A Review on Synthesis, Characterization, and Pharmacological Evaluation of Second-Line Antidiabetic Drugs

By

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy

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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The thesis titled "A Review on Synthesis, Characterization, and Pharmacological Evaluation of Second-Line Antidiabetic Drugs" submitted by Mafuza Islam (19146080), of Spring, 2023 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

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Ethics Statement

The study involved no animal or human trials.

Abstract

Diabetes Mellitus (DM) is a metabolic disorder that is spreading at an exponential rate and burdening healthcare systems everywhere. This review's main focus is on an overview of DM and the current and new pharmacological treatments for treating type 2 diabetes. Even though conventional drugs like insulin, sulfonylureas, and metformin, are still widely used; novel drugs that target different blood glucose-lowering pathways are now available. In this review, the effectiveness and safety profiles of several different second-line anti-diabetic drugs, along with different novel synthetic routes are discussed. It is challenging to select the most efficient synthesis method from a large number of studies, but an in-depth evaluation of effective synthesis methods is provided, along with a variety of optimization strategies. We expect that the review article will aid researchers with invaluable, compiled information in second-line anti-diabetic drugs. Further research on the synthesis of more successful anti-diabetic drugs with the potential for fewer side effects and dose-related issues may benefit from this review.

Keywords: diabetes; type 2 diabetes; novel drugs, diabetes management; novel synthetic routes

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List of Acronyms

GLUT4	Glucose Transporter 4
IDF	International Diabetes Federation
DKA	Diabetic Ketoacidosis
IDDM	Insulin-Dependent Diabetes Mellitus
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
PAI-1	Plasminogen activator inhibitor-1

Chapter 1

Introduction

1.1 Objective

Diabetes is a set of metabolic conditions that is affecting a large portion of the global population. A prolonged state of hyperglycemia developed from flaws in the release of insulin and malfunction of insulin is its primary defining feature. It is estimated that by 2030, there will be up to 643 million individuals living with diabetes worldwide. Despite the fact that the number of incidents of diabetes is rising constantly, no alternative successful therapy option has been discovered and employed as effectively as insulin and oral hypoglycemic medications. This current study offers insight regarding the pathophysiological and etiological features of DM as well as the potential therapies for this disease. Additionally, a brief overview of DM and multiple unique synthetic approaches for novel drugs are discussed in the paper. The primary goals of this review include a careful evaluation of previous systematic reviews and providing an up-to-date knowledge about all aspects of diabetes, existing and novel pharmaceutical treatments, along with safety profile, structural activity relationships, and novel synthetic routes.

1.2 Background

Diabetes is defined by high blood glucose levels resulting from either inadequate insulin production or impaired insulin response in cells, and caused by several genetic or environmental factors. The kidneys, eyes, blood vessels, nerves, and heart are all seriously harmed by persistently elevated blood glucose levels. The rate and number of diabetic incidences have progressively increased throughout the past several decades.. The International Diabetes Federation (IDF) has been releasing data on diabetes prevalence at the

global, regional, and country scale from 2000. According to Ramani et al. (2022), “285 million people had diabetes in 2009, followed by 366 million in 2011, 382 million in 2013, 415 million in 2015, and 425 million in 2017 and 463 million in 2019 worldwide”. The IDF estimates that “643 million people will have diabetes by 2030, and 700 million by 2045” (Ramani et al., 2022). There are 537 million people worldwide who have diabetes now or one in ten persons. 1 in 5 deaths in 2021 were caused by diabetes, which resulted in a total of 6.7 million deaths (Maliwal et al., 2022). Over 75% of diabetic patients live in countries with low to middle income(Adler et al., 2021). Incidence is greater in urban regions (10.8%) than in rural areas (7.2%), and prevalence is higher in high-income nations (10.4%) than in low-income countries (4.0%). One in two diabetic individuals (50.1%) has no idea about their condition (Ramani et al., 2022). The dysfunction or destruction of pancreatic β-cells is the cause of diabetes. The function of β-cells may be compromised or destroyed entirely due to a variety of circumstances, such as autoimmune disease, insulin resistance, and genetic inheritance (Smyth, 2020). The maintenance or improvement of glucose tolerance is possible through choosing the right therapy by distinguishing diabetes types based on β-cell dysfunction andinadequate β-cell mass or damage of β-cell.

1.3 Epidemiology

Diabetes Mellitus affects 1 in 11 adults worldwide (with 90%-95% of cases of T2DM) *(Sapra, 2022)*. Beginning in early childhood, T1DM gradually increases until reaching its highest stage between the ages of 4 and 6 and once again between the ages of 10 and 14 (Felner et al., 2005). About 2.3 out of 1,000 individuals under the age of 20 have it. The incidence of childhood T1DM does not appear to be affected by gender, despite the fact that most autoimmune disorders are more common in women. Certain groups, such as European males (over 13 years old), may have a higher prevalence of T1DM than others. In

comparison, men (3:2) are more at risk than women to acquire T1DM (Gale & Gillespie, 2001).T1DM is becoming more common worldwide. Rates of diabetic patients are rising by 2% to 5% yearly across Europe, Australia, and the Middle East *(Sapra, 2022)*. It is reported that 10% to 20% of cases of newly discovered pediatric T1D patients have a first-degree family member who is also suffering from it. Until the age of 20, individuals who have an affected brother or sister, or parent are at an increased risk of 3%–7% of developing diabetes (Tuomilehto, 2013).

Although the beginning of T2DM normally occurs in the later years of life, obesity has increased the prevalence of T2DM among younger groups. T2DM prevalence in the US overall population is at 9%, while it is approximately 25% in people over 65*(Sapra, 2022)*. "A global incidence rate of 6059 cases per 100,000 people was reported for T2DM in 2017, affecting about 462 million people worldwide, or 6.28% of the overall population (4.4% of people aged 15 to 49, 15% of people aged 50 to 69, and 22% of people over 70)" (Khan et al., 2019). Diabetes is the ninth most significant contributor to death and about 1 million people die annually because of this. Throughout the world and especially in industrialized countries like Western Europe, the prevalence of this disease is increasing rapidly. The same percentage of men and women suffer from this disorder, and the severity peaked at the age of 55–59 years. By 2030, the worldwide rate of T2DM is anticipated to reach 7079 cases per 100,000 people, demonstrating a steady increase in every region in the globe (Khan et al., 2019). Preventive medical actions as well as public health initiatives are required immediately.

1.4 Pathophysiology

Glucose is constantly needed by the brain for proper functioning to take place. The pancreatic beta cells begin to release insulin as blood glucose levels rise. Insulin lowers the elevated blood glucose level, therefore, helping in the conversion of food directly into energy, which is necessary for the brain. How well the body is able to create and utilize insulin affects the development of diabetes mellitus (DM).An imbalance in the metabolism of glucose and its influence on different metabolic pathways may lead to DM.A complete absence of insulin is a defining feature of T1DM. The body's peripheral tissues become resistant to insulin's effects in people with T2DM. In T1DM, lack of insulin causes uncontrolled gluconeogenesis and high glucose levels. The glucose transporter 4 (GLUT4), carried out insulin-regulated absorption of glucose into the adipose and muscle cells. As insulin facilitates GLUT4's absorption of glucose into the cells, in the absence of insulin GLUT4 also lacks the capacity to absorb blood glucose by adipocytes and muscle cells. As a result, elevated levels of blood glucose cannot be eliminated from the body. The peripheral muscle and fat tissues are starved for glucose despite the blood's extremely high levels of glucose. Moreover, insulin has a major role in regulating glucagon release from the pancreatic alpha cells and unopposed glucagon secretion decreases the synthesis of glycogen. This stimulates the processes of gluconeogenesis, glycogenolysis, and lipolysis. Adipocytes or fat cells release more fatty acids as a result of enhanced lipolysis brought on by inadequate insulin. Increased fatty acids are then partially absorbed by the liver and integrated into lipoproteins. This frequent anomaly in insulin-resistant diabetes might lead to a rise in VLDL production. Very-low-density lipoprotein production is a risk factor for heart diseases (Moini, 2019). Without insulin, ketone bodies that are generated as a result of excessive lipolysis cannot be suppressed. Ketone levels can become dangerously high, leading to a disease known as ketoacidosis. The sole available therapy is injecting the body with exogenous

insulin. Unfortunately, increased glucose and cholesterol levels harm tissues and eventually result in medical consequences even with the greatest management measures. Despite having high levels of insulin, T2DM is marked by insulin resistance, which leads the body to function just like it lacks the hormone. Although this kind of diabetes resembles type 1 in many respects, it varies from type 1 by the fact that the liver may still be able to cause glycogen synthesis and that the presence of insulin controls lipolysis. Plasma lipoprotein levels are often high, frequently as a result of poor diet and obesity.

1.5 Diabetes Complications

Diabetes mellitus is referred to as the "mother of all diseases" because it can lead to various additional diseases. Diabetes complications are a significant source of disability, lowered quality of life, and mortality. Consistent exposure of hyperglycemia can severely damage the blood vessels of the body. The blood cannot reach the necessary body parts if the blood vessels fail to function properly. Due to this, the nerve cannot function properly and certain parts of the body will become numb. The risk for complications increases with the increased HbA1c level. Glycated hemoglobin is known as HbA1c. This forms when glucose attaches to blood cells and accumulates in the circulation. A blood test is used to measure it, and the results display the past 3-month period's average blood glucose levels. An individual with a high HbA1c has too much blood sugar which increases the risk of complications. The risk rises even with a slightly high HbA1c. Problems associated with diabetes can affect different body parts and manifest differently in different persons. Diabetes can lead to two major types of complications (EmmaHook, n.d.-b):

I. Acute complications, can occur at any time, which include hypoglycemia, hyperglycemia, hyperosmolar hyperglycemic state (HHS), and diabetic ketoacidosis (DKA).

II. Chronic complications, which are significant and develop over time can be microvascular issues that's include diabetic retinopathy, nephropathy, neuropathy, and erectile dysfunction, or macrovascular issues including brain attack (stroke), coronary artery disease, peripheral arterial disease, and increased risk of infection.

1.5.1 Hypoglycemia

Hypoglycemia is characterized as a state where blood glucose level is low, putting patients at risk for potential injury. Low blood glucose or "hypoglycemia is defined for many people as having a level of blood sugar below 70 mg/dL, or 3.9 mmol/L" (*Hypoglycemia - Symptoms and Causes - Mayo Clinic*, 2022). People with T1DM frequently suffer from severe hypoglycemia, with annual incidence rates ranging from 3.3% to 13.5% (Nakhleh & Shehadeh, 2021). Despite having a lower chance of developing serious symptoms of hypoglycemia than those with T1DM, people with T2DM are frequently more at risk if they use insulin, sulfonylureas and meglitinides. Glucose lowering drugs when combined with insulin or insulin secretagogues, including metformin, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors, and thiazolidinediones have increased risk of hypoglycemia.

The hypoglycemic symptoms include increased heart rate, numbness, sweating, and anxiousness, can be caused by the hormone epinephrine, which is released as a result of hypoglyemia. Low blood glucose results in insufficient glucose delivery to the brain, and brain fails to function properly, which may lead to hypoglycemic shock. One may experience impaired vision, difficulty focusing, slurred speech, difficulty thinking, numbness, and sleepiness due to hypoglycemia. Seizures, coma, and even in some cases death may result from prolonged low blood glucose levels that starve the brain of glucose.

1.5.2 Hyperglycemia

Diabetes patients experience high blood sugar, often known as hyperglycemia. Hyperglycemia in diabetics may result from a number of different factors for example; stress, food habit, diseases, physical inactivity, and diabetes-unrelated drugs. Hyperglycemia can also result from skipping drug dosages, not taking sufficient doses of insulin, or using other blood sugar-lowering drugs (*Hyperglycemia in Diabetes - Symptoms & Causes - Mayo Clinic*, 2022). Without proper medication, severe hyperglycemia may result and cause potentially fatal medical conditions such as diabetic coma. Other medical conditions that impact the nerves, heart, vision, and renal function can arise from even slight hyperglycemia.

Blood glucose levels above 180 to 200 mg/dL, or 10 to 11.1 mmol/L, usually show symptoms of hyperglycemia. The signs and symptoms of hyperglycemia manifest gradually and worsen. More severe symptoms might develop if the blood glucose levels remain higher for a longer period. Individuals with T2DM experience high glucose levels for longer periods but they may not exhibit any symptoms. Early signs of hyperglycemia, such as frequent urination, blurred vision, increased thirst, weakness or extreme exhaustion, can help in identifying and treating it quickly.

1.5.3 Diabetic ketoacidosis (DKA)

A potentially fatal side effect of diabetes is diabetic ketoacidosis (DKA). DKA is more common in patients with T1DM but T2DM patients can also experience it. DKA results when the body doesn't produce enough insulin, and blood glucose cannot enter cells for cellular energy use (Diabetic Ketoacidosis, 2021). Therefore, by the metabolic process known as ketogenesis, the liver transforms fat into fatty acids which are also referred to as ketones. The

ketones, which are created by ketogenesis, offer the body a different supply of energy because the body cannot produce the necessary energy from glucose. Excessively high ketone production can cause the body to accumulate them in harmful amounts. DKA is caused by extremely high blood sugar (usually above 250 mg/dL), along with low insulin levels. DKA symptoms frequently come unexpectedly, often within a few hours. (Diabetic Ketoacidosis - Symptoms and Causes - Mayo Clinic, 2022). These signs and symptoms may be the initial indication of diabetes in some people. A variety of symptoms may occur such as increased blood sugar, high ketone levels in urine, extreme thirst, frequent urination, shortness of breath, stomach pain, exhaustion, feeling the need to vomit and do so, and weakness.

1.5.4 Hyperosmolar Hyperglycemic State (HHS)

When blood sugar levels are extremely high (Usually higher than 600 mg/dL or 33 mmol/L) for a prolonged period, it results in a life-threatening hyperosmolar hyperglycemic condition (HHS). Mainly Type 2 diabetes patients suffer from this condition. Hyperosmolar hyperglycemic state (HHS) and diabetes-related ketoacidosis (DKA) both have the potentially fatal effects of high blood sugar, but they are two distinct disease states (Professional, n.d.). Although HHS also involves low insulin levels, an individual often still produces enough insulin to stop ketone formation. The key difference between DKA and HHS is that hyperglycemia and ketoacidosis are related to DKA, whereas extreme hyperglycemia, hyperosmolarity, and dehydration are the key features of hyperosmolar hyperglycemia state. As many as 30% of DKA patients may also exhibit some HHS symptoms.

The symptoms of the two complications are similar and include altered mental status, frequent urination, and severe thirst. Too much blood glucose levels for extended period

results in highly concentrated blood (high osmolality) than normal, which causes severe dehydration, and drowsiness. Additionally, a high blood sugar level is typically a symptom of an underlying disease like an infection. HHS may result in serious complications like coma, organ failure, and seizures if it is not treated timely. In 10% to 20% of cases, these complications might result in deaths.

1.5.5 Microvascular

The most prevalent microvascular diabetic complication may be **diabetic retinopathy**. “In the United States, it accounts for about ten thousand new blind cases annually.” (Fowler, 2008). The chance of getting diabetic retinopathy is determined by the duration of hyperglycemia and its severity. The length and intensity of hyperglycemia determine the probability of getting different microvascular effects. The beginning stages of diabetic retinopathy often have no visible signs. However, some patients may develop visual impairments, which can make it difficult for them to read or see things in the distance. Such types of changes might occur and then disappear. During the more advanced stages of the illness, the blood vessels in the retina start to leak on the vitreous layer. Other harmful eye disorders such as diabetic macular edema (DME), neovascular glaucoma, and retinal detachment can develop as a result of diabetic retinopathy. DME is caused by fluid leakage into the macula, a region of the retina necessary for clear, central vision. The result is a hazy vision. The small blood vessels that provide oxygen and nutrients to the retina can get blocked gradually if there is a high level of blood glucose, eventually eliminating the retina's flow of blood. In response, the eyes try to develop additional blood vessels for proper functioning. Due to improper development, the resulting newly formed blood vessels are prone to leakage. The drainage of fluid from the eye may be obstructed by abnormal blood vessels that have grown from the retina. The result is a particular type of glaucoma, which

can impair eyesight and even cause loss of vision. Cellular damage brought on by hyperglycemia, may also be significantly influenced by oxidative stress. A high blood glucose level can promote the development of reactive oxygen species and free radicals.

Globally, End-stage renal disease (ESRD) and chronic kidney disease (CKD) is mostly brought on by **diabetic nephropathy**. Usually, it progresses gradually over the years and is found to be the most common reason for renal failure in the US. Proteinuria over 500 mg in 24 hours in a diabetic patient is what characterizes it, but lesser levels of proteinuria, or microalbuminuria, come prior to this (Fowler, 2008). Albumin excretion of 30 to 299 mg per 24 hours is referred to as microalbuminuria. Without treatment, microalbuminuric diabetic individuals often proceed to proteinuria and explicit diabetic nephropathy. Massive protein loss in the urine as a result of glomeruli destruction can result in low serum albumin levels and generalized body edema, or nephrotic syndrome. When the patients are initially diagnosed with type 2 diabetes, more than 7% of them might already suffering from microalbuminuria. T1DM (3.9% of cases), and T2DM (30%-50% of cases), contribute to CKD and ultimately ESRD (Vaidya, 2022). It is crucial to remember that diseases including urinary tract infections, exertion, and hematuria can all result in erroneously increased urine protein levels.As for all diabetes complications; prevention is the first line of defense for diabetic nephropathy. The likelihood of getting diabetic nephropathy and glucose control are significantly correlated just like there are with other microvascular complications associated with diabetes. Patients need to be provided with medications that reduce glucose concentrations in order to control diabetic nephropathy. The probability of progression of macroalbuminuria has been demonstrated to be reduced by as much as 60–70% by both ACE inhibitors and ARBs.

Diabetic neuropathy results when there is a peripheral nerve dysfunction in diabetic patients. Likelihood of getting diabetic neuropathy may be proportionally correlated with severity and duration of high blood glucose levels, similar to other microvascular problems, and certain people may be genetically predisposed to such issues. Although the precise nature of the damage caused by hyperglycemia to the peripheral nerves is unknown, it is most likely associated with polyol buildup, and oxidative stress.

Neurological dysfunction may be brought on by diabetic autonomic neuropathy and can occur in most organ systems. Symptoms of neurological dysfunction include gastroparesis, erectile dysfunction (ED), bladder problems, a rapid heartbeat, ischemia, and potentially cardiac arrest can occur. Silent myocardial ischemia and mortality risk are both elevated by cardiovascular autonomic dysfunction. Although various medications are available for managing its symptoms, diabetic neuropathy does not have particular treatments. The main objective of treatment is to enhance glycemic control in order to manage symptoms and stop neuropathy from getting worse. According to several researches, managing hyperglycemia and avoiding glycemic fluctuations may help with peripheral neuropathy symptoms. Painful symptoms can be treated with amitriptyline, citalopram, pregabalin, paroxetine, carbamazepine, duloxetine, topiramate, tramadol, gabapentin, and oxycodone. Some of these drugs' negative effects may make it difficult to treat certain conditions, and no single therapy is always beneficial. The affected organ system is the focus of treatment for autonomic neuropathy; however glycemic control is also optimized.

Gastroparesis risk is higher in people with diabetes. The stomach's nerves become injured and stop functioning properly when a person has gastroparesis. The digestive tract requires an

extended time to eliminate its contents, thus it becomes challenging in controlling the level of blood glucose. Changing diet might be helpful sometimes (Diabetes Complications, 2007).

Erectile dysfunction has become the most prevalent form of sexual issue among males. Men who have diabetes are three times more likely to experience erection-related problems. There may be a number of causes for this, including restricted blood flow, nerve injury (neuropathy), and damaged blood vessels brought on by prolonged high sugar levels. Incorporating a healthy lifestyle like stopping smoking, engaging in regular exercise, and managing stress may be beneficial in treating sexual dysfunction in some men.

Infections are also more likely to affect diabetic patients than individuals who are healthy. There is insufficient data to establish a definitive connection between diabetes and an elevated risk of infection. However, several specific infections mostly affect diabetic patients. Patients with diabetes have altered immunity in a variety of ways. There is proof that improving glycemic control enhances immune performance. Excessive blood glucose levels might compromise the body's immune system defenses. Persistent increased glucose levels may result in peripheral injury to nerves and may damage the blood vessels. As a result, there will be reduced blood supply to various body areas due to improper function of the blood vessels, and this will eventually increase the probability of various infections. Usually, high blood glucose causes tissues throughout the body to have higher sugar levels. As a result, bacteria can propagate more easily and infections can spread more quickly. The feet, bladder, gums, uterus, and skin are common infection sites (Diabetes Complications, 2007). Fungal cystitis, rhino-cerebral mucormycosis, urinary tract infections, and gingivitis are the common infections patients with diabetes experience. In addition, elevated prevalence

of T2DM was reported among people with chronic viral hepatitis C infection as well as fibrosis progression.

1.5.6 Macrovascular

The primary pathogenic mechanism in macrovascular disease is the process of atherosclerosis, which causes narrowing of the artery walls all over the body. The underlying reasons for atherosclerosis are assumed to be long-term inflammatory processes and damage to the artery walls in the peripheral or coronary vascular systems. LDL particle-derived oxidized lipids build up in the endotheliallining of the arteries as a result of endothelial cell damage and inflammatory conditions.These particles then subject to oxidation in response to angiotensin II. Due to this inflammatory condition, monocytes start diffusing into the artery wall and become macrophages, this then result in the accumulation of oxidized-lipids and transform into foam cells. After the foam cells have been produced, macrophages become mature and draw T-lymphocytes. These lymphocytes, therefore, promote the build-up of collagen and contribute to muscle growth in the artery walls. This ultimately leads to development of an atherosclerotic lesion that is lipid-rich. Myocardial infarction may result from the rupture of this lesion.

Lots of significant reports suggest that T2DM increases platelet adhesion and hypercoagulability in addition to atheroma development. Platelet aggregation may be aided by decreased production of nitric oxide, increased production of free radicals, and altered calcium control. Diabetes patients may also have impaired fibrinolysis due to elevated levels of endothelial PAI-1. In T2DM the danger of arterial occlusion also, coronary artery disease is likely further raised by the interaction of increased coagulability and impaired fibrinolysis.

Cardiovascular disease (CVD) is more likely to develop among people with diabetes. Diabetes and atherosclerotic plaque formation have a strong correlation. The main cause of sudden death among diabetic patients is cardiovascular disease. Compared to the average persons, diabetic patients have 2 to 6 times increased chance of having cardiovascular diseases. Numerous investigations have linked diabetes with coronary heart disease as one of the macrovascular complications related to diabetes.

Several metabolic syndromes may leads to T2DM, among those obesity, high blood pressure, hyperlipidemia, and increasing coagulability are highly linked. These additional factors may also encourage cardiovascular disease. T2DM is a separate source of danger for the development of ischemia, stroke, and even death. Women may be more susceptible to coronary heart disease than males among those with T2DM patients. The likelihood of coronary cardiac incidence is also predicted by the presence of microvascular conditions. Diabetic patients are more susceptible to dementia linked to stroke, stroke-related recurrence, and also stroke-related mortality. CVD affects T1DM patients more frequently than other patients. Studies have revealed that compared to the overall population, these patients have increased incidence of death from coronary artery disease. Women die from ischemic heart disease at a higher rate than male in people over the age of 40.

Chapter 2

Methodology

In order to gather information for this study, I reviewed articles from different well-known sources, including PubMed, ScienceDirect, European Journal of Medicinal Chemistry Reports, EMBASE, ResearchGate, Web of Science, and other Open-Access Journals. Several websites such as Centers for Disease Control and Prevention, American Diabetes Association, DiabetesJournals.org, and mayo clinic journals and publications are also used to obtain several data and structures. A number of keywords such as diabetes mellitus (DM); type 2 diabetes mellitus (T2DM); novel drugs, diabetes and its management, the prevalence of diabetes mellitus, or other equivalents keywords, were used to conduct the search.

2.1 Type I Diabetes mellitus

"T1DM also referred to as type 1A diabetes mellitus (DM), insulin-dependent diabetes mellitus (IDDM), or juvenile-onset diabetes, accounts for about 5–10% of all diabetes cases" (Banday et al., 2020). This is an autoimmune disease that results from the immune-mediated death of pancreatic beta-cells by the body's own T-cells, leading to a lack of insulin, and eventually causing hyperglycemia. Although there still has lack of information about the pathophysiology of this autoimmune response, it is currently determined that environmental as well as inherited factors are important.

This inflammatory condition that affects only pancreatic β-cells often first appears in babies and young children (juvenile onset), and it may gradually appear in adults (late onset). Adolescents and children are more susceptible to sudden destruction of pancreatic cells and eventual malfunction, as a result diabetic ketoacidosis (DKA) may occur, that is generally

thought to be an early indicator of diabetes. Some people might have very mild disease development that is associated with a slight rise in fasting plasma glucose levels; this can progress to a serious hyperglycemic condition when there are additional physiological stressors present, such as the development of other diseases or serious infections. There can be other scenarios like, when the beta cells are able to produce just the right quantity of insulin for the prevention of ketoacidosis for a long time. But with the development of gradual insulin deficit, severe hyperglycemia, and eventual ketoacidosis occurs. Although there are many variables of this kind of diabetes, people who suffer from it develop an absence of insulin in the early stages, halfway through, or the latter stages of life, making them dependent on insulin administration in order to live.

Several immunological markers, including autoantibodies, are particularly prominent in T1DM and that leads to the disease.“The autoantibodies include glutamic acid decarboxylase autoantibodies (GADAs) such as GAD65, islet cell autoantibodies (ICAs) to β-cell cytoplasmic proteins such as autoantibodies to islet cell antigen 512 (ICA512), autoantibodies to the tyrosine phosphatases, IA-2 and IA-2α, insulin autoantibodies (IAAs), and autoantibodies to islet-specific zinc transporter isoform 8 (ZnT8)” (Banday et al., 2020). For the clinical diagnosis of this disorder, at least one of these autoantibodies can be used; however, multiple immunological markers have typically been found in 85–90% of individuals with sudden T1DM. The prevalence of the IAAs, which are significant immunological indicators, declines with increasing age of diabetes onset in newborns and young children. A crucial sign that T1DM is developing in such individuals who have never received insulin treatment is that IAAs are present. During diagnosis, approximately 70% of all children and newborns have IAAs. In some circumstances, especially in people with late-onset of diabetes, the beta cells destruction happens very slowly and eventually the disease

frequently appears as T2DM. When this occurs, the autoantibodies allow for an accurate diagnosis of the disease as T1DM instead of the more prevalent T2DM. “Diabetes of this type is commonly referred to as "slowly progressing Insulin-Dependent Diabetes"; approximately accounts for 2-12% of all the cases of adult-onset autoimmune diabetes.

2.2 Type II Diabetes mellitus

“T2DM often referred to as non-insulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes, accounts for 90–95% of all cases of diabetes” (Banday et al., 2020). The main insulin-related problems that characterize T2DM are insulin resistance and beta cell dysfunction. Changes in several cellular processes trigger insulin resistance, thereby decreasing the responsiveness of cells in peripheral tissues, mainly the liver, muscle, and adipose or fat tissues. This reduced insulin sensitivity leads to hyperactive beta cells in the initial phases of the disorder, which result in increased production of insulin in order to maintain the normoglycemic condition. Thus, hyperinsulinemia, or elevated amounts of insulin in the blood, minimizes hyperglycemia risk. But over time, the beta cells' higher insulin secretion becomes insufficient to compensate for the lowering of insulin sensitivity of cells. Furthermore, beta cell activity gradually decreases, and this malfunction ultimately contributes to insulin insufficiency. Therefore, hyperglycemia develops since normoglycemia can no longer be sustained. Even though insulin levels are reduced, in most situations the insulin that is secreted is still enough to stop DKA from happening. However, in situations of high stress, for example, those brought through infections or other associated physiological disorders; DKA might occur.T2DM develops quite gradually and asymptomatically, alongside mild to moderate hyperglycemia progressing for a long time. Because of this, it often stays undiagnosed unless the condition has progressed into the advanced stage and the

typical symptoms of extreme hyperglycemia start to appear, which include losing weight, impaired vision, growth disorders, polydipsia, and excessive urine production.

The development of T2DM and obesity are directly related.. Obesity or increased body fat content increases insulin resistance by changing the responsiveness of certain tissues to insulin, and also causes hyperglycemia. Adipose tissue or body fat can secrete a number of hormones and cytokines which can cause chronic inflammation and insulin resistance. Abdominal body fat or visceral body fat is mostly related to this disease. “Adiponectin is peptides produced by adipocytes haveanti-inflammatory and insulin-sensitizing properties, whereas leptin is a hormone with an orexigenic activity that manages energy balance by decreasing appetite” (Artasensi et al., 2020).Inadequate levels of adiponectin anda leptin-resistant condition are more frequently found in obese people with a metabolic disorder.Insulin resistance caused by this metabolic disorder typically affects adipose, muscle, and hepatic tissues. T2DM patient tend to have different risk factors for cardiovascular disease due hypertension and metabolic issues. Metabolic abnormalities result in increasing the production and distribution of fatty free acids (FFA), increased amounts of triglycerides (LDLs) and decreased levels of high-density lipoproteins (HDLs). All these cases contribute to the insulin-resistant state.

The root cause of T2DM is complicated and incorporates both identified and unidentified factors. It may be defined as a combination of hereditary and major environmental triggers. More commonly, T2DM has been associated with increased age, becoming overweight or obese, genetic susceptibility to the disease, an unhealthy lifestyle, physical inactivity, and medical conditions such as hypertension and hyperlipidemia. Unlike T1DM, in T2DM there

is no connection between the disease and genes that govern the autoimmunity. Therefore, in this type, no immune-mediated pancreatic beta cell death occurs.

2.3 Gestational diabetes mellitus

Gestational diabetes mellitus (GDM) is a type of diabetes that is first observed in a woman during pregnancy, and it is related to any level of glucose intolerance. GDM may be divided into two categories: Diet-controlled GDM referred to as A1GDM, responds to dietary treatment and can be successfully managed with no need for medications. Contrarily, A2GDM is characterized as diabetes managed with medications to ensure adequate glycemic regulation. In the United States of America, 2 to 10% of pregnancies are affected by gestational diabetes. Over the course of 10 to 20 years following delivery, women who have GDM exhibit a high probability of getting T2DM.

The two primary contributors to GDM are believed to be the considerable increase in insulin resistance brought on by the secretion of placenta hormones and a malfunction or decreased sensitivity of the beta cells to blood glucose levels. A hormone known as human placental lactogen is secreted by the placenta throughout pregnancy. This hormone can trigger considerable metabolic changes which assist in maintaining the embryonic nutrition state and also alter and change the insulin receptors. “Growth hormone, as well as prolactin, corticotropin-releasing hormone, and progesterone, are additional hormones associated with the progression of GDM and promote insulin resistance and hyperglycemia during pregnancy” (Rodriguez, 2022).

Some clinical risk factors for gestational diabetes have been documented. These clinical indicators include a rise in body weight (a BMI over 25), first-degree relative suffering from

diabetes, a decrease in physical activity, metabolic comorbidities such as hypertension, low HDL, cholesterol greater than 250, past experience with GDM or a neonate with macrosomia, PCOS, abnormal tolerance to oral glucose, cardiovascular disease history from the past, any substantial indicator of insulin resistance (acanthosis nigricans), and hemoglobin A1C levels higher than 5.7.Maternal excessive glucose levels can cross the placenta and cause fetal hyperglycemia.

2.4 Other types of diabetes

Other types of diabetes are associated with a variety of medical conditions, which include several pathologies and many different diseases. These conditions represent lesser percentages of the total diabetic prevalence scenarios. Types of diabetes brought on by other factors include endocrinopathies, exocrine pancreas diseases, pancreatitis, neonatal diabetes, monogenic impairments in beta cell performance, maturity-onset diabetes of the young (MODY), genetic abnormalities in insulin functions, ketosis-prone diabetes mellitus, and chemical-induced diabetes brought on by glucocorticoid use, HIV/AIDS treatment, or organ transplantation (Artasensi et al., 2020).Pancreatic disorders involves cystic fibrosis, pancreatic neoplasia (adenocarcinoma and glucagonoma), trauma (pancreatectomy), chronic pancreatitis, and pancreas cancer (Banday et al., 2020).

2.5 Risk factors of Diabetes Mellitus

- T1DM has a direct significant hereditary component where immune system-mediated destruction of pancreatic beta cells occurs; hence it is an auto-immune disorder.
- Since the genetic makeup of an individual is a major determinant, genetics have a vital impact on the progression of T2DM. By far the prevalent types of T2DM are polygenetic, meaning that numerous genes have undergone mutations, and there have been over 20 variant

genes identified as probable causes of T2DM. Monogenic diabetes, on the other hand, is a rare subtype of diabetes caused by a single gene mutation. It is essential to distinguish it from T1DM, thus a clear diagnosis is required in order to receive the appropriate care.

- Environment-related factors also contribute to the progression of T2DM, associated with lifestyle, gut flora, and mechanisms causing microbiome intestinal dysbiosis. “Anything that changes the microbiota's makeup has the ability to affect the way the intestinal barrier functions and to trigger signaling and metabolic pathways linked to insulin resistance”(Artasensi et al., 2020).
- Having a body mass index (BMI) greater than or equal to 30 kg/m2 is the standard definition of obesity. One of the main diabetes risk factors is an increase in fat tissue. Also, if the body fat is most concentrated in the visceral region, there is clearly an association between the amount of fat and the number of insulin-resistance cells. Obesity affects over 80% of T2DM patients, but it is not a requirement for the disease.
- T2DM risk may rise with an inactive lifestyle because physical activity aids in controlling body weight and blood glucose levels.
- Diabetes risk is increased by diseases like hypertension (high blood pressure) and high triglyceride levels because they are frequently linked to insulin resistance.
- Women who suffer fromGDMduring pregnancy are athigher potential for the progression T2DM at some point in life.
- T2DM was typically diagnosed in adults and seniors until two decades ago. This was a result of the altered body composition (more fat tissues), a decreased capacity to burn sugar, and the gradual decline in physical activity, which all combined to develop insulin resistance. The usual age of onset of diabetes is declining, and diabetes is now present in children, due to the significant rise in obesity incidence.

- Prediabetes is characterized by elevated blood glucose levels that are not yet excessively high to be classified as T2DM. Most of the patients are not aware that they have it. Prediabetes is identified by a blood glucose level of 100 to 125 mg/dL (5.6 to 6.9 mmol/L). A patient with prediabetes has a higher probability of getting T2DM, cardiovascular problems, and stroke. With the help of lifestyle modification, prediabetes can be treated by taking preventative measures.

Chapter 3

Pharmacological Therapy

Although currently, no specific cure for the disease is available, it can be treated and managed through different drugs. These pharmacological therapies are necessary to maintain normoglycemia and to prevent or even delay the onset of diabetes. Clinically, several anti-diabetic medications function in a number of different pathways. This review paper mainly focuses on the second-line therapies available for diabetes.

3.1 Insulin

Insulin is the pancreatic peptide hormone that is essential for controlling the body's metabolism of glucose. “The β-cells in the Islets of Langerhans secrete the hormone, and it is a 51-residue anabolic protein” (Weiss, 2014). Two chains make up the mature hormone, chain A and chain B are linked by disulfide bonds, and it is the post-translational byproduct of a single-chain precursor known as proinsulin. Through the two primary complementary actions, insulin regulates glucose homeostasis. Insulin facilitates the absorption of glucose from the bloodstream to the cell and the inhibition of hepatic gluconeogenesis. Insulin is categorized based on the duration that it remains active inside the body. During mealtimes, rapid- or short-acting insulin helps lower blood glucose levels, while intermediate (NPH) or long-acting (Basal) insulin may help in controlling the overall normal blood glucose levels of the body. Mixed insulin is made up of intermediate-acting insulin along with either rapid-acting or short-acting insulin that has been pre-mixed (Department of Health & Human Services, n.d.).

3.1.1 History of Development

In the history of medicine, notably in the management of diabetes, the discovery and subsequent development of insulin served as a major turning point. It has been nearly 100 years since the discovery of insulin (Karas et al., 2021). In the history of medicine, notably in the management of diabetes, the discovery and subsequent development of insulin served as a major turning point. In the past ancient peoples were aware of the signs of diabetes, like extreme thirst along with frequent urination. But until the 19th century, the reason behind the disease and how to cure it was unknown. Paul Langerhans, a German physician, in 1869 found specialized cell clusters in the pancreas that looked to be connected to metabolism. Later, these clusters came to be known as the "islets of Langerhans." Researchers started connecting the pancreas to diabetes in the late part of the 19th century. German scientists Oskar Minkowski and Joseph von Mering established in 1889 that removal of the dog pancreas resulted in the onset of diabetes mellitus. Many researchers contributed substantial discoveries in the early twentieth century to improve their knowledge of insulin's function in diabetes. Schafer initially hypothesized in 1916 that pancreatic islets secreted "insulin," an anti-diabetic hormone. Later on, Barron observed in 1920 that pancreatic duct ligation with exocrine pancreas destruction only caused DM if the islets were also removed. The invention of insulin had its breakthrough in 1921 when Frederick Banting and Charles Best isolated and effectively extracted insulin from the pancreas of dogs. To improve the insulin extraction procedure, Banting and Best worked with MacCleod and Collip. Then, dogs who had diabetic symptoms were treated with insulin, which significantly reduced their signs and symptoms. Through this research, it was found that this pancreas extract had the surprising capacity to lower blood glucose levels. Worldwide excitement over the insulin discovery led to an increase in the hormone's demand. These pancreatic extracts were successfully used to treat

DM patients by 1923. Insulin's remarkable clinical effectiveness sparked widespread popular support for research into medicine. (Weiss, 2014)

3.1.2 Mechanism of Action

The insulin receptor (IR) is a particular cellular receptor that is activated by insulin that acts as a ligand. The activation of the insulin receptors, which are members of a subfamily of receptor tyrosine kinases, modifies a number of post-receptor signaling processes. In response to insulin stimulation, some membrane transporters enhance the transfer of glucose inside the cells, lowering blood glucose levels. After being transported, the glucose is either used as fuel for metabolism or stored as glycogen. Numerous tissues have been identified that contain the Na + -dependent glucose transporters. These transporters exist in the lumenal side of the cells in the kidney and intestine, and they function in absorbing glucose by regulating the entry of glucose and Na+ into the cell. Na + can be used as a cotransporter for glucose entry into cells because it is traveling down its electrochemical gradient. This means that the Na + / K + -ATPase ion pump, which regulates Na+ ion concentrations within and outside cells, is necessary for the activity of the transporter.

The only transporters that have insulin-responsive isoforms are Na + -independent. The Na + -independent glucose transporters consist of multiple isoforms, making it easier for glucose to flow through the cell membrane. The transporter which is present in greatest concentration in insulin-sensitive tissues is the GLUT4. The cells of skeletal muscle, cardiac muscle, and adipose tissue have GLUT4, and can increase the amount of glucose they absorb through the GLUT4 isoform and to a limited extent, the GLUT1 isoform, which helps to reduce blood glucose levels. Because of the rapidly occurring phosphorylation of glucose to glucose-6-

phosphate and the resulting conversion into different metabolic products, the intracellular amount of glucose is low.

Amount of transporters in the target cells' cell membrane is increased by insulin, which ultimately improves glucose uptake into the cell. Insulin first acts in adipocytes (white fat cells), then in skeletal and cardiac muscle. To improve glucose uptake, insulin stimulation in these cells releases transporters from intracellular storage areas and moves them to the cell membrane. Insulin promotes the movement of GLUT4 glucose transporters from internal membranes to the cell surface to increase glucose absorption into the target cells. When the insulin stimuli start to fall a decrease in glucose transport is followed by a corresponding decline in the total amount of receptors on the plasma membrane. Hyperglycemia after a meal in Type 2 DM is a result of the decreased ability of insulin to initiate GLUT4 translocation from intracellular reserves after binding to and activating the IR. A reduction in the translocation of glucose transporters from intracellular membranes to the cell surface in muscle cells has been linked to insulin resistance. Also, reduced insulin levels might lessen GLUT4 expression in muscle cells as well as transporter translocation. Through the activation of the enzyme protein kinase B (PKB), insulin facilitates the production of glycogen, which is the stored form of glucose, in muscle and liver cells. Insulin reduces the activity of vital enzymes involved in gluconeogenesis, which is the process of producing glucose. Gluconeogenesis occurs in the liver and insulin prevents the liver from synthesizing glucose. Insulin stimulates the absorption and preservation of triglycerides or triacylglycerols (TAGs), and LDLs in adipocytes while preventing the breakdown of fat stores (lipolysis) in adipose tissue. Triacylglycerols (TAGs) hydrolyze to form their basic compounds, glycerol and free fatty acids (FFAs), during lipolysis.

3.1.3 Structure-Activity Relationship (SAR) of Insulin

The native structure of insulin has its monomeric, dimeric, and hexameric conformations. Insulin's conformational state is caused by its concentration and environmental pH. As the insulin concentration increases, the monomers transform into dimers. Similarly, when zinc is present (10 mM Zn++, pH 6.0) and the insulin concentration appears high; the monomers combine into higher-order conformations that are known as hexamers. Insulin breaks down into its monomeric form as a result of electrostatic attraction and a drop in insulin concentration after the hexamers are released from the beta-cell and flow through the circulation. Therefore, the stored form of insulin is called the hexamer, whereas its active form is the monomer (Fu, 2013).

The monomeric form of insulin is made up of 51 amino acids arranged between the "A" chain with 21 amino acids and a "B" chain with 30 amino acids. Three disulfide bonds contribute to the structure of the monomer, two of which form between the A and B chains (A7-B7, A20-B19), and the other one forms inside the A chain (A6-A11). When the monomers combine to create dimers, the nonpolar amino acid residues are buried. It is already mentioned that the insulin monomers combine to produce dimers at micromolar quantities.

In particular, “the N- and C-terminal segments of the A chain (Gly A1 - Ile A2 -Val A3 -Glu A4 and Tyr A19 -Cys A20 -Asn A21), the central α-helix of the B chain (especially Val B12), and the C-terminal segment of the B chain (GlyB23, Phe B24 -Phe B25 -Tyr B26) have the potential in the primary receptor-binding surface of insulin” (Weiss, 2014). Since they have their proximity to the surface of insulin, all of these residues are capable of interacting with the insulin receptor.

There are multiple significant regions on the A chain to bind receptors. When the amino terminus is N-acetylated, receptor binding is 30% reduced, demonstrating the need of an amino terminus that is unbound and positively charged in order to bind receptors. For the proper placement of the peptide, Gly1 is necessary, removing it shown 15% reduction in effectiveness.

In terms of structure-activity relationships, the B chain, especially the carboxy-terminal domain, is most extensively researched. While deleting HisB5 results in a significant decrease in activity (retaining approximately 15% of the receptor binding activity), deleting the amino terminus, or the B chain's first four residues results in only minor decrease in the binding of receptors (containing about 70% activity). Additionally, the deletion of LeuB6 resulted in a form of mutation with a mutant binding affinity of less than 1%, which makes it essential for binding activity. The maintenance of the disulfide bond between chain A and chain B clearly highlights the significance of CysB7.

The carboxy-terminal domain of the B chain is the region of the chain that has been the subject of the greatest research about structure-activity correlations. When AspB10 is replaced with HisB10, proinsulin is not converted into insulin, which results in a rise in circulating proinsulin. HisB10 is essential for the highest level of insulin action. But surprisingly, compared to "wild type" synthetic insulin, the AspB10 alteration in synthetic insulin exhibits a 500% higher binding affinity. In particular, PheB24 establishes the hydrogen-based bonding that is essential for dimer formation, and PheB25 exhibits various function to make up the dimer, suggesting its importance for the conformation of the native insulin structure. In conclusion, even though many amino acid residues, specifically those in

the N-terminal A chain and the C-terminal B chain, are crucial for the binding of insulin to the insulin receptor (Fu, 2013).

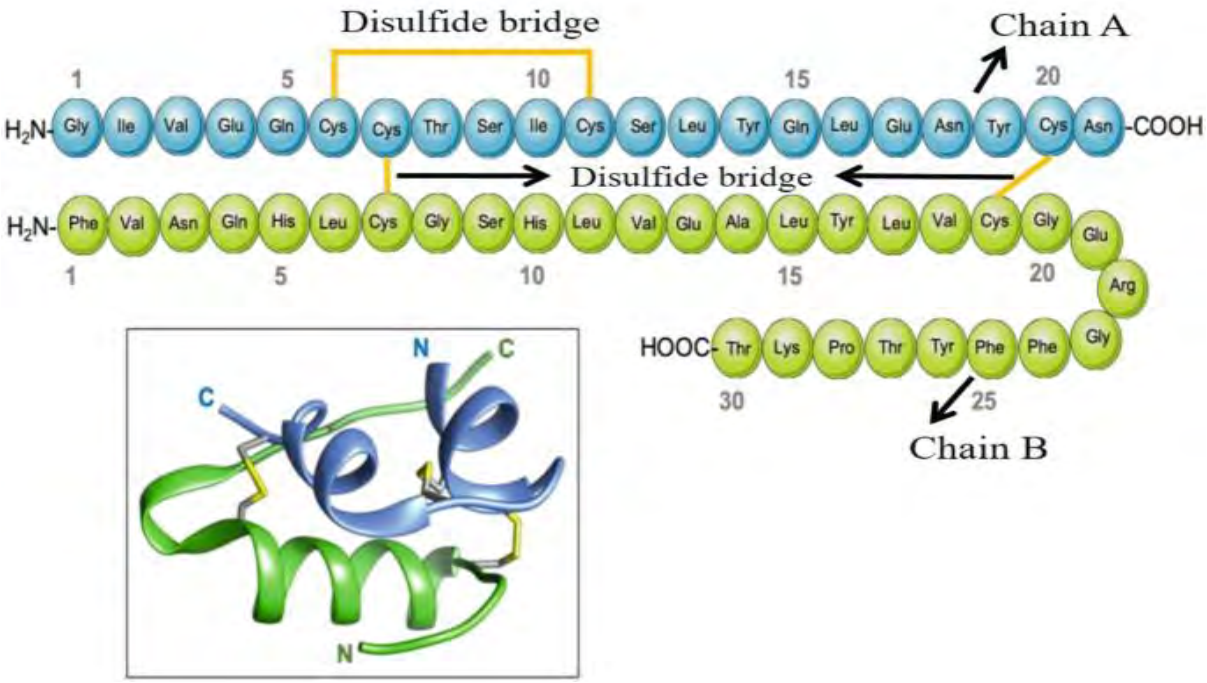


Figure 1: 3D Structure of Insulin

(Prabu et al., 2023), [54]

3.1.4 Chemical Synthesis of Insulin

There have been two distinct eras in the development of insulin therapy throughout the past century. Sixty years after the hormone was discovered, the first stages focused on improved purity with a focus on acquiring the human sequence, and that was subsequently became achievable mostly through rDNA technology. The attempts to find insulin analogs with better pharmacokinetic properties during the past 40 years have mostly involved combining biosynthetic and semi synthetic techniques. After insulin was first discovered over a century ago, insulin therapy has significantly improved, setting the standards for efficacy and safety that any future changes to the structure of the hormone must exceed. It's an exciting era

because synthetic chemistry for insulin has developed to the point where it's challenging to use it in suitable therapies.

Insulin Analogs:

Human insulin analogs have been created and produced through the use of recombinant DNA technology. In order to change the pharmacokinetic characteristics of insulin, which largely impact how well the drug is absorbed from the subcutaneous tissue, analogs are the result of a slight modification of the structure of the insulin molecule. The amino acids are often replaced in the B26–B30 region of the B-chain of the insulin molecule because this portion is not necessary for insulin receptor recognition. As a result, the insulin analogs continue to attach to the insulin receptor and be detected by it. “Insulin aspart, lispro, and glulisine are three rapid-acting insulin analogs, whereas insulin glargine, detemir, and degludec are three long-acting insulin analogs” (Donnor, 2023). NPH (neutral protamine hagedorn) is a kind of intermediate-acting. When given once or twice a day, reduces glucose level within 1 to 2 hours. Detemir and degludec insulin is produced by deleting the B30 of the B chain and putting 14-C and 16-C fatty acids respectively, glargine can be produced by adding 2 arginines at the B30 position, and substituting asparagines (Asn) with glycine at the A15 position of the A chain. Rapid-acting insulins are produced by simply replacing different amino acids. Proline at position B28 near the COOH terminal was replaced with Asp in aspart, B28-29 was reversed in lispro. For glulisine, amino acid asparagines (Asn) at B3 is replaced with lysine (Lys), also the lysine at B29 is replaced with glutamic acid (Glu).

Diselenide Insulins:

It is evident that chain A and chain B has innate ability to be folded in a thermodynamically stable conformation favors the native disulfide coupling, but oxidative recombination can continue successfully even without the presence of a linking peptide. A6-A11 diselenide insulin analog was recently prepared by Metanis and colleagues using a more advanced variation. The intra A6-A11 native disulfide bridge is produced between CysA6-CysA11. Despite being a close isostere of cysteine, selenocysteine possesses a less pKa and less oxidation potential than sulfur due to the selenol group. The process required creating the A-chain by replacing the A6-A11 cystein residue with selenocysteine, then performing chain fusion using the S-sulfonate of the B-chain, which produced 31% folding yield. According to the authors, the appropriate folding of the interchain disulfides was made easier by the early synthesis of the A6-A11 intramolecular bond, leading to quicker production and increased yield of the finished product. The newly developed analog had potency similar to insulin and was more resistant to reduction and GLU-C proteolysis.

Cystathionine insulin:

Recent advances in directed disulfide bond production have also made it possible to synthesize a number of new insulin analogs with disulfide isosteres. For instance, Karas and colleagues replaced the cystine with cystathionine to convert the A6-A11 disulfide into a thioether. After the B19 S-pyridyl (S-Pyr) of B chain is activated and a free cysteine at position A20 is available, the A-chain containing A6-A11 cystathionine was cross-linked with the B chain. Through the iodine-oxidation of the appropriate (S-Acm) shielded cysteines, the final A7-B7 disulfide bond was created.

Methylene thioacetal insulin:

Wade and coworkers first proposed the idea of extending with a charged solubility tag, which was later successfully applied to address the A-chain's limited aqueous solubility. The Chou group recently used a cleavable linker in combination with a tri-lysine tag. The physical characteristics of the A-chain were improved by this "helping hand" method. Using this technique, it was made possible to develop cystein mimetic, A6-A11 methylene thioacetal insulin that used “adimedone-based, hydrazine cleavable N-terminal linker bearing a poly-Lys solubilizing tag” (Karas et al., 2021). It was found that their disulfide analog had a biological activity that was similar to that of native insulin, had improved structural stability as determined by a lower tendency to physically agglomerate and was resistant to heat or enzyme denaturation.

Single-Chain Insulin (SCI):

Another strategy was employed in the chemical synthesis of insulin consists of a variety of single-chain synthetic intermediates which can be converted to two-chain peptides using chemical or enzymatic processes. Having the ability to perform native oxidative intramolecular folding is a major attraction of the single-chain method. Weiss and colleagues discovered a SCI with a GGGPRR C-chain that had increased thermal stability, perhaps as a result of a limitation on potential conformational variations. Ultrastable analogs that don't necessarily require refrigeration might be useful as safer forms of insulin therapy. Three unprotected pieces were combined into "SCI-57" using NCL. A7-A21 was created using Fmoc SPPS, while fragments B1-B6 and B7-A6 (which comprise the C-peptide) were generated using Boc-SPPS. To avoid intramolecular cyclization, thiazolidine was substituted for cysteine at position B7. B7-A21 was initially put together via thiophenol-mediated NCL at pH 6.9, and then methoxyamine was added to convert the N-terminal

thiazolidine to native cysteine. Following that B1-B6 underwent a second ligation step. The precipitate that generally develops during folding is made up of insulin that has been folded incorrectly, so it was folded twice to increase yields. After that, preparative RP-HPLC was used to purify the entire sample. The entire process results in a yield of 24.4%.

DesDi insulin was produced by a fusion between the C-terminus of the B-chain to the N-terminus of the A-chain using a precursor. Compared to proinsulin, it was 37 amino acids shorter. and had a single lysine in place of the native residues B28–B30. It has been established that DesDi insulin folds well and is able to readily convert from the single chain to the double chain form through a single proteolytic step. A recent thorough disulfide scan was carried out and showed the versatility of this method. A sequence of 49 or 50 residue peptides using cutting-edge resin-based peptide assembly was prepared with no amide backbone alterations, and two Cys (Acm) were carefully inserted at different places. 20 analogs of insulin were produced in single-chain DesDi form, and they folded as effectively as the native sequence.

Insulin with four disulfide bonds:

A fourth disulfide bond was more recently added by Chou et al. between residues close to the C-terminus of the B chain and expanded insulin A chain. In mice, this derivative had equivalent in vivo efficacy to natural insulin and proved less susceptible to aggregation because of the additional disulfide bridge between residues A22 and B22.

This serves as an illustration of how recent developments in synthetic methods have made it possible for us to recognize analogs that are completely active in their native three-disulfide form or when bound by a fourth disulfide. If the disulfide is substituted for a glucose-

sensitive tether, these findings could serve as a foundation for the development of glucose-responsive insulin (Brunel et al., 2020).

3.1.5 Problems associated with insulin therapy

Hypoglycemia may affect the majority of diabetic patients, occurring when a person's blood glucose level drops below 70 mg/dL or 3.9 mmol/L. In patients with T1DM and T2DM who use insulin, perhaps the most detrimental adverse effect of insulin therapy is hypoglycemia, which also serves as the major barrier to glycemic target achievement. In the Diabetes Control and Complications Trial (DCCT), individuals with T1DM receiving high-dose insulin for a long time had an increase of 2-4 folds in severe hypoglycemia (SH). Research findings on prolonged therapy for T2DM, showed that intensive therapy produced considerably greater SH than regular therapy did. In addition to causing coma, seizures, SH has been reported to being the reason for death in 4–10% of T1DM patients. According to the degree of clinical complexity and level of treatment intensity, the estimated likelihood of SH in T2DM patients varied from 1.02 to 3.04%. Among insulin-treated patients, elderly age, prolonged diabetes, impaired kidney function, hypoglycemia unawareness, and decreased HbA1c levels are risk factors for hypoglycemia (Donnor, 2023).

A common adverse effect of insulin therapy is weight gain. In repeated hypoglycemic conditions, the patients eat more calories to correct their decreased glucose levels; this could lead to weight gain. The stimulation of fatty acid absorption into adipose tissue is one of insulin's anabolic actions. There will be more insulin present to convert blood glucose into stored fat. Compared to NPH or glargine insulin, detemir insulin causes less weight gain. The reason why detemir causes less weight gain than NPH or glargine is not fully known. Compared to biphasic insulin aspart or prandial aspart insulin, basal insulin given with oral

antihyperglycemic medications causes less weight gain. When coupled with oral antihyperglycemic drugs, lispro mix insulin causes more weight gain than insulin glargine.

With human insulin and insulin analogs, severe allergic responses and skin reactions are quite uncommon. Rarely, hypersensitivity reactions to insulin or one of its components (protamine, for instance) arise. These reactions might cause local inflammation, pruritus or itching, a wheal, or even more severe systemic events, such as anaphylaxis. Constant subcutaneous insulin infusions and the administration of the less allergenic lispro insulin are effective treatments for insulin sensitivities. Although lipoatrophy is now uncommon with insulin analogs and is thought to be immune-mediated, it was previously prevalent with the use of less pure and animal insulins. Administration of the insulin glargine, aspart, and lispro has been linked to incidents of lipoatrophy.

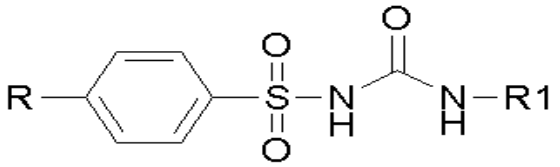
3.2 Sulfonylureas

The use of insulin, which lowers glucose synthesis and increases glucose uptake into the cell, can be used to treat hyperglycemia. However, insulin delivery is limited by its ineffectiveness when administered orally, short shelf life, need for refrigeration, and potential for deadly hypoglycemia in the case of overdose. Sulfonylureas are known as insulin secretagogues, which promote the body's production of insulin and consequently enhance the levels of insulin in the blood, ultimately reducing blood glucose levels. The first-generation sulphonylurea, tolbutamide, was eventually replaced by the second-generation sulphonylureadrugs, gliclazide, glipizide, and glibenclamide (glyburide), as well as the third-generation drug, glimepiride. The side effects of these agents include acute and even deadly hypoglycemia, an increased appetite, anorexia, and stomach disturbances such as nausea, vomiting, and heartburn. Although it is extremely challenging to maintain normoglycemia in

people with DM, such hypoglycemic drugs are still being extensively considered. Medicinal chemists are still experiencing difficulty in finding novel hypoglycemic scaffolds having the least amount of side effects (Suaifan et al., 2015). Over 12,000 sulfonylureas have been created since the early periods, and some of these have been shown to be very effective.

3.2.1 Chemistry:

The common core structure (Figure 2) of sulfonylureas is the basis of their naming. The ability of these drugs to treat diabetes depends on the presence of a sulfonylurea moiety, or R-SO2-NH-C(O)-NHR'. The ATP-sensitive potassium (KATP) channels in beta cells are closed as a result of the formation of hydrogen bonds with a particular receptor site on those channels, which causes the release of insulin. Different arylsulfonylureas have different pharmacologic and pharmacokinetic properties because of substitutions at each end of the arylsulfonylurea. Small, polar, water-soluble substitutions are present in first-generation sulfonylureas including chlorpropamide, tolbutamide, and acetohexamide. Second-generation sulfonylureas such as glipizide and glyburide tend to be more potent because they have big, nonpolar, and lipophilic substitutions that can more easily pass through plasma membranes. Third-generation sulfonylureas have more substitutions than second-generation sulfonylureas, it has yet to be determined if glimepiride has enough of a difference to qualify. Glimepiride essentially has hydrophobic nature.



name	R	R1
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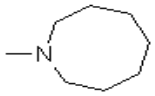
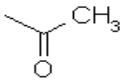
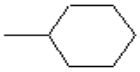
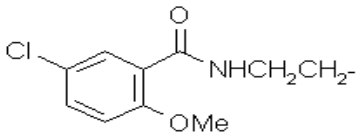
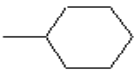
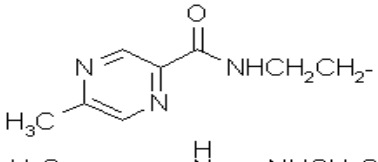
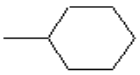
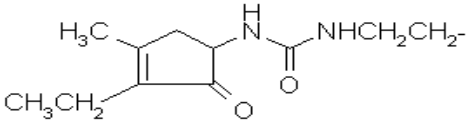
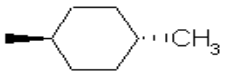
Chlorpropamide	$-Cl$	$-CH_2CH_2CH_3$
Tolazamide	$-CH_3$	
Acetohaxamide		
Glyburide		
Glipizide		
Glimepiride		

Figure 2: Graphic structures of sulfonylureas

(Sulfonyl Ureas, n.d.) [15]

3.2.2 Structure-Activity Relationship (SAR) of Sulfonylureas

The pharmacological activity and potency of sulfonylureas are influenced by modifications to their chemical structure.

- The potency and selectivity of sulfonylureas are influenced by different substituents on the benzene ring. The methyl, amino, acetyl, chloro, bromo, methylthio, and trifluoromethyl groups are among the substituents that tend to improve hypoglycemic action.
- The second-generation agents, which are composed of compounds containing p-(-b-arylcarboxamidoethyl) substituents, are far more effective than the first-generation agents. It

is assumed that this happens considering there is a particular distance between the substituent's nitrogen atom and the sulfonamide nitrogen atom (*Sulfonyl Ureas*, n.d.).

- The group linked to the terminal nitrogen should have an appropriate size and should have lipophilic characteristics. The characteristics and size of the N-substituent have an impact on the metabolic stability and binding affinity to the receptor site. While N-propyl and N-hexyl are the most active, N-methyl and N-ethyl are the least active. If the N-substituent has 12 or more carbons, activity is reduced.
- The distribution, absorption, and duration of action of sulfonylureas are all influenced by their lipophilicity, which is determined by whether there is hydrophobic groups or not. Improved oral bioavailability and tissue penetration can be obtained by increased lipophilicity.

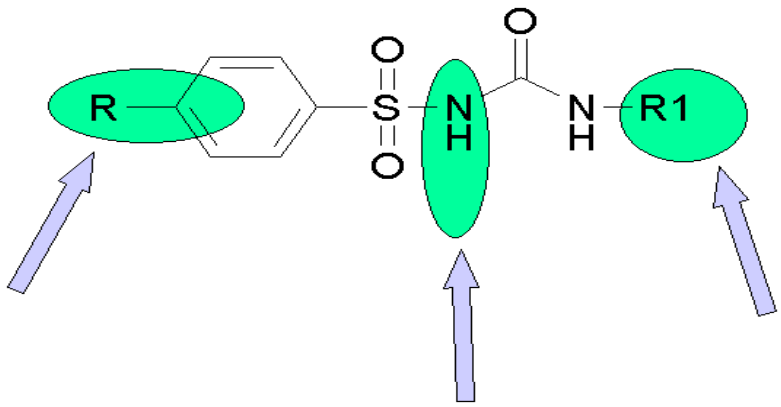


Figure 3: Structure-Activity Relationships of Sulfonylureas

(Sulfonyl Ureas, n.d.) [15]

3.2.3 Synthesis of Sulfonylureas

1. Synthesis of sulfonylureas based on disconnection a): N/C-carbonyl:

In order to synthesize sulfonylureas, it is often necessary to couple sulfonamides to appropriate carbon-centered electrophiles, such as isocyanates or activated carbamoyls with

ideal leaving groups at the electrophilic carbonyl (Figure 4). Although procedures without the salification step have also been presented in the literature, sulfonamides are often deprotonated by a stoichiometric base in order to enhance their nucleophilicity. The commercial, patented sulfonylurea drug syntheses include a two-step base-mediated reaction between sulfonamides and isocyanates.

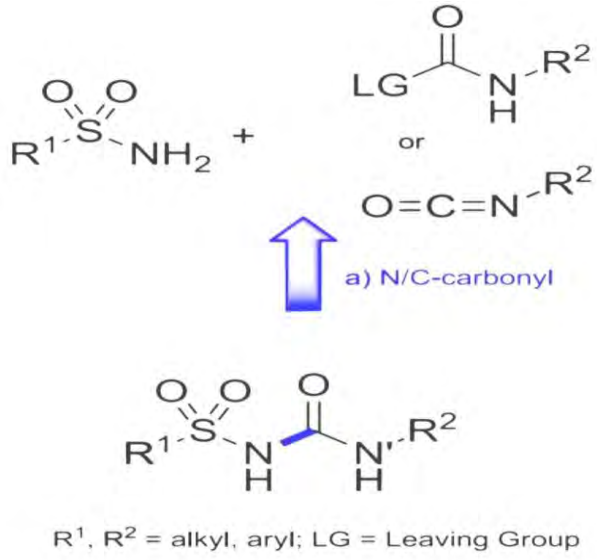


Figure 4: Syntheses from sulfonamides and electrophilic isocyanate or carbamates

(De Ventura & Zanirato, 2021), [17]

2.Synthesis of sulfonylurea through CuCl-catalyzed direct C-N coupling of sulfonamides and isocyanates:

In 1990, Cervello and Sastre published their findings of the direct C-N coupling of sulfonamides 1 and isocyanates 2 in N, N-dimethylformamide (DMF) solution using CuCl as the catalyst to produce sulfonylureas 3. The approach had the advantage of not requiring a very alkaline media, and it produced a number of N-Ts, N'-aryl/alkyl sulfonylureas in large quantities (Figure 5). This catalytic method of sulfonylurea synthesis was eventually extended to mechanochemical reaction conditions, offering a straightforward, rapid method to produce sulfonylureas with medicinal importance. In particular, without the need for a

solvent, the process makes it possible to quickly and easily synthesize the first- and second-generation sulfonylurea drugs tolbutamide, chloropropamide, and glibenclamide.

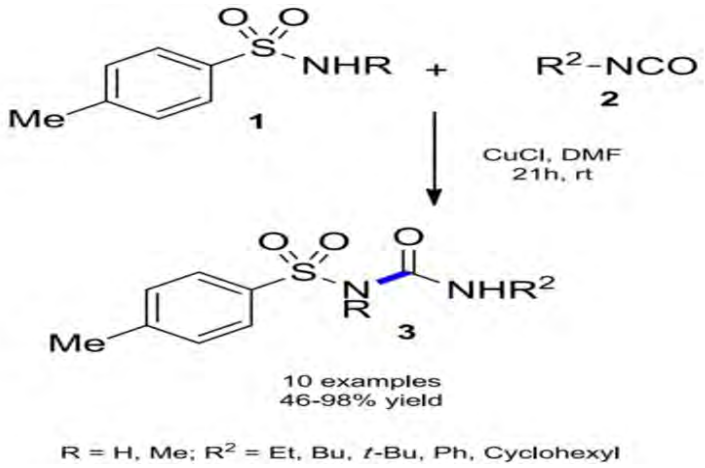


Figure 5: Sulfonylurea through CuCl-catalyzed direct C-N coupling of sulfonamides and isocyanates (De Ventura & Zanirato, 2021), [17]

3. Synthesis of sulfonylureas from carboxylic acids and sulfonamides via an in situ Curtius rearrangement:

Through the in situ synthesis of the relevant isocyanates, sulfonylureas 14 were easily obtained from the associated sulfonamides 12 and aliphatic/aromatic carboxylic acids 13. To do this, acyl azide was created from the acid using diphenylphosphorylazide (DPPA), which was then used to create isocyanate via Curtius rearrangement (Figure 6). The approach made it possible to quickly access a range of sulfonylureas that would have been challenging to manufacture using other techniques since it did not need the isolation of isocyanates or comparable intermediates.

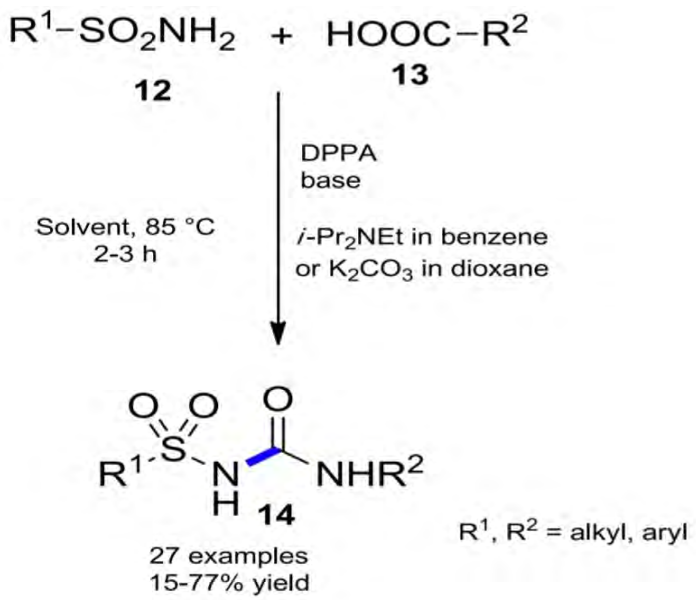


*Figure 6: Synthesis of sulfonylureas from carboxylic acids and sulfonamides via Curtius rearrangement (*De Ventura & Zanirato, 2021), [17]

4. Synthesis of glimepiride:

Both the urea and sulfonylurea moieties of glimepiride have been produced using the electrophilic properties of the phenyl carbamate group (Figure 7). The lactam derivative 24 and the amine 28 were reacted with diphenyl carbonate as a carbonyl source to produce the carbamate intermediates 25 and 29, which were then used to readily complete the synthesis of the insulin secretagogue. The carbamate 25 combined with 26 to produce the arylsulfonamide 27 as indicated in Scheme 5. The latter captured the in-situ produced cyclohexyl isocyanate 30, which was produced from 29. This practical method made it possible to produce the desired compound under favorable reaction settings, with a better overall yield and excellent purity.

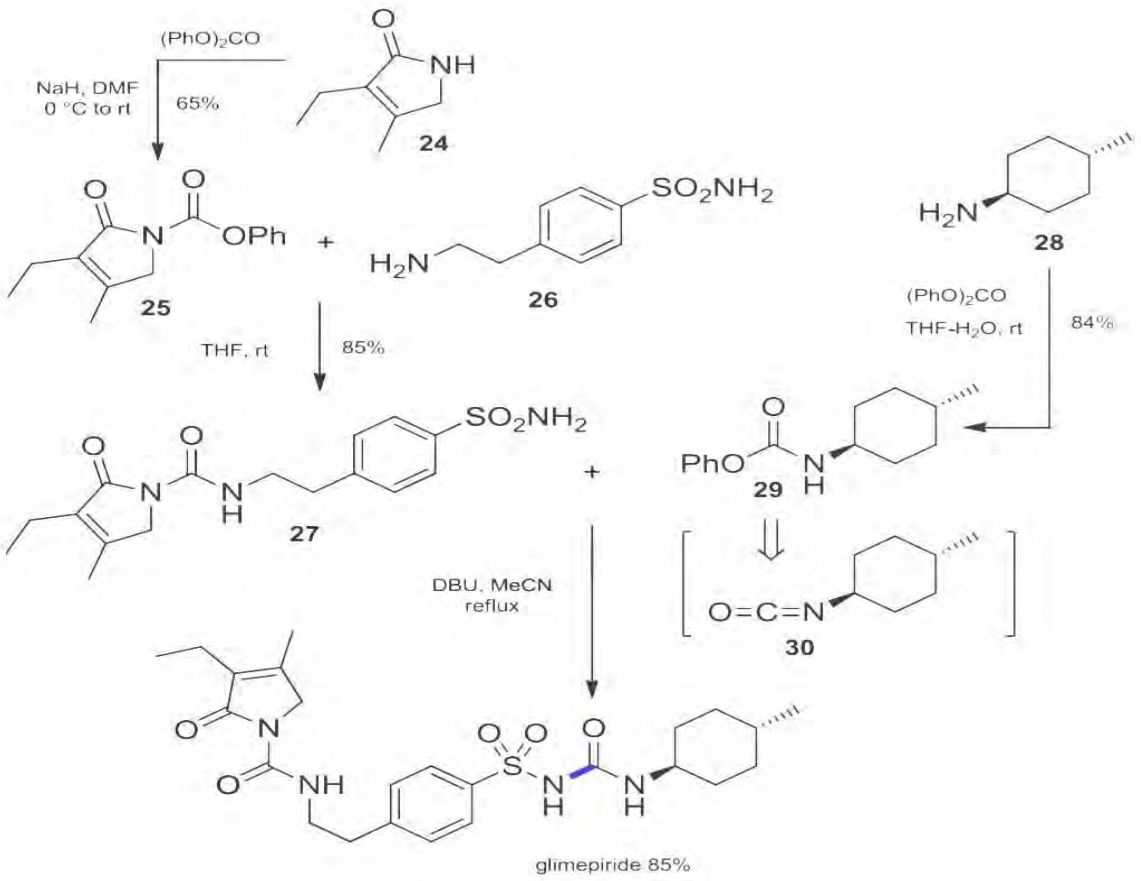


Figure 7: Synthesis of glimepiride

(De Ventura & Zanirato, 2021), [17]

5. Single-step synthesis of sulfonylureas from sulfonyl chlorides and amines:

Since the early years of the nineteenth century, sulfonyl chlorides and cyanate anions have been used in a distinct manner to produce sulfonyl isocyanates. According to the patent literature, aliphatic sulfonylureas are made (Figure 8) by treating sulfonyl chloride with sodium cyanate while a base is present, then adding amine. Both aliphatic and aromatic sulfonylureas 60, as well as a number of derivatives having an impact on the regulation of zinc metalloenzymes, are readily accessible by the NaOCN-mediated single-step reaction, that functions with a range of sulfonylchlorides 60 and amines 61 (Figure 8).

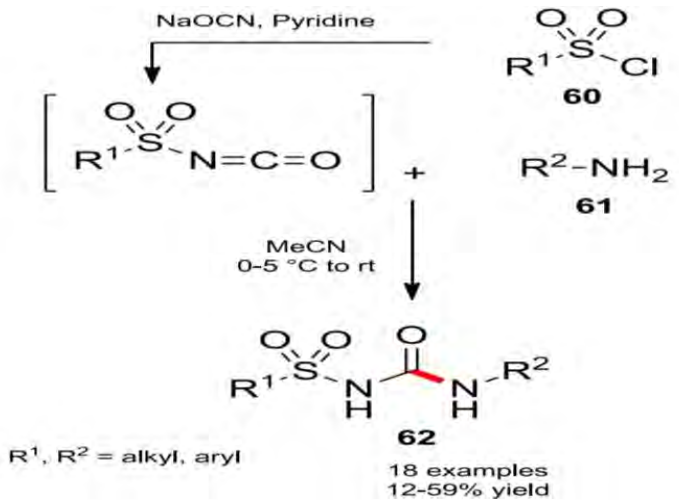


Figure 8: Single-step synthesis of sulfonyl ureas from sulfonyl chlorides and amines

(De Ventura & Zanirato, 2021), [17]

6. Synthesis of glibenclamide

The synthesis of glibenclamide 83 is possible by coupling cyclohexylamine 82 to sulfonylchloride 81. This reaction was done by the presence of Pd(OAc)2 catalyst and NaN3 base. Through implementing this technique an excellent yield of sulfonylureas was obtained.

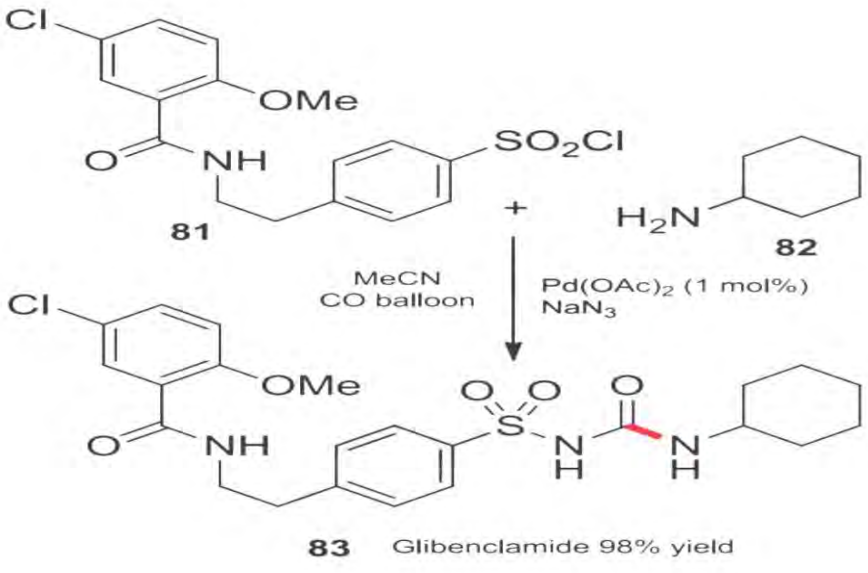


Figure 9: Synthesis of glibenclamide

(De Ventura & Zanirato, 2021), [17]

3.2.4 Pharmacological Evaluation of Sulfonylureas:

Sulfonylureas bind to receptors connected to ATP-sensitive K+ (KATP) channels on the surface of pancreatic beta cells, initiating a series of processes that releases insulin. The membrane depolarizes when the KATP channel closes, signaling the pancreatic beta cell to secrete insulin (Campbell, 1998). Sulfonylureas connect to several locations on the pancreatic beta cell membrane. Compared to other sulfonylureas, glimepiride's attachment to this particular receptor protein results in a less fixed blockade. In comparison to glyburide, glimepiride exhibits a two- to three-fold higher rate of interaction and an eight-nine-fold faster rate of detachment at the receptor site.

Sulfonylureas may potentially reduce glucose levels using extrapancreatic processes. Several sulfonylureas in vitro and in vivo studies were done to determine the ratio of each drug's mean plasma insulin increase to mean blood glucose decrease (PI/BG) to assess each one's respective extrapancreatic actions. The increased extrapancreatic activity was observed as it shows that a decreased glucose concentration which is not followed by a significant rise in insulin level. The PI/BG ratios for healthy fasting dogs given equal hypoglycemic dosages of sulfonylureas were ranked as glimepiride <glipizide < gliclazide < glyburide. Yet another in vivo study found that glimepiride lowered blood glucose by 40%, plasma insulin concentrations by 50%, and glycosylated hemoglobin (HbA1C) by 33%, whereas glyburide and gliclazide possessed no influence on these factors. The study used insulin-resistant diabetic KK-Ay mice. Although these results' clinical relevance has yet to be verified.

Measuring a sulfonylurea's actions on glucose transport, the translocation of the GLUT4, and lipogenesis and glycogenesis in muscle and adipose cells are additional ways to determine the amount of extrapancreatic activity. According to in vitro experiments, glimepiride promotes

glucose uptake and use via translocating GLUT4 in fat and muscle cells. Glimepiride is about twofold as effective as glyburide in promoting lipogenesis and glycogenesis. Results from clinical studies support the extrapancreatic activity data from experiments. In an investigation comparing glimepiride with glyburide, the T2DM patients using glimepiride had considerably decreased fasting insulin and C-peptide concentrations, even though blood glucose reductions were similar. Similarly to other sulfonylureas, it is unclear how long-term glimepiride dosing decreases blood glucose.

Studies conducted both in vitro and in vivo demonstrate persistent variations in the cardiovascular effects of sulfonylureas at equipotent dosages. Compared to glyburide and glipizide, glimepiride tends to have less cardiovascular action. Although the precise cause of the variations among sulfonylureas in vivo is unclear, in vitro evidence points to the involvement of KATP channels (Campbell, 1998).

Although oral sulfonylureas have already been used effectively in conjunction with insulin for patients having secondary failure, glimepiride is the only type of drug that has received FDA approval. Glimepiride dramatically reduced the need for exogenous insulin in type 2 diabetic patients who are suffering from sulfonylurea treatment failure. In this investigation, type 2 diabetes that was resistant to sulfonylureas was diagnosed when the fasting plasma glucose (FPG) was more than 150 mg/dL following the quitting of previous therapy. Later, patients were randomly given either a placebo or insulin together with glimepiride 16 mg/d. Therefore, two groups of patients were investigated, one group received only insulin and the other group received insulin with sulfonylurea. The glycemic control of the two therapy groups was then compared. So, in comparison to the insulin-only group, the group that also got glimepiride had a considerably lower mean daily insulin dosage. However, combining

sulfonylurea with insulin treatment increases the risk of hypoglycemia compared to using either drug alone.

3.2.5 Safety profile of sulfonylureas

More than 5000 individuals were included in randomized clinical studies that were carried out in the US and Europe, evaluating the efficacy and safety of glimepiride. Glimepiride 1-32 mg was given to 3,500 patients every day for a period of two weeks to 2.8 years. The rest of the patients were given gliclazide, glipizide, glyburide, or a placebo. For adverse events that may be developed during therapy, patients were thoroughly monitored. According to combined data from these clinical studies, glimepiride's overall rate of adverse events was comparable to or potentially lower than other sulfonylureas. The primary adverse effects of taking glimepiride were headache and dizziness; however, none of these side effects were seen in over 2% of individuals.

There were two ways to describe hypoglycemia. Hypoglycemia that manifests as symptoms, such as perspiration, drowsiness heart palpitations, lightheadedness, or impaired vision, is known as symptomatic hypoglycemia. These symptoms might be brought on by other medical disorders, so these were not specific. In a US-based study with a control group that received a placebo, the average rate of symptomatic hypoglycemia was 13.9% with glimepiride and 2.0% with placebo. According to a second comparison trial in Europe, glimepiride was similarly linked to a lower risk of hypoglycemia (11%) than glyburide (14%) (Campbell, 1998).

A few uncommon side effects of sulfonylurea treatment include leukopenia, agranulocytosis, hemolytic anemia, thrombocytopenia, and aplastic anemia. The development of hyponatremia

is a rare side effect of glimepiride as well as other sulfonylureas, but it can happen in individuals who have a greater chance of experiencing the syndrome of insufficient antidiuretic hormone production due to a preexisting health issue or concurrent medication therapy. Sulfonylureas are often associated with cases of hepatic porphyria, however, glimepiride is not known to be linked with such cases

3.3 Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

Insulin and sulfonylureas are examples of conventional antidiabetic drugs with limitations like short half-lives, oral unavailability, or unfavorable adverse events. “To address these issues, treatments for controlling blood glucose including sodium-glucose co-transporter 2 (SGLT2) inhibitors, DPP-4 inhibitors, and glucagon-like peptide-1 (GLP-1) receptor agonists have recently been developed” (Zhang et al., 2020). DPP-4 medications have multiple benefits over previous types of anti-diabetic medications, including lacking incidence of weight gain and lowered incidences of hypoglycemia. The DPP-4 enzyme is directly involved in how DPP-4 inhibitors work. Particularly the incretin hormones, GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), boosts the synthesis of insulin, and aid in regulating glucose levels. The serine protease DPP-4 quickly inactivates both hormones, reducing the efficacy of their therapeutic use. DPP-4 inhibitors function by preventing the action of DPP-4, an enzyme that degrades the incretin hormone.

Twenty years ago, the concept of blocking DPP-4 was proposed as a potential novel treatment T2DM. Until now, twelve DPP- 4 inhibitors are become approved for the treatment of T2DM (Li et al., 2018). When administered at the proper dosage, each of these reversible competitive inhibitors is capable of inhibiting the DPP-4 enzyme by more than 70% (Rahman et al., 2021). Particularly because of the self-limiting nature of DPP-4 inhibition and the

dependence of incretin hormones on glucose, it is well tolerated and does not pose a danger of drug-induced hypoglycemia. Each of these gliptins has been linked to adverse effects such as headache, nasopharyngitis, and infections of the upper respiratory tract. Pancreatitis and hypersensitivity responses, however, are the main side effects associated with all of these gliptins. Therefore, there is still a lot of interest in creating new DPP-4 inhibitors because certain current drugs have these unwanted side effects. The primary goal of current research on diabetes is to find novel medication candidates that have the capacity to block DPP-4 and prevent GLP-1 breakdown with lesser incidents of side effects. There are several novel DPP-4 inhibitors has been discovered in recent years, and many of them are extremely potent in the low-nanomolar range of IC50 values (Maslov et al., 2022).

3.3.1 Sitagliptin:

Sitagliptin is a potent and specific DPP-4 inhibitor and is the active component of the many recently approved drugs for the treatment of T2DM (Hansen et al., 2009).

3.3.2 Structure-Activity Relationship (SAR) of Sitagliptin

- The central pyrimidine ring structure interacts significantly with the DPP-4 active site. The ring strengthens the enzyme's binding affinity by forming hydrogen bonds with important amino acids.
- Trifluoromethyl (CF3) group with pyrazine ring is believed to be accountable for sitagliptin's activity. More inhibition is provided by the pyrazine structure than the pyrimidine ring (Rahman et al., 2021).
- Trifluoro-benzene at one end of sitagliptin increases the inhibition potential by increasing the compound length.

- This further additional substitution of the pyrimidine ring can significantly alter the level of inhibition.

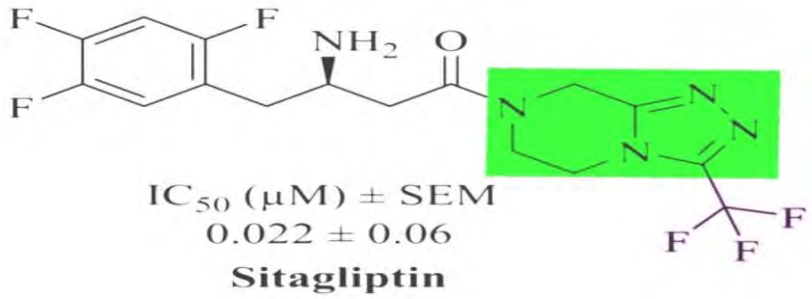


Figure 10: SAR of Sitagliptin

(Rahman et al., 2021), [20]

3.3.3 Synthesis of novel omarigliptin:

1. Synthesis of the novel fluorinated omarigliptin (compound 1):

Fluorine has been demonstrated to be a magical element in medicinal chemistry because of its special characteristics, including an extremely small atomic radius, strong electronegativity, lipophilicity, and electrostatic interaction. The addition of fluorine to medication formulations may improve pharmacologic effectiveness, metabolic stability, or membrane permeability.

For omarigliptin's pharmacokinetic characteristics, the insertion of fluorinated moieties at the 4- or 6-position on the tetrahydropyran ring may be advantageous. To verify the theory, QuickPrep in MOE was used to repair any structural flaws and add hydrogens to the crystal structure of DPP-4 coupled to omarigliptin. The R-Vectors tool in MOE was then used to investigate potential locations for adding groups to omarigliptin. The axial

positions of the 4 and 6 on the tetrahydropyran ring were marked as prospective locations for structural alteration, which is an interesting finding. Fluoro and trifluoromethyl groups have been selected as the optimal fluorinated structural units because of their easy synthetic accessibility (Zhang et al., 2020).

At first, chemical 1a was asymmetrically fluorinated using Barbas's technique, resulting in 4-fluoro ketone 1aa. Then, amine 1c might be produced by deprotecting substance S1 with 4 N HCl in an ethyl acetate solution. The desired compound 1 with the configuration of (2R,3R,4R,5S) might be produced by further reductive amination using amine 1c with compound 1aa followed by Boc deprotection (Figure 11).

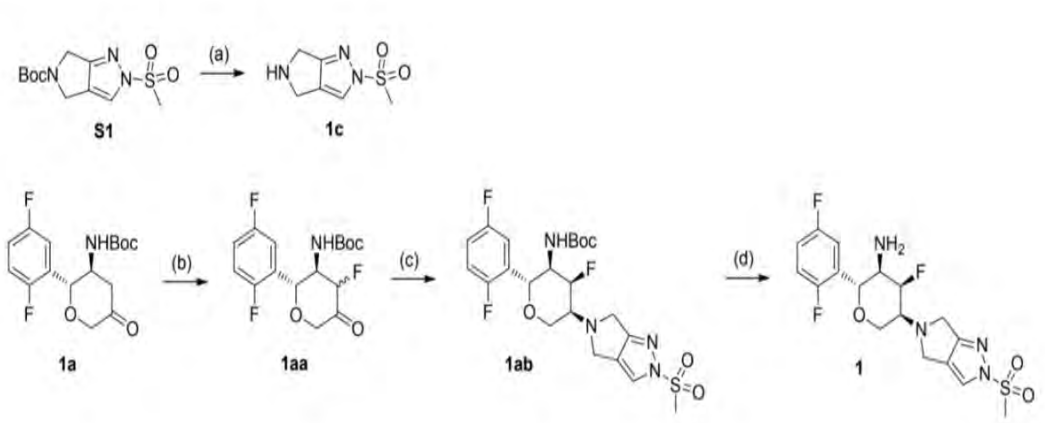


Figure 11: Synthesis of the novel fluorinated DPP-4 inhibitor omarigliptin

(Zhang et al., 2020), [18]

Reagents and conditions: (a) 4*N* HCl in EA; (b) HCl salt of (*2R*,*4S*)-4-hydroxypyrrolidine-2-carboxylic acid, NFSI, Na2CO3, THF; (c) **1c**, PhSO3H, NaBH(OAc)3, DMF; (d) TFA,DCM.

2. Synthesis of the novel fluorinated Compounds (compound 2, 6 and 9):

To make compound 2, morpholine is initially mixed with compound 1a to create the enamine intermediates 1ac and 1ac'. The resulting combination then went through a simple trifluoromethylation reaction with Umemoto's reagent, S-(trifluoromethyl)dibenzothiopheniumtrifluoromethanesulfonate), to produce the 6-trifluoromethyl ketone 1ad. Compound 2' was produced by the subsequent stepwise reductive amination of compounds 1ad and 1c (Figure 12, condition c). Under condition d, compound 2' may be scaled up to 100 grams upon optimization. After that, compound 2 with the configuration (2R,3S,5R,6S) was generated by deprotecting compound 2' with trifluoroacetic acid. Additionally, compound 6 was created from starting material compound 1b using the same synthetic process. Also, compound 2 was easily converted to compound 9 by the t-BuOK treatment.

Reagents and conditions: (a) morpholine, toluene, reflux in Dean-Stark appartus; (b)Umemoto's reagent, DMAP, DMAc; (c) step 1: **1c**, toluene, reflux; step 2: NaBH(OAc)3, CH3COOH, 1,2-DCE; (d) step 1: **1c**, CHCl3, reflux in Dean-Stark apparatus; step 2:NaBH(OAc)3, CH3COOH, 1,2-DCE; (e) TFA, DCM; (f) *t*-BuOK, THF.

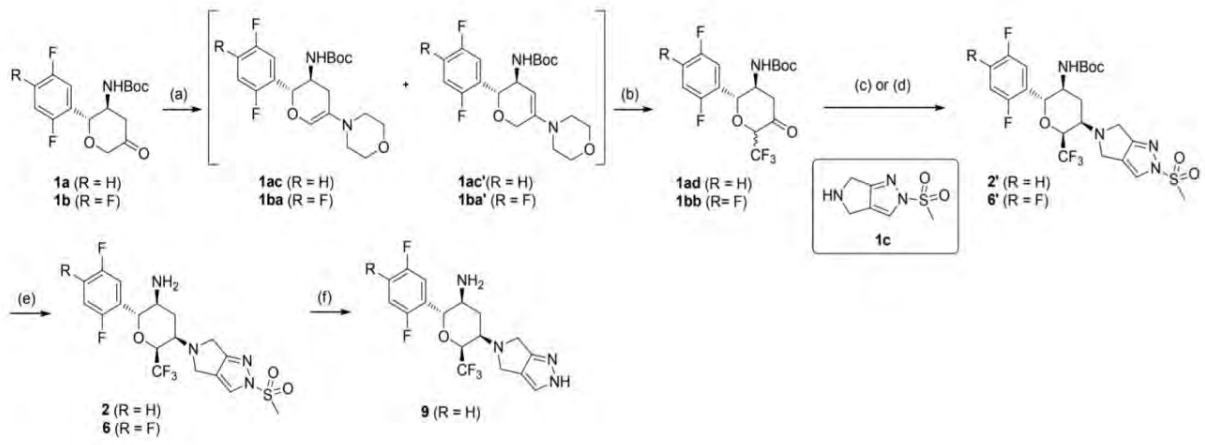


Figure 12: Synthesis of Compounds 2, 6 and 9. (Zhang et al., 2020), [18]

Zhang et al., 2020 successfully utilized fluorine chemistry in the approach of developing new anti-diabetic drugs, leading to the identification of a number of novel elements, including compound 1, compound 2 and compound 6, that have powerful DPP-4 inhibition effects and significantly better pharmacokinetic and pharmacodynamic profiles than omarigliptin in ob/ob mice. Additionally, compound 2 showed good preclinical safety profiles and exceptionally long-acting anti-diabetic effectiveness in rhesus monkeys. Compound 2 is now the subject of phase II clinical investigation for T2DM in China, and the findings will describe its clinical progression in the near future.

3.4 Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors:

SGLTs are transmembrane glycoproteins that are a member of the SLC5 (human sodium-glucose co-transporter family) family of solute carriers. They transport a variety of substrates across the intestines and the lumen of renal tubule. These two cotransporters, SGLT1 (Sodium-Glucose Co-Transporter 1, or SLC5A1) and SGLT2 (Sodium-Glucose Co-Transporter 2, or SLC5A2), are crucial mediators of epithelial glucose transport. They both are the well-characterized cotransporters in this category. Modern oral non-insulin anti-hyperglycemic medication that lowers blood glucose levels involves the use of SGLT2 inhibitors, because it could hinder the reabsorption of glucose into the proximal tubules of the kidneys and enhancing urinary glucose excretion (UGE) (Haider et al., 2019). Additionally, SGLT2 inhibitors have been demonstrated to lower the incidence of getting cardiovascular diseases and diabetes by reducing blood pressure, arterial stiffness, body weight, fat distribution, and vascular resistance.

The initial SGLT inhibitor that was identified is Phlorizin, which has the potential to inhibit both SGLT1 and SGLT2 but was never able to be approved for use in humans

because of its low bioavailability and significant gastrointestinal (GIT) complications. Since then many researchers are looking for a new, effective, safe, and selective SGLT2 inhibitor. This led to the creation of an entirely novel class of anti-diabetic medications known as gliflozins. The US Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the Pharmaceutical and Medical Devices Agency, Japan (PMDA) have approved seven gliflozins as anti-diabetic medications. Several drugs are now in the last stages of development. Currently, the USFDA and EMA have granted approval for gliflozins such Dapagliflozin, Canagliflozin, Empagliflozin, and Ertugliflozin. Recently, PMDA Japan authorized Ipragliflozin, Tofogliflozin, and Luseogliflozin. The development of gliflozins such Sotagliflozin, Baxagliflozin, and Remogliflozin is close to its final phase (Haider et al., 2019).

In normal conditions, all filtered glucose is reabsorbed in the kidney tubules, leaving no glucose in the urine. 80% to 90% of the filtered glucose is reabsorbed by SGLT2s found in the early S1 segment of the proximal tubule, while the remaining 10% to 20% is reabsorbed by SGLT1s found in the S2/S3 segment (Tentolouris et al., 2019). The SGLT2-I restricts the reabsorption of glucose in the proximal convoluted tubule (PCT) by inhibiting the SGLT2 protein and promoting the renal glucose excretion. Due to the inhibition of SGLT2, urine glucose excretion is expected to be quite close to the filtered glucose concentration (Ramani et al., 2022).

3.4.1 Dapagliflozin

Dapagliflozin is chemically (2S,3R,4R,5S,6R)-2-[4-chloro-3-[(4-ethoxy phenyl)methyl] phenyl]-6-(hydroxymethyl) oxane-3,4,5-triol and was first approved in November 2012 in Europe, and then later approved by USFDA in January 2014 (Haider et al., 2019). In comparison to placebo, dapagliflozin significantly lowers HbA1c by 0.11% to 0.44%. Additionally, it significantly lowers postprandial glucose (PPG) with no or few hypoglycemia episodes, and fasting prandial glucose (FPG), as well as improving beta cell activity.

Furthermore, dapagliflozin exhibits a slight drop in blood pressure and weight, thus offering some benefits to overweight or high blood pressure patients. For the treatment of T2DM, dapagliflozin is well-tolerated, safe, and efficient. Dapagliflozin also reduces the development of liver fibrosis and glomerulosclerosis linked to diabetes by reducing oxidative stress and tissue inflammation driven by hyperglycemia. It can be formulated as both a single treatment and a combination treatment with other antihyperglycemics. When combined with pioglitazone, certain trials suggest improved glycemic effects, higher HbA1c decrease, and blood pressure reduction.

Dapagliflozin side effects include tiredness and fast weight loss (which can cause dehydration), excessive glycosuria, that may reach up to 70 g per day, and an elevated risk of diabetic ketoacidosis (DKA) (Kshirsagar et al., 2020). A rise in urine glucose levels worsens diabetes-related conditions already present, most often urinary tract infections and candidiasis.

3.4.2 Structure-Activity Relationship (SAR) of Dapagliflozin

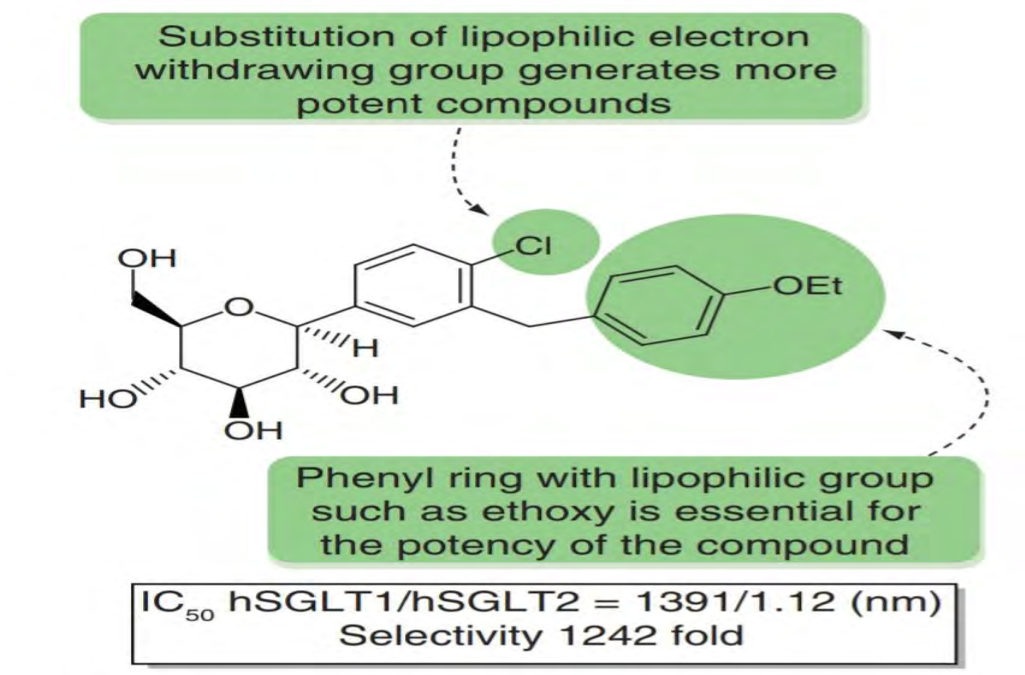


Figure 13: Structural–activity relationship of Dapagliflozin

(Manoj et al., 2020), [27]

- To enhance the pharmacokinetic characteristics and metabolic stability of dapagliflozin, substituents on the central phenyl ring have been studied. These changes may have an effect on the solubility, lipophilicity, and enzymatic metabolism of the drug. More potent and active molecules are produced when lipophilic electron-withdrawing groups (halogen) are substituted. Substitution with Me, Cl, and F would improve the activity of the drug.
- The selectivity and potency of the molecule depend on the presence of a lipophilic group, such as ethoxy, on the peripheral phenyl ring.
- The drug's efficacy and selectivity can be increased by altering the linker chain between the central and peripheral phenyl ring. The relative position of dapagliflozin within the SGLT2 receptor's binding site can be affected by structural differences in this area.

3.4.3 Synthesis of Dapagliflozin:

Commercially available 2,3,4,6 tetrabenzylglucose 13 is used in the synthesis of dapagliflozin (Figure 14) to produce the glucoside moiety 14, which may then be treated with 15 to produce the lactol 16 intermediate. In order to reduce 16 and positively produce 17, which is costly and challenging to produce on a big scale, sterically inhibited silanes were necessary. The last step deprotection step is performed that reduces 17 to provide product 2 (Dapagliflozin). By using only pure reactants, this procedure decreases the probability of byproducts and impurities.

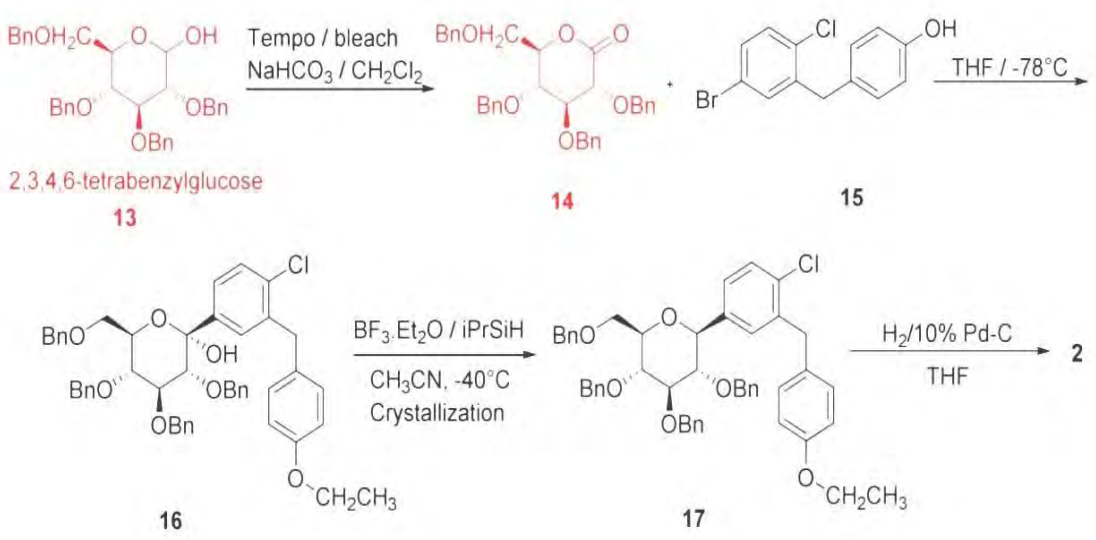


Figure 14: Synthesis of Dapagliflozin

(Haider et al., 2019), [25]

3.4.4 Canagliflozin

The USFDA approved canagliflozin on March 29, 2013, establishing it as the first sodium-glucose co-transporter inhibitor. Canagliflozin inhibits the activity of SGLT2, which lowers plasma glucose levels by promoting urine glucose excretion. Canagliflozin dosages of 100 and 300 mg per day were examined both separately and together with other anti-diabetic medications in large placebo-controlled studies. Canagliozin showed a

significantly lower statistics in HbA1c from the baseline compared to the placebo at both dosages when administered alone as well as combined with sulfonylureas and insulin. The HbA1c reductions from baseline at doses of 100 and 300 mg when taken as a sole treatment were 0.91 and -1.16, respectively. The placebo-subtracted difference varied from -0.62 to -0.92 when canagliozin was given together with other antidiabetic medications. Another observation was a weight loss of 0.4% to 3.3% on average across many studies of individuals receiving 100 and 300 mg of canagliflozin. The average systolic blood pressure (SBP) was reduced by 0.1 to 7.9 mmHg on average across studies, while HDL-C was elevated in comparison to placebo. Slight variations in triglyceride levels were inconsistent. Any effects that canagliflozin may have had on these two lipid markers were balanced by the rise of LDL-C levels, which ranged from 4.6 to 12% for a dosage of 300 mg and from 2-8% for a dose of 100 mg.

Canagliflozin and other SGLT-2 inhibitor therapy can have certain undesirable effects, including a rise in LDL cholesterol, increased urination, dehydration, decreased blood pressure, and a higher possibility of urogenital infections. Canagliozin is therefore not recommended for use in persons with impaired kidney function, a low GFR, or renal issues (Kshirsagar et al., 2020). Cardiovascular events were seen more often in canagliflozin-treated individuals (0.45%) over the first 30 days of the trial in comparison to placebo-treated patients (0.07%), indicating a greater chance of cardiovascular events at the beginning of the treatment. A higher risk of stroke also seems to be seen in canagliflozin-treated individuals. Some SGLT2 inhibitors, including canagliflozin, have been linked to the onset of ketoacidosis, according to a May 2015 FDA notice. The FDA also released a medication safety statement for canagliozin in September 2015 noting that reduced bone density may develop, which may increase the risk of bone fracture. It was

also included in the drug's adverse effects section. However, in 2017, in clinical research with 666 T2DM patients, canagliflozin showed favorable cardiovascular benefits (Kshirsagar et al., 2020).

3.4.5 Structure-Activity Relationship (SAR) of Canagliflozin

- The inhibitory potential is frequently altered by modifications to the linkage between the central and peripheral phenyl rings. The efficacy and selectivity toward hSGLT2 both improve when the phenyl is replaced with thiophene.
- The compounds' potency is significantly changed by changes to the para position. Strong lipophilic electron-withdrawing groups give maximum activity. To inhibit SGLT2, a lipophilic group like F must be substituted.
- The efficacy and selectivity of the molecule are considerably changed by substitutions at the para position of the aglycone moiety. The probability of its action decreases as the size of the substituents on the core ring grows. On the core phenyl ring, lipophilic substitutions are preferred in the fourth position. The para-positional methyl (CH3) group is necessary for the inhibition of SGLT2.

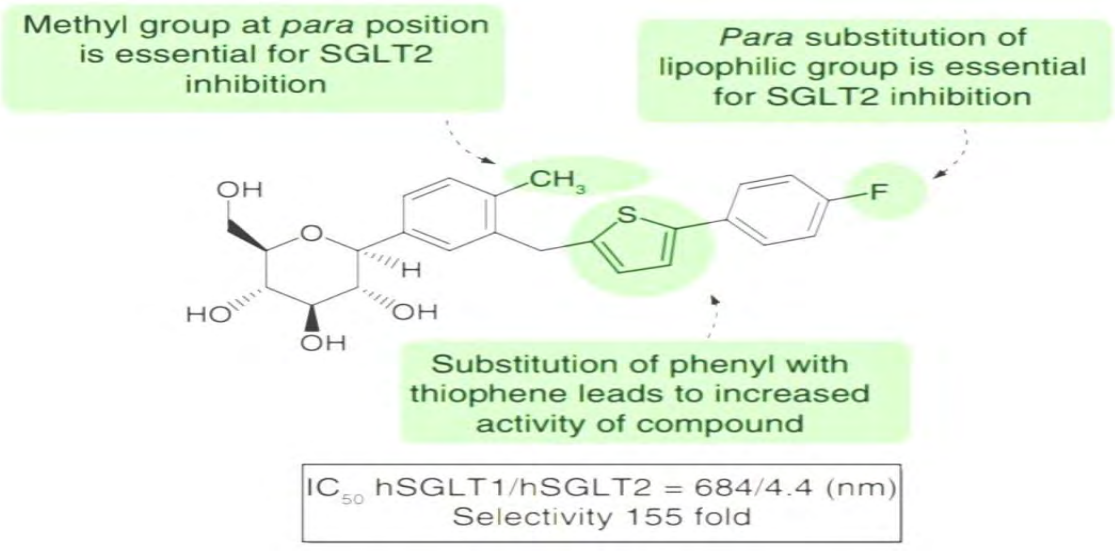


Figure 15: Structural–activity relationship of Canagliflozin (Manoj et al., 2020), [27]

3.4.6 Synthesis of Canagliflozin:

By using novel intermediates, the current patented work by Reddy et al. offers a novel method for the synthesis of 3 (Figure 16). (5-bromo-2-methylphenyl) 5-(4-fluorophenyl)thiophen-2-yl methanone 24 interacts with trimethylorthoformate / trimethylorthoacetatewhen there was acid to produce 25, which in condensation with tetrakis-O-trimethylsilyl-D-glucano lactone and Grignard reagent leads to the creation of intermediate 26. The next step is to deprotect this intermediate in the presence of acid and methanol to produce compound 27, which is then reduced with trialkylsilane and a Lewis acid to produce the finished product, canagliflozin.

