Dapagliflozin – structure, synthesis, and new indications

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Abstract

Dapagliflozin is a sodium-glucose co-transporter-2 (SGLT2) inhibitors used in the treatment of patients with type 2 diabetes. An aryl glycoside with significant effect as glucose-lowering agents, Dapagliflozin also has indication for patients with Heart Failure and Chronic Kidney Disease. This review examines the structure, synthesis, analysis, structure activity relationship and uses of the product. The studies behind this drug have opened the doors for the new line of treatment – a drug that reduces blood glucoses, decreases the rate of heart failures, and has a positive effect on patients with chronic kidney disease.

Keywords

Dapagliflozin, SGLT2-inhibitor, diabetes, heart failure

Structure of dapagliflozin

C-glycosides have a remarkable rank in medicinal chemistry as they are considered as universal natural products (Qinpei and Simon 2004). Selective sodium-dependent glucose cotransporter 2 (SGLT-2) inhibitors are potent medicinal candidates of aryl glycosides that are functional against diabetes (Lee et al. 2005; Lemaire 2012; Mironova et al. 2017). Embodiments of (SGLT-2) inhibitors include dapagliflozin, canagliflozin, empagliflozin and ipragliflozin, shown in Figure 1. It has molecular formula of C_{24}H_{35}ClO_{9}.

IUPAC name (2S,3R,4R,5S,6R)-2-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-6-(hydroxymethyl)oxan-3,4,5-triol[2S]-propane-1,2-diol;hydrate.

Synthesis

Dapagliflozin is an approved drug by U.S. Food and Drug Administration (FDA). Dapagliflozin is a representative of SGLT-2 inhibitors, actively considered to cure diabetes type 2. Thus, methodology of dapagliflozin synthesis has rarely published (Ellsworth et al. 2002; Meng 2008). Scheme 1 have shown the general synthetic route for the synthesis of dapagliflozin. Gluconolactone 3 which was protected by trimethylsilyl TMS was treated with aryl lithium. Aryl lithium was obtained by reacting aryl bro-
mide 2 (exchange of Li/Br) with n-BuLi. Methyl C-aryl glucoside 4 was produced by treatment of resulting mixture with methane sulfonic acid in the presence of methanol. Compound 4 was subjected to acetylation in the presence of Ac₂O, resulted in the formation of 5 followed by reduction of 5 to 6 with the help of Et₃SiH and BF₃·OEt₂. Finally, dapagliflozin 1 was produced via hydrolysis of 6 by LiOH (Deshpande et al. 2008; Meng 2008).

Jun et al. has reported a few improvements to the scheme 1. In the improved methodology scheme 2, trimethylsilyl chloride was added to gluconolactone 7 in the presence of N-methylmorpholine and tetrahydrofuran THF (Horton et al. 1981), followed by the formation of persilyated lactone 3. After completing the reaction of aryl bromide 2 with n-BuLi, added to persilyated lactone 3. Intermediate lactol 8 was produced by treating resulting reaction mixture with trifluoroacetic acid in aqueous form. Then ethyl C-aryl glycoside 9 yielded when subsequently compound 8 was subjected to methane-sulfonic acid in ethyl alcohol. Crude product 9 in the form of oil was secured after the screening of solvents. Jun et al. proposed that more than 98% pure 9 was collected as crystalline solvate after the crystallization of crude oil from n-propanol and n-heptane mixture (Yu et al. 2019). Moreover, Wang et al. proposed that a high extent of diastereoselectivity obtained after the reduction of tetra-O-unprotected methyl C-aryl glucoside by utilizing Et₃SiH and BF₃·OEt₂ (Wang et al. 2014). The nature of active pharmaceutical ingredient is amorphous foam which is isolated after the reduction of 9. Production of cocrystalline complex facilitate the isolation and purification of API (Deng et al. 2017). It is concluded that more than 99.7% pure dapagliflozin produced in overall 79% yield, after the crystallization of a mixture consists of n-heptane and ethyl acetate (Yu et al. 2019).

Zheng et al. designed the production methodology of dapagliflozin by introducing NO donor group at the last steps of general route of dapagliflozin synthesis (scheme 1). Novel hybrids achieved by the combination of dapagliflozin and NO donor, having excellent dual characteristics of anti-hyperglycemic and anti-thrombosis. The figure 2 represent the modifiable site (4-position) of dapagliflozin.

Scheme 3 has shown the formation strategy of new hybrids of nitric oxide with dapagliflozin. During the synthesis process, the compound 6 was treated with BBr₃ that result in the formation of phenol 10, which was further subjected to condensation with bromoalkane and then undergo hydrolysis and produce 11 intermediates. Target compound was obtained by the reacting 11 with silver nitrate in acetonitrile (Li et al. 2018).

Lin et al. fabricated green route (scheme 4) for the production of dapagliflozin. 5-bromo-2-chlorobenzoic acid 12 and gluconolactone were utilized to initiate the synthesis. By taking BF₃·Et₂O in catalytic amount to produce 13, overall yield of 76% was obtained in one-pot way via considering the Friedel-Craft acylation and ketillation. There was no need to do work-up operations to separate the diaryl ketal 13 as it was easily crystallized from the mixture. Compound 14 was produce as a result of condensation between 13 and 3. Overall yield of 68% of compound 15 was produced by the deprotection of silyl group in ethyl alcohol media. In THF presence, single crystals of 15 was achieved and characterized by XRD-analysis. High yield of dapagliflozin was obtained after the reduction of 15 that was carried out by triethylsilane in the presence of boron trifluoride diethyl etherate in dichloromethane. Upon crystallization from the mixture having heptane and ethyl acetate, greater than 98% pure dapagliflozin was produced by green synthetic pathway (Hu et al. 2019).
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Structure analysis of dapagliflozin

Manasa et al. has reported the reverse phase HPLC protocol to analyze the dapagliflozin in active pharmaceutical ingredients. To conduct this analysis, a BDS column was maintained at ambient temperature, mobile phase was prepared by utilizing the mixture of acetonitrile and phosphoric acid, PDA detectors were used, and detection noted at 245 nm. Manasa et al. estimate the stability of dapagliflozin by considering degradation in the presence of heat, UV, acidic, alkaline, and neutral conditions. For degradation studies, he treated dapagliflozin with acidic solution, alkali, heat, water and UV rays. Table 1 shows the percentage of degradation with all the mentioned medium (Sanagapati et al. 2014).

Table 1. Degradation study of Dapagliflozin by Manasa et al.

<table>
<thead>
<tr>
<th>Degradation condition</th>
<th>% of degradation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrogen peroxide</td>
<td>5.1</td>
</tr>
<tr>
<td>Acid</td>
<td>7.4</td>
</tr>
<tr>
<td>Alkali</td>
<td>6.4</td>
</tr>
<tr>
<td>Thermal (Dry heat)</td>
<td>4.4</td>
</tr>
<tr>
<td>UV</td>
<td>1.4</td>
</tr>
<tr>
<td>Neutral (Water)</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Structure activity relationship

The structure-activity relationship in the structure shown in (figure 2) can be assessed by considering the linkage at 4-position in dapagliflozin, the linking of NO donor (Xu et al. 2011). One of the signaling molecules, nitric oxide is a notable molecule which has excellent signaling profile. The assortment of physiological cycles in cardiovascular system, including the restraint of platelet accumulation, unwinding of vascular smooth muscles, diminishing adherence and actuation of neutrophil is substantially accomplished by the action of NO (Guzik et al. 2003). SGLT-2 inhibitor coupling with donor of NO give rise to exotic hybrids, having dual pharmacological potential such as anti-hyperglycemic and anti-thrombosis and consequently mitigate the prevalence of cardiovascular issues (Palmer et al. 1989).

Xuekun et al. reported that coupling of various substituents at the distal aryl ring of dapagliflozin has paved a synthetic path towards a series of novel hybrids of C-aryl glycosides and their estimation against hypoglycemic and type 2 diabetic rats has confirmed their anit-diabetic and anti-hyperglycemic activity. Introduction of electron donating and electron withdrawing groups impart specific characteristic to dapagliflozin. Experimental results demonstrated that when the distal aryl ring is occupied by electron donating group, normal mice has reported improved tolerance against glucose, whereas this tolerance destroyed in the presence of electron withdrawing group (Figure 3). Upon administration of glucose at a dose of 3 g.kg^{-1} along with compound 13c in normal mice, increase in urinary glucose levels in diabetic rats (Wang et al. 2015).

USES

Diabetes

Gerg et al. stated that oral medication of dapagliflozin is given to patients having diabetes, which is inhibitor of sodium-glucose cotransporter 2. Increase in glucose rich urinary excretion and reduction of glucose level in blood has been caused by dapagliflozin as it suppresses the SGLT-2 transporter proteins and reduce the reabsorption of glucose in renal proximal tubules of nephron. The mode of action of dapagliflozin do not depend on the secretion of insulin or its action. When dapagliflozin used in combination with anti-hyperglycemic drugs, it gives complementary treatment. Findings collected from many clinical trials with dapagliflozin (mono or dual therapy) have clearly shown reduction in the body weight, glycosylated based hemoglobin and glucose concentration in
fasting plasma. A very less chances of hypoglycemia has been reported by the usage of dapagliflozin. The patients having moderate or severe renal dysfunction are not treated with dapagliflozin drug. Dapagliflozin is recommended as a safe drug to cure type 2 diabetes because of its ubiquitous mode of action, high efficacy and good tolerability profile. Although diabetic complications observed during medication of dapagliflozin are still be evaluated (Plosker 2014).

Heart failure

Heart failure stays the principal cause of death and morbidity in advanced nations with an estimated perversiveness of around 1–2% and hitting >10% among patients that are more than 70 years old (Mosterd et al. 2007). It is also a well-established fact that Type 2 diabetes mellitus (T2DM) is a determinant condition for heart failure and that some form of cardiomyopathy is linked with hyperglycemia (Kannel et al. 1974).

