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Review Article

Update on the Chemistry of Jardiance (Empagliflozin)

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Abstract

In this perspective, we put forth glimpses of type 2 diabetes (T2DM), SGLT-2 inhibitors (gliflozins), jardiance (Empagliflozin) and synthetic approaches towards empagliflozin and literature is covered up to date.

Key words: type 2 diabetes (t2dm); sglt-2 inhibitors (gliflozins); jardiance (empagliflozin)

Introduction

Diabetes is a long-term metabolic illness marked by high blood glucose (blood sugar) levels. Serious damage to the heart, blood vessels, eyes, kidneys, and nerves can result from diabetes over time. The most prevalent kind, type 2 diabetes, usually affects adults and is brought on by insufficient or resistant insulin production in the body. Type 2 diabetes (T2DM) has been much more common over the last three decades in all nations, regardless of economic status.[1] Diabetes type 1 is a chronic illness in which the pancreas generates little or no insulin on its own. It was formerly referred to as juvenile diabetes or insulin-dependent diabetes. Having access to reasonably priced therapy, such as insulin, is essential for the survival of those with diabetes. By 2025, there is a goal set globally to stop the rise in diabetes and obesity.

Approximately 422 million individuals globally suffer from diabetes, with the majority residing in low- and middle-income nations. The disease is directly responsible for 1.5 million fatalities annually. Over the past few decades, there has been a steady rise in both the number of cases and the incidence of diabetes.

The World Health Organisation (WHO) introduced the worldwide Diabetes Compact in April 2021. This worldwide initiative aims to support low- and middle-income nations while promoting sustained gains in diabetes prevention and care.[2] The World Health Organisation introduced the Global Diabetes Compact in response to the growing global burden of diabetes. The launch takes place on the 100th anniversary of insulin's discovery. The goal of the WHO Global Diabetes Compact is to lower the risk of diabetes and guarantee that everyone with the disease has access to fair, thorough, reasonably priced, and high-quality care. The work that is being done as part of the Compact will also help to prevent type 2 diabetes from being brought on by obesity, poor diet, and inactivity. The World Health Assembly passed a resolution in May 2021 aimed at enhancing diabetes prevention and control. The World Health Assembly approved five worldwide goals for diabetes treatment and coverage in May 2022, with an objective of achieving them by 2030.[3]

Certain individuals diagnosed with type 2 diabetes may require medication to assist in controlling their blood sugar levels. Injections of insulin or other medications are examples of these. Sulfonylureas, metformin, and inhibitors of the sodium-glucose co-transporter type 2 (SGLT-2) are a few examples.

SGLT-2 inhibitors (Gliflozins)

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors are antihyperglycemic agents acting on the SGLT-2 proteins expressed in the proximal convoluted tubules. These medications work by stopping the tubular lumen's filtered glucose from being reabsorbed. [4-6] A new class of glucose-lowering medicines known as gliflozins is defined by derivatives of β-D-glucoside that have an aryl or heteroaryl aglycone linked to the anomeric carbon (**Figure 1**). [28].A methylene bridge joins the aryl and heteroaryl groups in the β-C-glucoside aglycones.

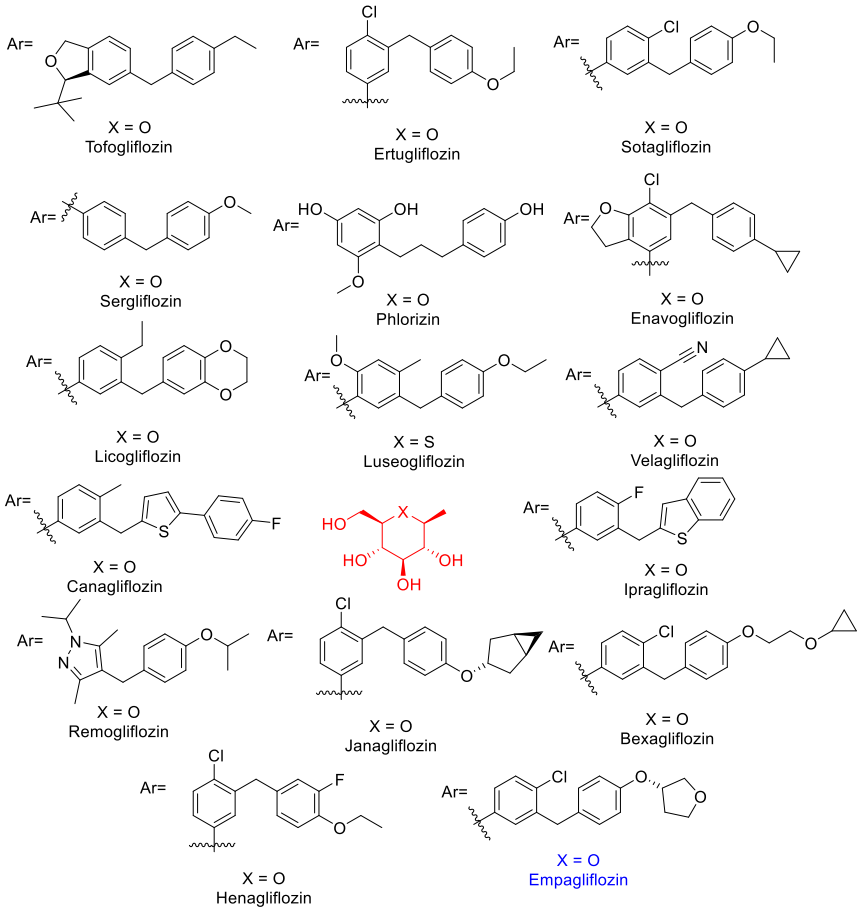


Figure 1. SGLT-2 inhibitors **(**Gliflozins)

In the US, there are presently three SGLT2 inhibitors on the market. The US Food and Drug Administration (FDA) approved dapagliflozin in January 2014, empagliflozin in August 2014, and canagliflozin in March 2013 (FDA news release 2013).[7-9] While canagliflozin exhibits dual blockage of SGLT1 and SGLT2, dapagliflozin and empagliflozin are highly selective for SGLT2. All of these drugs are strong competitive inhibitors of the SGLT2 protein. Empagliflozin, out of the three SGLT2 inhibitors that are currently on the market, has the highest selectivity for SGLT2 (2500-fold) when compared to SGLT1. [10-13].

At least two of the other three medications in this class-ipragliflozin, luseogliflozin, and tofogliflozin-are presently being studied, and ertugliflozin and remogliflozin are the other two that are marketed in Japan. Steglatro is the brand name under which ertugliflozin was approved in the United States in December 2017. Clinical trials on remogliflozin etabonate were terminated. Phase II trials saw the discontinuation of sergliflozin etabonate. Sotagliflozin, a combination SGLT1 and 2 inhibitors, was also undergoing clinical studies. Under the brand name Zynquista, sotagliflozin is a dual SGLT1/SGLT2 inhibitor undergoing phase III trials through March 2019. If authoriZed, sotagliflozin, which was developed by Lexicon Pharmaceuticals, would be the first oral medication used in conjunction with insulin to treat type 1 diabetes mellitus. According to a press statement from Sanofi and Lexicon, the FDA completed its response letter to a new drug application in March 2019 about oral sotagliflozin, a first-in-class dual SGLT1 and SGLT2 inhibitor for adults with type 1 diabetes. In this viewpoint, we provide a quick overview of the latest developments in the synthesis and uses of empagliflozin, with a particular emphasis.

Jardiance (Empagliflozin)

Empagliflozin, also marketed as Jardiance (BI 10773, **Figure 2**), is a strong, competitive, and specific inhibitor of the sodium glucose transporter SGLT2,[14-22] which mediates most of the kidney's total glucose reabsorption as well as glucose reabsorption in the early proximal tubule. As a result, therapy with empagliflozin enhanced the excretion of glucose in the urine. An FDA-approved pill called Jardiance is used to treat persons with heart failure or cardiovascular disease who also have type 2 diabetes (T2DM) lower their risk of cardiovascular complications. Jardiance helps the kidney increase the amount of glucose that passes into the urine, which reduces blood glucose levels (HbA1c). Jardiance is not advised for those with type 1 diabetes mellitus because it may raise their chance of developing diabetic ketoacidosis, which is characterised by elevated blood or urine ketones.

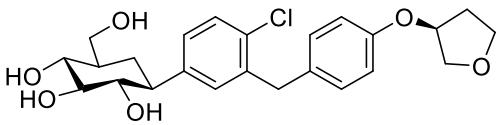


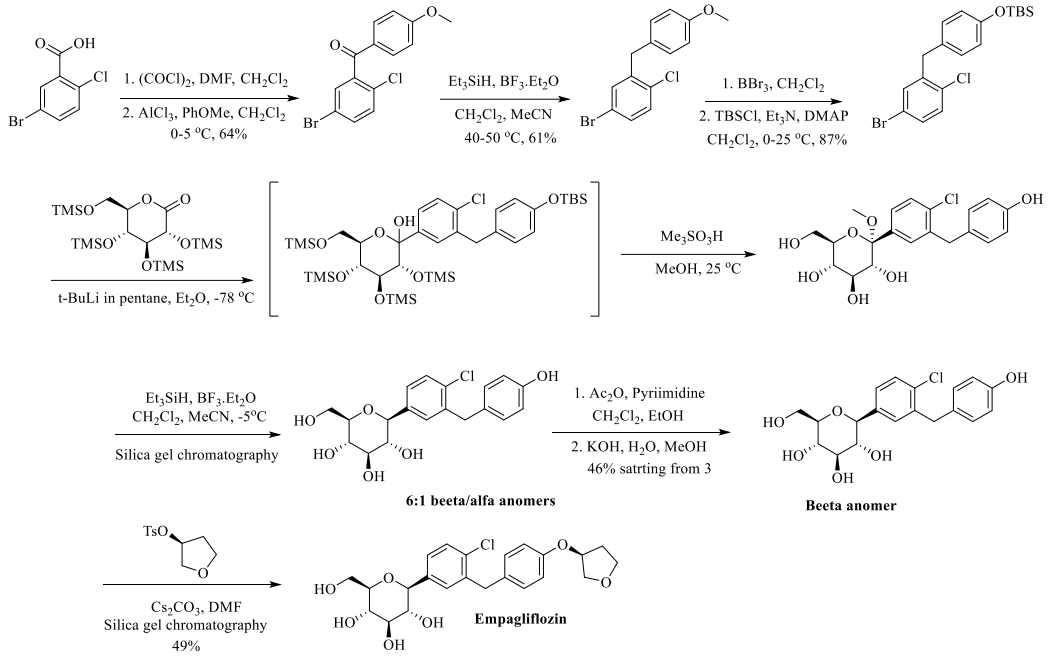
Figure 2. Jardiance

In 2014, both the European Union and the United States approved the medicinal use of empagliflozin. It is included in the List of Essential Medicines by the World Health Organisation. With around 8 million prescriptions, it ranked as the 85th most often prescribed drug in the US in 2021. The US Food and Drug Administration (FDA) has approved it for use as a generic drug. As of May 2013, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) had received applications for marketing approval from Boehringer and Lilly. The medication received approval in the US in August 2014 after receiving approval in the EU in May of the same year. Four postmarketing studies were mandated by the FDA: two studies involving children, a toxicity study with animals connected to the paediatric trials, and a cardiovascular outcomes trial. There are currently four different formulations available on the market: Synjardy (empagliflozin and metformin, film-coated tablets: 5 mg or 12.5 mg/1000 mg, and 5 mg/850 mg), Glyxambi (empagliflozin and linagliptin, 10/5 mg or 25/5 mg tablets), and Jardiance (empagliflozin, 10 mg/25 mg tablets). Very recently, absolute configuration of empagliflozin was re-confirmed by Sun et al.[23] A small number of study groups also conducted qualitative analyses of the empagliflozin impurity profiles. [24-26] An alginate-chitosan nanocarrier technology for efficient empagliflozin delivery was described by Mahmoodi and Ramazanzadeh.[27] There have been numerous patents and articles since its discovery and FDA approval. The short description and synthesis of empagliflozin can be found below.[28-29]

Synthetic approaches towards Empagliflozin

a) Martin et al. (2006)[30]

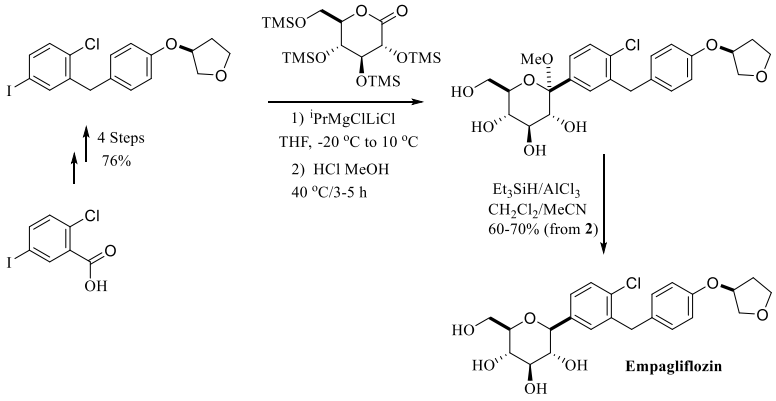
An early discovery patent (WO2006117359, 2006) describing the synthesis of empagliflozin is discussed in **Scheme 1** The synthesis involved a total of eight steps with an overall yield of 8% and commences from commercially available 2-chloro-5-bromobenzoic acid.



Scheme 1. Martin's synthetic approach

b) Wang et al. (2014) [31]

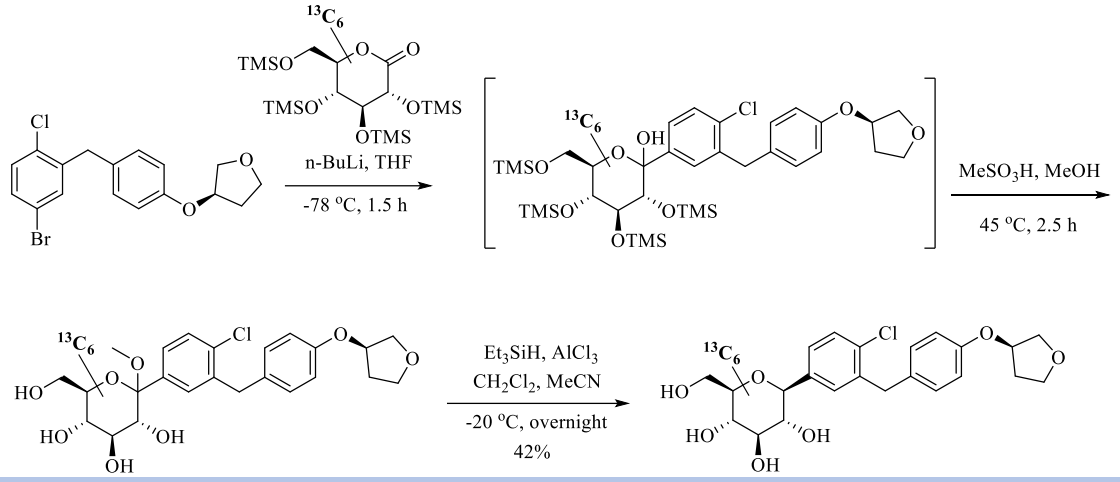
An efficient production synthesis of the SGLT-2 inhibitor Empagliflozin from acid 2-chloro-5-iodobenzoic acid is described (**Scheme 2).** The key tactical stage involves I/Mg exchange of aryl iodide 2 followed by addition to glucono lactone in THF. Subsequent *in situ* treatment of the resulting lactol with HCl in MeOH produces β-anomeric methyl glycopyranoside which is, without isolation, directly reduced with Et_3SiH mediated by $AlCl_3$ as a Lewis acid in CH_2Cl_2/MeCN to afford empagliflozin in 50% overall yield. The process was implemented for production on a metric ton scale for commercial launch.



