatives-and-glycomimetic-compounds-in-established-and-investigational-therapies-of->

**INTECH**  
open science | open minds

### **InTech Europe**

University Campus STeP Ri  
Slavka Krautzeka 83/A  
51000 Rijeka, Croatia  
Phone: +385 (51) 770 447  
Fax: +385 (51) 686 166  
[www.intechopen.com](http://www.intechopen.com)

### **InTech China**

Unit 405, Office Block, Hotel Equatorial Shanghai  
No.65, Yan An Road (West), Shanghai, 200040, China  
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元  
Phone: +86-21-62489820  
Fax: +86-21-62489821

© 2011 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the [Creative Commons Attribution 3.0 License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen