CHAPTER 7

SGLT2 Inhibitors for Type 2 Diabetes

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1. INTRODUCTION

Type 2 diabetes mellitus is a progressive disease characterized by hyperglycemia, increased peripheral insulin resistance, and declining insulin secretion. Over the past two decades, the prevalence of type 2 diabetes has increased to near epidemic proportion in both developed and developing countries [1]. As of 2011, diabetes affects 25.8 million people in the USA, or 8.3% of the population. In 2007, the estimated economic burden from diabetes in the USA was $116 billion for direct medical costs and another $58 billion for indirect costs related to disability, work loss, and premature mortality. Among all diabetic patients, greater than 90% have type 2

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diabetes, while the remainder constituting type 1 diabetes are characterized by an inability to produce insulin due to destruction of pancreatic β-cells [2]. Currently available medications for type 2 diabetes are not sufficient to halt this epidemic and reduce its burden. Moreover, most current drugs are insulin dependent (improve insulin sensitivity or increase insulin levels) and lose their effectiveness to control hyperglycemia over time due to the progressive decline of β cell function. As a consequence, many patients receive multiple antidiabetic medicines and eventually require insulin therapy. The lack of sufficient control of hyperglycemia, even under therapy, contributes to the progressive nature of type 2 diabetes, which results in many burdensome complications such as diabetic retinopathy, neuropathy, nephropathy, and cardiomyopathy [3]. In addition, since a majority of diabetic patients are overweight or obese, the fraction of current therapies that are associated with weight gain exacerbates this condition.

Given the difficulty in achieving sufficient glycemic control for many diabetic patients using current therapies, there is an unmet medical need for new antidiabetic agents, especially insulin-independent therapies. Blocking glucose reabsorption in the kidney and lowering blood glucose levels through glucose excretion into the urine would provide a novel insulin-independent therapy [4]. Filtered plasma glucose is reabsorbed in the renal tubule mainly by sodium glucose cotransporter 2 (SGLT2) and reenters the systemic circulation. Recent Phase II and Phase III clinical data of SGLT2 inhibitors and genetic studies of SGLT2 mutations in humans have provided strong evidence for SGLT2 as a promising new target to treat diabetes. This potential new therapy may be used as a monotherapy or in combination with existing therapies to achieve an additive effect in controlling blood glucose levels. This review summarizes the biological rationale, the clinical trials, and preclinical research of SGLT2 inhibitors.

2. SGLT2 PHYSIOLOGY

2.1. Renal glucose reuptake by SGLT2 and SGLT1

The kidney was not previously appreciated as a diabetes target organ until the emergence of the role of SGLT2 in renal glucose recovery. Kidneys have a dynamic function in maintaining plasma glucose homeostasis through gluconeogenesis and reabsorption of glucose from the glomerular filtrate, as well as allowing overspill into the urine when glomerular glucose levels exceed renal tubule recovery capacity. In healthy humans, about 180 g of plasma glucose is filtered daily, almost all of which is reabsorbed in the kidneys. SGLT2 plays a major role in this process as shown in Figure 1. Micropuncture studies in mouse renal

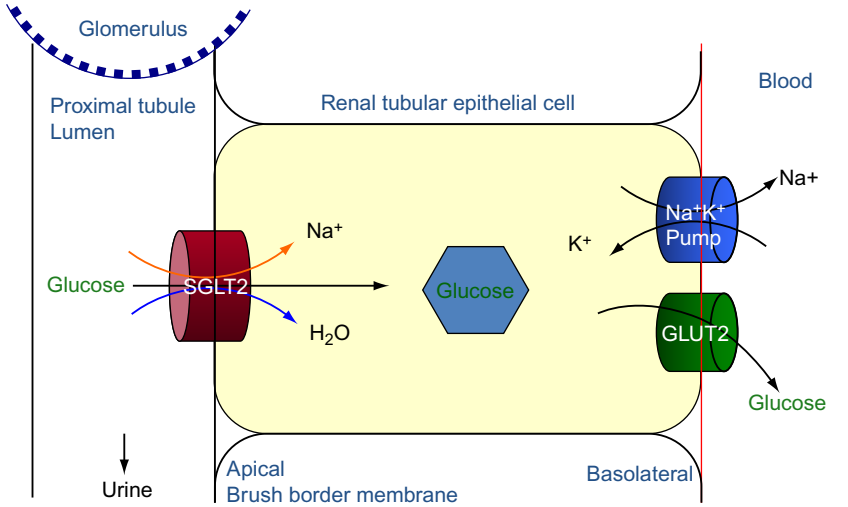
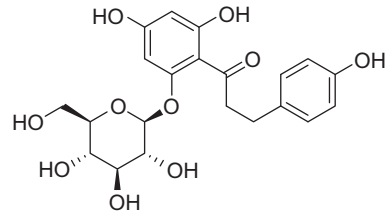