Scheme 2. Wang's synthetic approach

c) Latli et al. (2014) [32]

Authors reported the synthesis of carbon-13 and carbon-14 labeled empagliflozin. Carbon-13 labeled empagliflozin was prepared in five steps and in 34% overall chemical yield starting from the commercially available α-D-glucose-[^{13}C6] (**Scheme 3**). For the radiosynthesis, the carbon-14 atom was introduced in three different positions of the molecule. In the first synthesis, Carbon-14 D-(+)-gluconic acid δ-lactone was used to prepare specifically labeled empagliflozin in carbon-1 of the sugar moiety in four steps and in 19% overall radiochemical yield. Carbon-14 labeled empagliflozin with the radioactive atom in the benzylic position was obtained in eight steps and in 7% overall radiochemical yield. In the last synthesis carbon-14 uniformly labeled phenol was used to give [^{14}C] empagliflozin in eight steps and in 18% overall radiochemical yield. In all these radiosyntheses, the specific activities of the final compounds were higher than 53 mCi/mmol, and the radiochemical purities were above 98.5%.

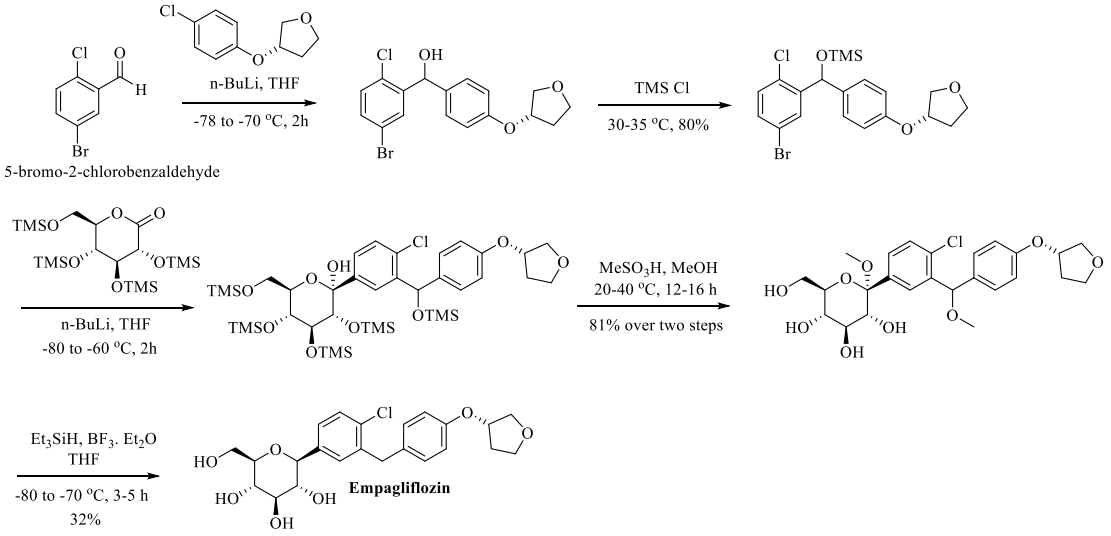


Scheme 3. Latli's synthetic approach

Furthermore, numerous studies in the literature have focused on the synthesis of radiolabelled empagliflozin. Hrapchak's team have detailed the synthesis of ^{13}C- and ^{14}Clabelled empagliflozin, commencing from a-D-glucose-[^{13}C6] (Scheme 3). This five-step process resulted in the desired ^{13}C-labelled empagliflozin with an overall yield of 34% starting from a-D-glucose-[^{13}C6] intermediate, which was itself prepared from the corresponding carboxylic acid.

d) Kaushik et al. (2015) [33]

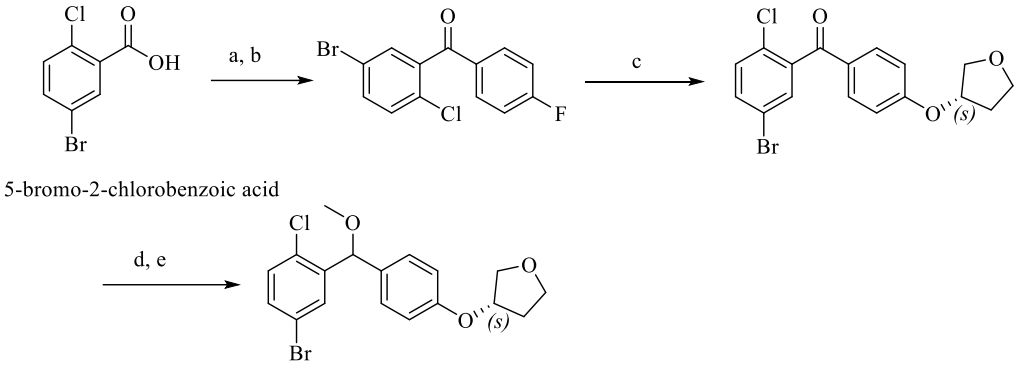
In 2015, Kaushik and co-workers patented an improved process for synthesizing empagliflozin starting from 5-bromo-chlorobenzaldehyde (**Scheme 4**).



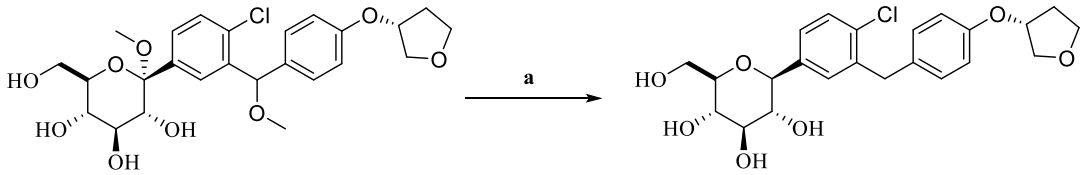
Scheme 4. Kaushik's synthetic approach

e) Sethi et al. (2018) [34]

An efficient synthetic process consisting usage of two novel intermediates namely [(5-Bromo-2-chlorophenyl) {4-[(3*S*)-tetrahydrofuran-3-yloxy] phenyl} methyl and 1-*C*-[4-chloro-3-(methoxy{4-[(3*S*)-tetrahydrofuran-3-yloxy] phenyl} methyl) phenyl]-α-Dglucopyranose has been developed to produce compound empagliflozin. This manuscript describes the comprehensive experimentation of this innovative and scale-up with ease synthetic route.



Reagents: (a) $(COCl)_2$, DMF, CH_2Cl_2; (b) Flurobenzene, $AlCl_3$, CH_2Cl_2; (c) t-BuOK, THF, (S)-tetrahydrofuran-3-ol; (d) $NaBH_4$, MeOH; (e) CH_3SO_3H, MeOH