Large clinical preliminaries including patients with type 2 diabetes have shown that inhibitors of sodium–glucose cotransporter 2 (SGLT2) decrease the danger of hospitalization for cardiovascular breakdown (Sarafidis et al. 2015; Hao 2021). It has been observed that treatment with SGLT-2 in the patients who undergo these trials, face less chances of incident failure of heart, which is a benefit of SGLT-2 medication. After randomization, a significant decrease in hospitalization for failure of heart has been observed that ultimately raised the mechanism of action that varied from those normally hypothesized to clarify the cardiovascular advantages of glucose lowering treatments (Packer et al. 2017; Verma 2018). McMurray J et al. estimate the efficacy and safety of dapagliflozin medication in patients who were suffering from heart failure and reduced ejection fraction, despite of their diabetes positive or negative status, by formulating a trial known as DAPA-HF (Dapagliflozin and Prevention of Adverse outcomes in Heart Failure). Placebo-controlled trial in HFrEF patients have shown that there was a lower risk of primary outcomes of deteriorative heart failure and death rate in patients who were treated with dapagliflozin as compared to those who were treated with placebo. The patients without diabetes type 2 have shown 55% effectiveness of dapagliflozin than diabetes positive patients. The results of this trial demonstrated that dapagliflozin is a potent pharmaceutical candidate that effectively decrease the risks of severe heart failure and deaths cases originated by cardiovascular issues in patients who were administered by dapagliflozin than who were treated with placebo, regardless of diabetes active or inactive status (McMurray et al. 2019).

In May 2020, the U.S. Food and Drug Administration approves dapagliflozin oral tablets for adults with heart failure with reduced ejection fraction to reduce the risk of cardiovascular death and hospitalization for heart failure. (Food and Drug Administration 2020)

Chronic kidney disease

The definition and classification of chronic kidney disease (CKD) have evolved over time, but current international guidelines define this condition as decreased kidney function shown by glomerular filtration rate (GFR) of less than 60 mL/min per 1·73 m2, or markers of kidney damage, or both, of at least 3 months duration, regardless of the underlying cause. Diabetes and hypertension are the main causes of CKD in all high-income and middle-income countries, and also in many low-income countries. Incidence, prevalence, and progression of CKD also vary within countries by ethnicity and social determinants of health, possibly through epigenetic influence. Many people are asymptomatic or have non-specific symptoms such as lethargy, itch, or loss of appetite. (Webster et al. 2017)

A study conducted with 4304 participants concludes that among patients with chronic kidney disease, regardless of the presence or absence of diabetes, the risk of a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes was significantly lower with dapagliflozin than with placebo. (Heerspink et al. 2020)

In April 2021 the U.S. Food and Drug Administration approves dapagliflozin oral tablets to reduce the risk of kidney function decline, kidney failure, cardiovascular death and hospitalization for heart failure in adults with chronic kidney disease who are at risk of disease progression. (Food and Drug Administration, 2021)

Side effects

Common side effects (Saeed et al. 2014)

- Back pain
- Increase hematocrit
- Dizziness
- Dyslipidemia

Adverse effects:

Genital infections

Genital contaminations are by a wide margin the commonest symptom of dapagliflozin. Genital effects include vulvovaginitis and balanitis. Pooled data collected after analyzing 12 studies shown that when study subject was treated dapagliflozin at a dose of 5mg, 10 mg and placebo, resulted in the infection rate of 5.7%, 4.8% and 0.9% respectively, shown in graph 1. The first six months have shown mild infections with less chances of reoccurrence with long term therapy. There was a higher risk of emergent infections with those having previous history. These diseases reacted to standard oral anti-infection treatment (Johnson et al. 2013).
Urinary tract

The usage of dapagliflozin has reported infections of urinary tract. Patients administered with dapagliflozin of 5mg, 10mg and placebo demonstrated percentage of infection of 5.7%, 4.3% and 3.7% respectively, graph 2. These infections were not acute and reported in response to anti-diabetic therapy followed by oral medication (Johnsson et al. 2013).

Hypoglycemia

Monotherapy of dapagliflozin nor therapy in combination with metformin linked with hypoglycemia. When medication of dapagliflozin pursued along with hypoglycemic agents (insulin and SUs), it increases the risk factor for hypoglycemia. It is recommended that at the beginning of therapy, hypoglycemic risks can be minimized by reducing the dose of other agents during dapagliflozin medication (Langkilde et al. 2013; Zhang 2014).

Dehydration

Dapagliflozin based therapy do not reported severe effects of dehydration and considered as uncommon effects (Brooks et al. 2009).

Conclusion

Dapagliflozin-drug indicated for manifesting hyperglycaemia which is a sodium-glucose cotransporter 2 inhibitor. It helps to control glycaemic index by hindering glucose resorption in proximal tubule of the nephron, when integrated with dietary improvements and exercises. It has decreased the rate of hospitalization due to heart dysfunction in diabetic patients suffering from heart disorders. The studies have opened the doors for the new line of treatment, using this drug. The need of an hour is to search possibilities for the effective pharmaceutical that can address this dual epidemic, and specifically decreases the rate heart failures and positive effect on patients with chronic kidney disease.

References


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