Figure 1 Tubular glucose reabsorption by SGLT2 in the kidney.

tubules and the phenotype of severe human SGLT2 mutations indicated that about 90% of renal glucose reabsorption is mediated by SGLT2 [5–7]. The SGLT2 localization in the S1 segment of the early proximal tubule and its high capacity for glucose transport fit well with its major role in renal glucose reabsorption. The remaining 10% of the filtered glucose is absorbed by SGLT1, a low capacity transporter which is localized in the S3 segment of the late proximal tubules [8,9]. SGLT1 and SGLT2 mediate the active transport of glucose across the apical membrane into the tubular cells via coupling with downhill cotransport of Na^+. The inward Na^+ gradient is maintained by ATP-driven Na^+/K^+ pumps. The glucose then passively diffuses out of the tubular cells and into blood stream across the basolateral membrane through facilitative glucose transporters GLUT2 and GLUT1 [9,10].

2.2. Glucosuria and regulation of plasma glucose

Phlorizin (**1**, Figure 2), a naturally occurring compound extracted from the root bark of an apple tree in 1835 and later identified as a SGLT1 and SGLT2 dual inhibitor, played a key role in elucidating the mechanism of renal glucose absorption and providing initial proof of principle for SGLT2 as a diabetes target. Treatment with phlorizin induced urinary glucose excretion (UGE) without renal abnormalities in dogs, and significantly lowered plasma glucose levels and normalized insulin sensitivity in diabetic rats [11,12].



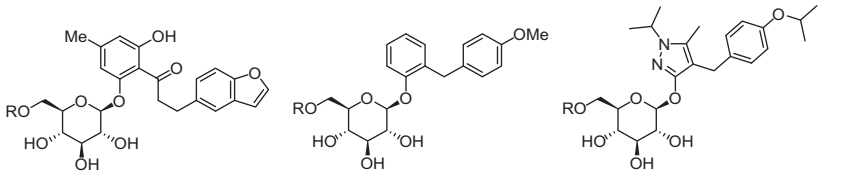
1, Phlorizin

Figure 2 Phlorizin, a starting point.

Interest in SGLT2 as a diabetes target was bolstered by studies of human SGLT2 mutations. SGLT2 mutations result in familial renal glucosuria (FRG), which is asymptomatic and benign. Although patients with SGLT2 mutations excrete glucose in varied amounts into the urine (<1 to >150 g/day), they present normal blood glucose levels and no noticeable kidney dysfunction [6,7]. Cases of severe glucosuria were found in patients with homozygous or compound heterozygous SGLT2 mutations [7]. Because SGLT2 mutations do not seem to lead to any clinical consequences, pharmacological inhibition of SGLT2 to prevent glucose reabsorption could potentially be as safe. On the other hand, SGLT1 inhibition appears less attractive since human SGLT1 mutations lead to glucose/galactose malabsorption (GGM) and are associated with severe diarrhea in infants on diets containing glucose/galactose [13]. Although blocking both SGLT1 and SGLT2 could increase efficacy, the potential side effects associated with SGLT1 inhibition make the selective inhibition of SGLT2 a more appealing strategy.

3. CLINICAL TRIALS

In addition to its role in elucidating the mechanism of glucose reabsorption in kidney, phlorizin also served as a starting point for the optimization of glucoside-based SGLT2 inhibitors. Indeed, all the SGLT2 inhibitors tested in human clinical trials thus far are glucoside-based inhibitors derived from phlorizin [14]. O-glucoside SGLT2 inhibitors **2a**, **3a**, and **4a** as their respective carbonate prodrugs T-1095 (**2b**), sergliflozin (**3b**), remogliflozin etabonate (**4b**) as well as AVE2268, TS-033, and BI44847 entered development (Figure 3) but have been discontinued due to lack of sufficient stability in the gut and post-absorption [10]. All SGLT2 inhibitors currently in development are C-glucosides, which exhibit increased metabolic



2a, R = H
2b, R = COOMe, T-1095

3a, R = H
3b, R = COOEt, Sergliflozin

4a, R = H, Remogliflozin
4b, R = COOEt, Remogliflozin etabonate

Figure 3 Disclosed structures of O-glucoside SGLT2 inhibitors previously in clinical trials.

stability, good potency, selectivity, and oral bioavailability [10,14]. The SGLT2 inhibitors currently in Phase II and Phase III clinical trials as of April 2011 are listed in Table 1. The structures of five of these inhibitors, dapagliflozin (**5**), canagliflozin (**6**), TS-071 (**7**), tofogliflozin (CSG-452, **8**), and ipragliflozin (ASP-1941, **9**), have been disclosed (Figure 4) [15,17,27–29]. Based on an analysis of the patent literature, all C-glucoside SGLT2 inhibitors in clinical trials are likely to have similar structures [14].

The clinical status, SGLT2 potency and selectivity over SGLT1, and dose ranges of inhibitors in the Phase II and Phase III clinical trials are also listed in Table 1. The *in vitro* SGLT2 potencies are similar for these compounds; all exhibit good selectivity over SGLT1 [15,17,19,21,23,26,27], except LX-4211, which is being positioned as a dual SGLT1 and SGLT2 inhibitor [16,26].

The Phase II and Phase III data of C-glucoside inhibitors was recently summarized [16]. The most advanced inhibitor in development is dapagliflozin for which data has been published for the completed pivotal Phase III clinical trials [30]. In addition to demonstrating good efficacy for lowering plasma glucose levels, dapagliflozin and other inhibitors have provided additional beneficial effects. These include insulin independence which may help β cell preservation, a low risk of hypoglycemia, and weight loss [16,31]. SGLT2 inhibitors are being tested as monotherapy and as add-on to existing antidiabetic therapies, including metformin, DPPIV inhibitors, sulfonylureas, and insulin. They induced robust hemoglobin A1c (HbA1c) reduction and moderate body weight loss as a monotherapy, and exhibited additive effects as an add-on therapy to the above-mentioned antidiabetic drugs. The SGLT2 inhibitor class also has been well tolerated, with no major safety signals; however, an increase in genitourinary infections was of significance in recent clinical trials [16]. In summary, clinical trials with multiple SGLT2 inhibitors are progressing well with no differentiating features as yet apparent in terms of efficacy and side effect profiles [16].

Table 1 SGLT2 inhibitors in Phase II and Phase III trials

Compound	SGLT2 IC_{50} (nM)	Selectivity over SGLT1	Clinical status	Dose range in the clinical studies
Dapagliflozin (BMS-512148)	1.1 [15]	1200 [15]	Phase III	2.5–10 mg q.d. (Phase III) [16]
Canagliflozin (TA-7284)	2.2 [17]	414 [17]	Phase III	100–300 mg q.d. (Phase III) [18]
BI 10773	3.1 [19]	>2500 [19]	Phase III	10–25 mg q.d. (Phase III) [20]
Ipragliflozin (ASP-1941)	7.4 [21]	255 [21]	Phase III[a]	50–300 mg q.d. (Phase II) [16,22]
Tofogliflozin (CSG-452)	2.9 [23]	2930 [23]	Phase III[a]	2.5–40 mg q.d. (Phase II) [24]
PF-04971729	n.a.	n.a.	Phase II	1–25 mg q.d. (Phase II) [25]
LX-4211	1.8 [26]	20 [26]	Phase II	150–300 mg q.d. (Phase II) [16,26]
TS-071	2.3 [27]	1765 [27]	Phase II[a]	n.a.

[a]Clinical studies in Japan.

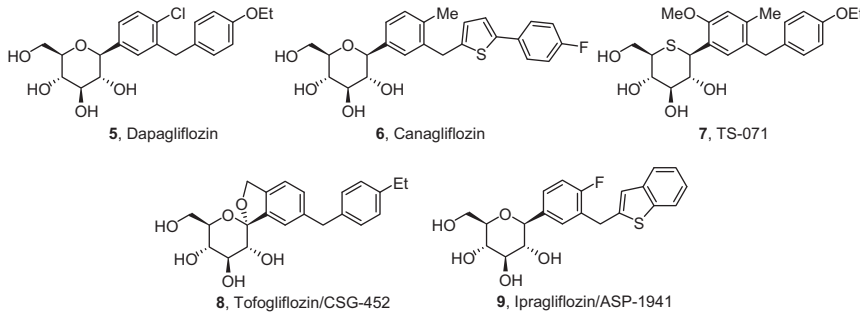


Figure 4 Disclosed structures of C-glucoside SGLT2 inhibitors in clinical trials.

4. SGLT2 INHIBITORS

4.1. Glucoside-based inhibitors

Industrial research efforts on phlorizin-derived inhibitors prior to 2009 were analyzed based on patent publications and have been nicely summarized in recent reviews [10,14]. As mentioned in Section 3, O-glucoside inhibitors are generally far inferior to C-glucoside inhibitors. There were no reports of N-glucoside inhibitors moving forward in development, even though they had good potency and pharmacokinetic (PK) properties [14]. In addition to summaries of key data for representative SGLT2 inhibitors, these reviews also discussed the evolution of the C-glucoside class of inhibitors and presented a structure–activity relationship (SAR) overview.

Around the time of the publication of these reviews, peer-reviewed articles of C-glucoside inhibitors began to appear in the literature. Here, we summarize articles published after 2009. Patent applications for C-glucoside inhibitors published after 2009, which were extensions of previously reviewed patents, are not summarized here.

All C-glucoside inhibitors published thus far are structurally related to dapagliflozin. Analogous to dapagliflozin, all of the C-glucoside inhibitors have an aromatic aglycone moiety (A ring) at the C1 position of the glucoside (Figure 5). The aglycone moiety is substituted 1,3 with a glucose-like moiety and a methylene-linked second planar ring (B ring). Recently reported modifications to this structure fall into three groups: the center A ring and its substitutions, the distal B ring and its substitutions, and glucoside modifications (Figure 5).

The B ring and its *para* R^4 substituent are tolerant of many changes. The most noteworthy examples are canagliflozin and ipragliflozin, for which the B ring is a thiophene and benzothiophene, respectively [17,29]. Replacement of the ethoxy group in dapagliflozin with 2-cyclopropoxyethoxy generated EGT1442 (**10**), which was evaluated extensively in *in vivo* studies, including UGE studies in Sprague–Dawley (SD) rats and dogs, an antihyperglycemic study in db/db mice, and a study evaluating prolonged survival effect of **10** in spontaneously hypertensive stroke prone (SHRSP) rats [32]. Other B ring modifications comprising substituted pyridazine, pyrimidine, thiazole, and thiadiazole generally resulted in loss of potency compared to dapagliflozin [33–37]. Recently, disclosed variations of the A ring comprise substitution at the C6′ position (R^2, Figure 5), such as **11a** and **11b** [38], spiro connection of the A ring to the glucoside (**12** and **13**), and heterocyclic replacements [39–43]. These modifications generally afforded potent compounds (such as **11a**–**13**) with the exception of the A ring heterocyclic replacements. The glucoside moiety does not tolerate many changes. Recently published glucoside

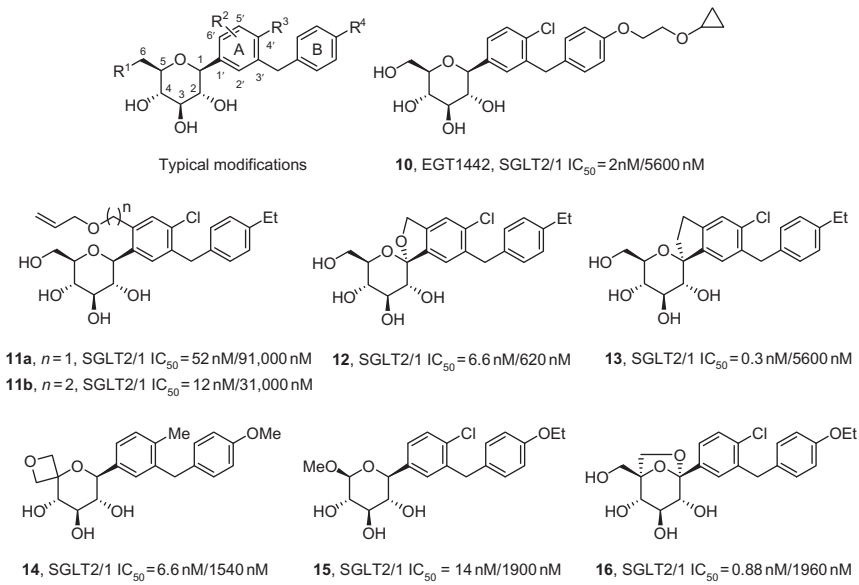


Figure 5 Exemplary modifications of glucoside-based SGLT2 inhibitors.

modifications include changes at the C6 position (such as **14**) [44,45], methoxy substitution of the C5 hydroxymethyl group (L-xylose derivatives, **15**) [46], incorporation of a [1–3]-bridged ketal system (**16**), and thioglucoside replacement of the glucoside [27,47]. Thioglucoside replacement in combination with minor modifications of the aglycone moiety produced TS-071 [27].

EGT1442 and L-xylose derivatives demonstrated excellent efficacy in animals [32,46]. However, a few recently reported SGLT2 inhibitors, such as **13** and **14**, were not as efficacious at promoting UGE as dapagliflozin in SD rats, despite *in vitro* potency that was comparable or better than dapagliflozin [41,45]. The inferior *in vivo* efficacy profiles were attributed to less than optimal PK properties in rats.

4.2. Non-glucoside-based inhibitors

While hundreds of patent applications disclosing glucoside-based SGLT2 inhibitors have published, only five applications disclosing non-glucoside SGLT2 inhibitors, all from one group, have appeared [48–52]. Representative structures from these disclosures include imidazopyrimidine **17** and imidazopyridine **18** (Figure 6), and only SGLT2 IC_{50} ranges (10–1000 nM) were reported. This disparity also exists in the peer-reviewed publications: there are only two recent articles reporting one industrial

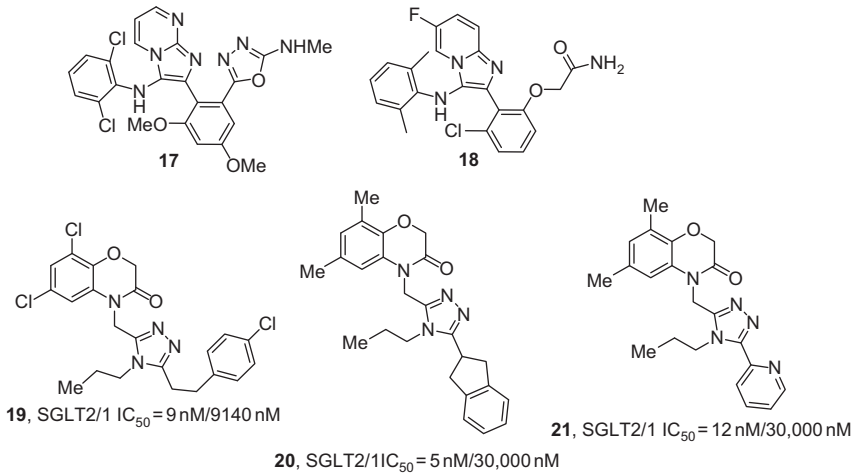


Figure 6 Non-glucoside-based SGLT2 inhibitors.

research effort on non-glucoside-based SGLT2 inhibitors [53,54]. A class of benzooxazinone SGLT2 inhibitors was discovered through high-throughput screening (HTS). Optimization afforded compounds such as **19–21** (Figure 6), which possessed similar SGLT2 potency and better SGLT1 selectivity compared to dapagliflozin. The compounds also completely displaced [^{3}H]-dapagliflozin in a binding assay (IC_{50} 16 nM for **19**). However, these compounds were judged to have inadequate microsomal stability. No *in vivo* efficacy data were reported for these compounds [53,54].