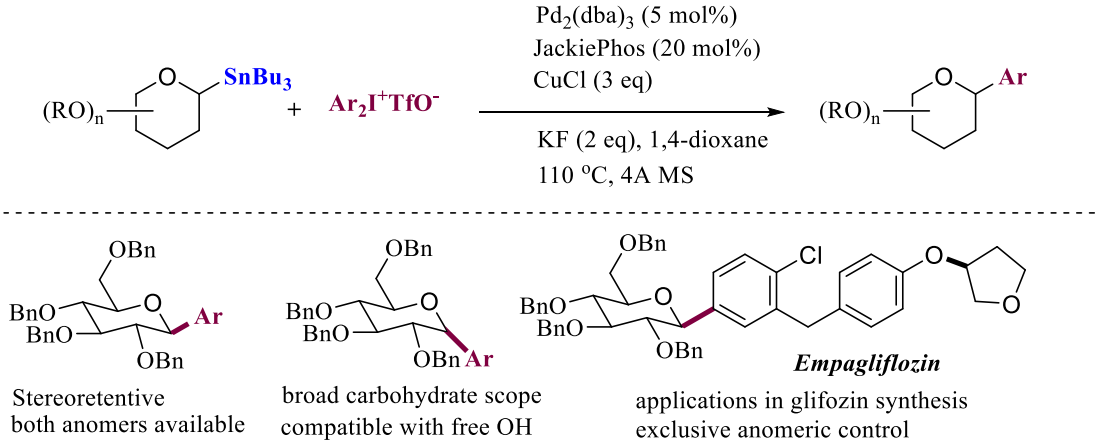


Reagents: (a) $AlCl_3$, Et_3SiH, ACN, CH_2Cl_2, EtOAc, EtOH

Scheme 5. Sethi's synthetic approach

f) Walczak et al. (2018) [35]

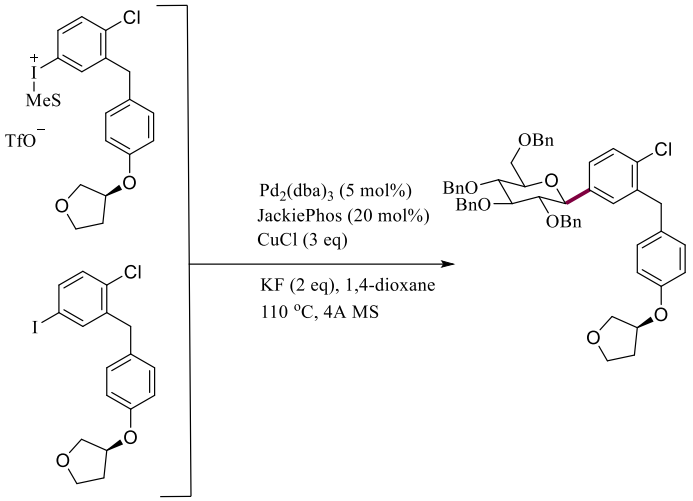
A stereospecific cross-coupling reaction of anomeric nucleophiles with diaryliodonium triflates resulting in the synthesis of aryl C-glycosides was reported (**Scheme 6**). This process capitalizes on a stereoretentive reaction of configurationally stable C1 stannanes and is promoted by a palladium catalyst in the presence of a bulky phosphine ligand that suppresses the undesired β-elimination. The utility of this reaction has been demonstrated in the preparation of a series of C-glycosides derived from common saccharides resulting in exclusive transfer of anomeric configuration from the anomeric nucleophile to the product, and in the synthesis of empagliflozin, a commercial antidiabetic drug.



Stereoretentive
both anomers available

broad carbohydrate scope
compatible with free OH

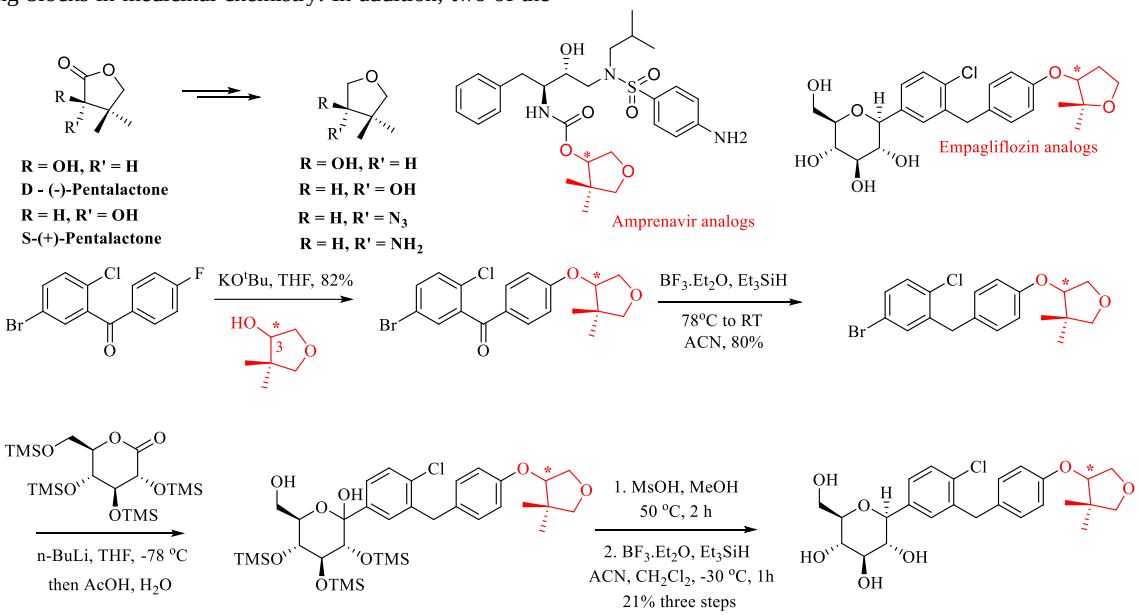
applications in glifozin synthesis
exclusive anomeric control



Scheme 6. Walczak's synthetic approach

g) Reddy et al. (2019) [36]

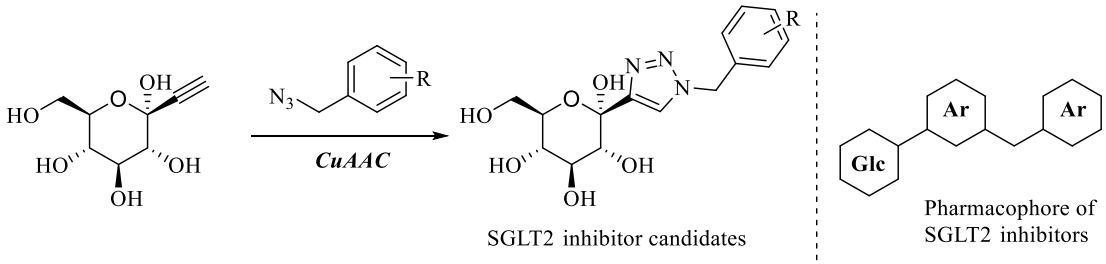
Chiral 4,4-dimethyl tetrahydrofuran (THF) derivatives were synthesized from commercially available D-(-)/ L-(+) pantolactones, which can serve as chiral building blocks in medicinal chemistry. In addition, two of the synthesized building blocks were utilized for the synthesis of new amprenavir (HIV protease inhibitor) and empagliflozin (anti-diabetic) analogs **Scheme 7**. The synthesized analogs may have beneficial effects in terms of pharmacokinetics and modulation of bioactivity.



Scheme 7. Reddy's synthetic approach

(g) Kitamura et al. (2023) [37]

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are clinically available to control blood glucose levels in diabetic patients *via* an insulin-independent mechanism. It was found that some carbasugar analogs of known SGLT2 inhibitors exert a high inhibiting ability toward SGLT2 and have a prolonged blood glucose lowering effect. In this study, authors designed new candidates of carbasugar SGLT2 inhibitor that can be synthesized using copper-catalyzed azide–alkyne cycloaddition (CuAAC) into an aromatic ring (**Scheme 8**), which is a part of the pharmacophore at the final stage in the synthetic protocol for the easier discovery of superior SGLT2 inhibitors. Based on the results of molecular docking studies, some selected compounds have been synthesized. Evaluation of these compounds using a cell-based assay revealed that the majority of these compounds had SGLT2 inhibitory activity in a dose-dependent manner.



Scheme 8. Kitamura's synthetic approach

Conclusion

The purpose of this perspective is to provide brief glimpse about type 2 Diabetes mellitus (T2DM), SGLT-2 inhibitors (gliflozins), with a special focus on synthetic routes to jardiance (empagliflozin) and its uses. We do hope that young researchers from the field get benefitted from this concise and critical outlook.

Acknowledgement

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