In addition to this single HTS and optimization effort, only one other company has reported efforts to develop assays suitable for HTS against SGLT2 [55]. Given the large number of patent applications related to phlorizin-based SGLT2 inhibitors and clinical proof of concept for this mechanism, identification of non-phlorizin-based inhibitors is attractive. It seems likely that additional HTS campaigns have been conducted, but the lack of patent applications and publications suggests that tractable chemotypes structurally unrelated to phlorizin have been difficult to identify. This apparent intractability could be related to an inability to identify HTS hits, or more likely, it could be related to difficulties encountered in hit optimization. With regard to the latter, it is noteworthy that at least some SGLT2 inhibitors in clinical development possess distinct PK/pharmacodynamic (PD) characteristics.

In a Phase I single ascending dose study of dapagliflozin, a near-maximal PD response (~3 g/h UGE) was maintained in healthy volunteers for at least 24 h after a single dose of 20 mg, while the plasma concentration decreased to a range of 10–20 nM at 24 h from a C_{max} of

600–700 nM [56]. Taking into account plasma protein binding, this corresponds to an unbound dapagliflozin plasma concentration of <2 nM 24 h post-dose which is in the vicinity of its *in vitro* SGLT2 IC_{50} (1.1 nM). To the best of our knowledge, there has not been any published data suggesting that *in vitro* potency overestimates the *in vivo* drug concentration needed to inhibit SGLT2. BI 10773 has a human PK/PD profile similar to that of dapagliflozin such that, after administration of single doses of BI 10773 to healthy volunteers, rapid onset of UGE responses occurred and they were maintained long after plasma concentrations had diminished [57,58]. Plasma levels of BI 10773 peaked at about 2 h, while maximal UGE rates (5.2 g/h at the 400 mg dose) occurred at about 7 h across a range of doses (10–800 mg) and did not drop nearly as rapidly as plasma concentrations [57,58]. It is also interesting to note that following oral administration of a 1 mg/kg dose of TS-071, a close structural analog of dapagliflozin, rats exhibited kidney/plasma ratios of 35 at 4 h post-dose despite the fact that TS-071 was primarily excreted by hepatic metabolism [27].

Taken together, the available data with dapagliflozin, BI 10773, and TS-071 suggest that the glucoside-based SGLT-2 inhibitors may preferentially distribute to the site of action in the kidney and/or have a slow off-rate from SGLT2, resulting in the observed favorable PK/PD profiles. Favorable distribution to the kidneys could be a result of active renal secretion affording high local drug concentrations in the proximal tubule. However, dapagliflozin has low renal clearance that is insignificant compared to its hepatic clearance [59]. On the other hand, renal secretion delivering pharmacologically relevant concentrations of dapagliflozin to the proximal tubule could be masked by renal reabsorption [60,61]. The human metabolite profile of dapagliflozin suggests that active metabolites do not significantly contribute to the PD response especially since dapagliflozin is primarily eliminated as a pharmacologically inactive glucuronide metabolite [59].

In summary, the mechanism responsible for the favorable PK/PD characteristics of glucoside SGLT2 inhibitors in development remains unclear. However, the inherent molecular properties of the inhibitors underlying their favorable PK/PD properties may be difficult to confer to non-glucoside SGLT2 inhibitors and could explain why these have not featured prominently in the patent or primary literature to date.

5. CONCLUSION

Inhibition of renal glucose reabsorption by SGLT2 inhibitors and subsequent glucose excretion into urine is a unique mechanism of action to lower blood glucose levels. Recent clinical data demonstrate that this potential new insulin-independent antidiabetic therapy not only can reduce HbA1c levels as effectively well as existing therapeutic agents

but also confers other beneficial features, such as body weight loss and low propensity for causing hypoglycemia. Overall, the available data show that SGLT2 inhibitors have demonstrated good benefit-risk profiles in human clinical trials. The U.S. Food and Drug Administration accepted a New Drug Application for dapagliflozin for review in March, 2011. It is hoped that dapagliflozin and other SGLT2 inhibitors will become important treatment options for type 2 diabetic patients.

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