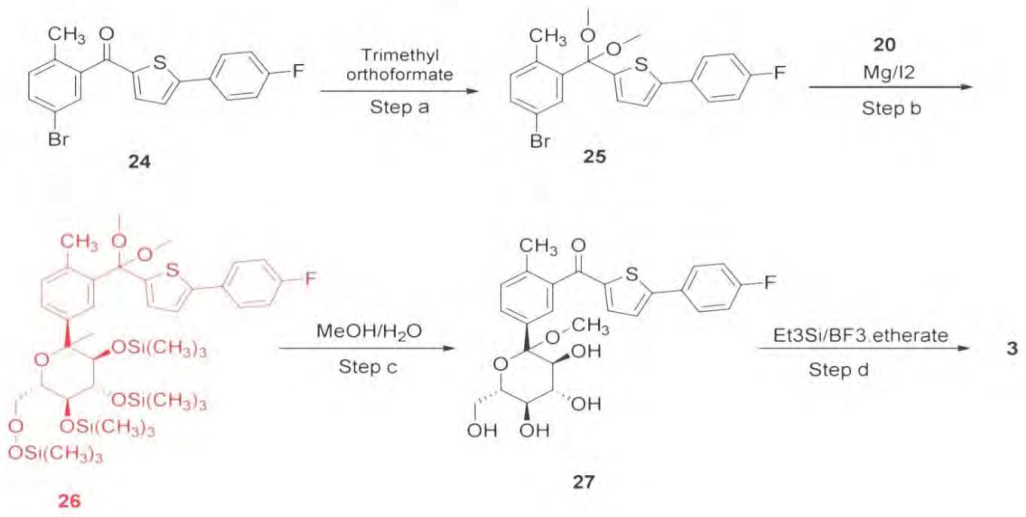


Figure 16: Synthesis of Canagliflozin

(Haider et al., 2019), [25]

3.4.7 Ipragliflozin

On January 17, 2014, the PMDA of Japan authorized ipragliflozin. It is a next-generation SGLT2 inhibitor that may be used orally and has a 254-fold selectivity for SGLT2 over SGLT1. The published IC50 values for human SGLT1 and SGLT2 are 1876 nM and 7.38 nM, respectively. Ipragliflozin is offered in Japan as 25 and 50 mg tablets under the brand

name Suglat and is used once a day before or after meals. It lowers blood sugar levels by blocking renal glucose absorption in a dose-dependent manner. In T2DM patients, ipragliflozin once-daily therapy of 50 mg dosage for a period of 24 weeks significantly lowers HbA1c level by 0.79%, fasting plasma glucose by 32.89 mg/dl, and reduced body weight by 1.10kg, and also enhances beta-cell function (Haider et al., 2019). Ipragliflozin has relatively fewer adverse effects than other gliflozins, such as urinary tract infections, and has a low chance of hypoglycemia. Phase II clinical investigations for the treatment of T2DM with ipragliozin were completed satisfactorily in the US, the EU, and other nations, either alone or in combination with other antihyperglycemics (Kshirsagar et al., 2020).

3.4.8 Structure-Activity Relationship (SAR) of Ipragliflozin

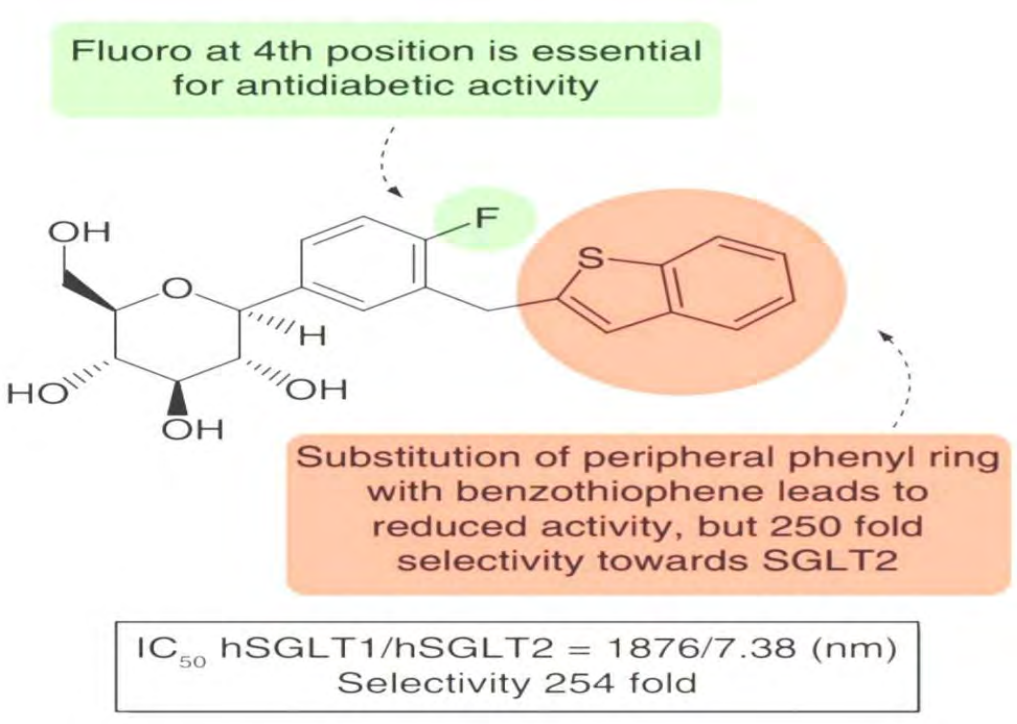


Figure 17: Structural–activity relationship of Ipragliflozin

(Manoj et al., 2020), [27]

- On the core phenyl ring, lipophilic substitutions are preferred in the 4th position. For antidiabetic action, fluoro at position 4 is crucial.
- Ipragliflozin is created by enlarging the thiophene to benzothiophene in the peripheral phenyl ring, which results in compounds with higher selectivity but a decreased potential. This suggests that replacing the peripheral phenyl with heterocycle-bearing sulfur could improve the activity of the resulting molecules.
- Benzothiophene substitution in the peripheral phenyl ring reduces activity while increasing the selectivity of SGLT2 by 250-fold.

3.4.9 Synthesis of Ipragliflozin:

Ipragliflozin L-proline could be synthesized in three simple steps using a clear and useful approach described recently by Ma Shuai et al. (Figure 18), which yields a compound with a purity of 99.92% and an overall yield of 52%. This process is simple to use on a massive scale, and the product is produced with excellent yield and high purity. Starting material 2-[(5-bromo-2-fluorophenyl)-methyl]-1-benzothiophene 63 is converted to the arylzinc species 65 in the presence of n-BuLi in the mixed solvent (toluene/DBE), followed by transmetalation with ZnBr/LiBr complex in DBE, and then the active species is reacted with 2,3,4,6-tetra-O-pivaloyl-a-D-glucopyranosyl bromide 64. Protective groups of 65 are removed by treatment with sodium methoxide in refluxing methanol, and 6 is obtained through recrystallization. Finally, through filtration and drying the final product, Ipragliflozin L-proline is produced.

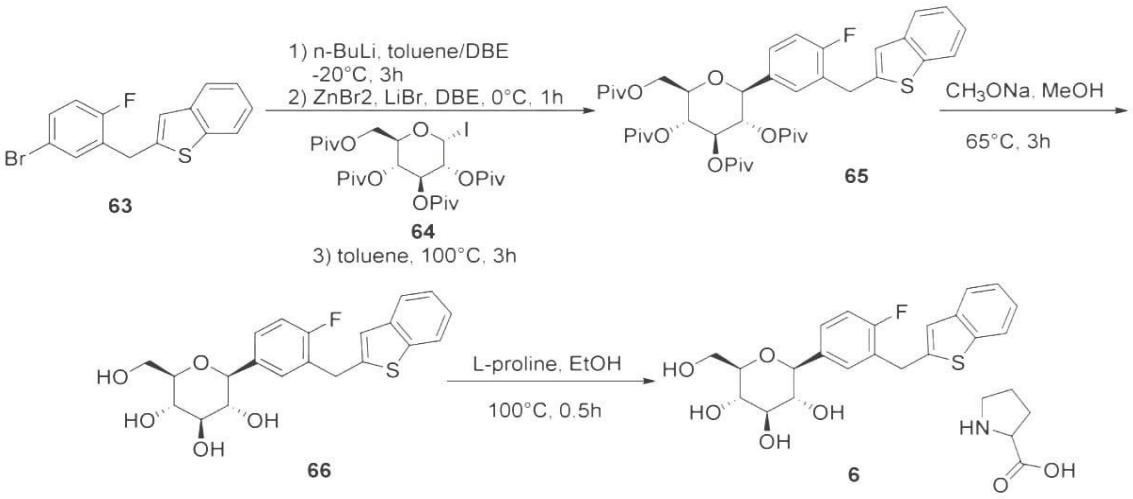


Figure 18: Stereoselective synthesis of Ipragliflozin L- proline

(Haider et al., 2019), [25]

3.5 Thiazolidinediones

T2DM is treated orally using a family of medications known as thiazolidinediones (TZDs), sometimes referred to as Glitazones. Due to the therapeutic benefits of treating insulin resistance and maintaining glycemic control, TZDs were first developed in the late 1990s and have been used extensively ever since. Troglitazone, the very first thiazolidinedione drug approved by the FDA, was taken off the market within the first three years as a result of significant liver damage in certain patients. Rosiglitazone and pioglitazone are the only thiazolidinedione drugs that are available in the market and in use currently. Soon after it was found that myocardial infarction (MI) risk was shown to be higher when using Rosiglitazone, the FDA started limiting access to the drug in November 2011. It was only available to people without cardiovascular risk and whose diabetes cannot be adequately controlled with other treatments. However, the FDA withdrew the limitation in November 2013 as a result of current research showing no risk of heart failure from using rosiglitazone.

The mechanism of action of TZDs is well-understood and it is currently a widely used drug in the treatment of T2DM. The thiazolidinedione ring binds to and activates the peroxisome proliferators-activated receptor γ (PPAR-γ), which increases glucose consumption, especially in adipose tissues. Peroxisome proliferator-activated receptor γ is a nuclear receptor that controls the transcription of the gene responsible for inflammatory responses as well as insulin-responsive genes involved in the control of lipid and glucose metabolism. Additionally, it has been demonstrated that thiazolidinediones have potent anti-inflammatory properties, which might be advantageous for people who have both diabetes and atherosclerosis. Thiazolidinediones may also be used for various purposes, as evidenced by their anti-cancer qualities and the idea that they may help Alzheimer's and dementia sufferers with their cognitive function (Damkaci et al., 2022).

3.5.1 Structure-Activity Relationship (SAR) of Rosiglitazone

For greater antihyperglycemic action, glitazones typically require a hydrophobic ring as the tail, a hydrophobic benzyloxy moiety as the trunk connected by a two-carbon atom, and a polar thiazolidinedione ring system as the head. The thiazolidinedione's keto group is the component that interacts most favorably with the PPAR-γ binding site (Patel et al., 2021).

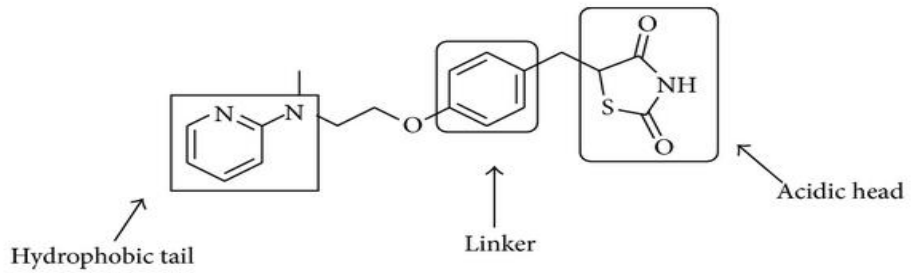


Figure 19: SAR of Rosiglitazone

(Dixit &Bharatam, 2013), [30]

3.5.2 Synthesis of Rosiglitazone:

Overall, there are four steps in the established path. In order to produce 5-(4-fluorobenzylidene) thiazolidine-2,4-dione (9), the first step involves the Knoevenagel condensation of 4-fluorobenzaldehyde (4) and 2,4-thiazolidinedione (6). Freshly made deep eutectic solvent, a safer nonvolatile solvent, was used to carry out this condensation. At 80 C, the condensation turned out to be finished in under two hours. The intermediate 2-(N-ethyl-N-(pyridin-2-yl) amino) ethanol (3) has been created in the second stage using a method from the literature. In the presence of potassium carbonate, the compound (3) was then condensed with 5-(4-fluorobenzylidene) thiazolidine-2,4-dione (9) in dimethyl sulfoxide to produce (Z)-5-[[4-[2-(methyl-2-pyridinylamino) ethoxy] phenyl]- methylene]-2,4-thiazolidinedione (7) within 4 hours. Rosiglitazone (8) was produced from chemical (7) after reduction with methanol-Mg.

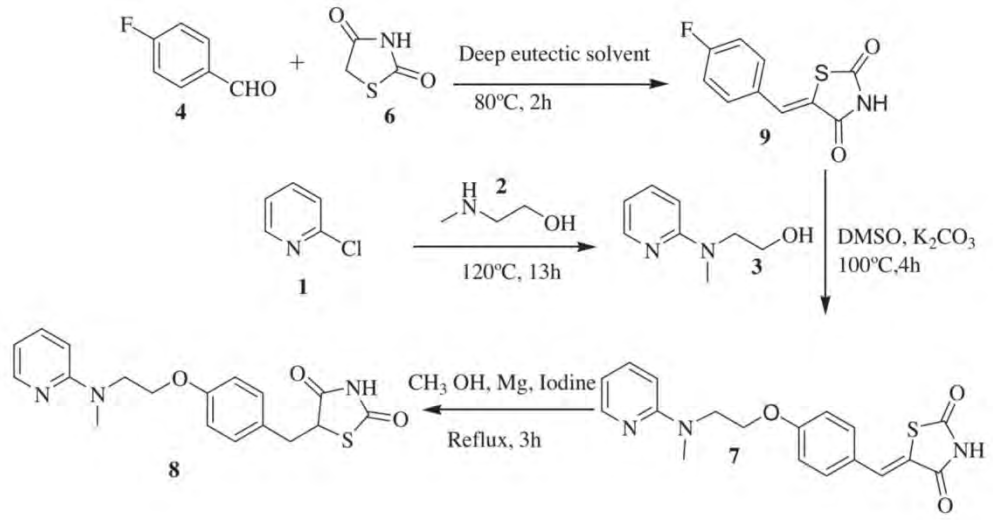


Figure 20: A convenient present synthetic route for the synthesis of rosiglitazone

(Jawale et al., 2012), [31]

3.6 GLP1 (glucagon-like peptide 1) receptor agonists

Glucagon-like peptide-1 receptor (GLP1R) agonists offer an advantage over other diabetes therapies in preserving beta cell mass and enhancing insulin production that is dependent on glucose with a reduced danger of hypoglycemia. GLP1R is a member of the secretin-like receptors family of G-protein coupled receptors. Multiple signaling pathways are activated by GLP-1 interaction with the receptor. The stimulation of Gαs, which in turn stimulates membrane-associated adenylyl cyclases, is one of the mechanisms that guarantee β-cell mass and insulin production. When adenylyl cyclase is active, intracellular cAMP levels rise. An increase in cAMP activates PKA that phosphorylates Ser133 of cAMP response element–binding protein (CREB), inducing β-cell proliferation (Girdhar et al., 2022).These drugs also function by stimulating the pancreatic GLP-1 receptors, resulting in greater secretion of insulin while decreasing glucagon secretion.

It is possible to manage diabetes mellitus with exenatide, liraglutide, and other long-acting GLP-1 analogs. However, because of their peptide composition and the mode of administration, they have a number of drawbacks, including high cost and instability. Since the previous 20 years, several small molecule GLP1R agonists have been developed to address the drawbacks of peptide agonists; however, none of them had received therapeutic use approval till last year.

The U.S. Food and Drug Administration have authorized oral semaglutide as the first GLP-1 receptor agonist (Kshirsagar et al., 2020). “Semaglutide is a long-acting GLP-1 Receptor Agonist that has a 94% similarity to the structure of natural GLP-1” (Liu et al., 2020).

3.6.1: Synthesis of semaglutide:

The solid-phase peptide synthesis (SPPS) method has been the basis for all semaglutide synthetic methods but results in expensive manufacturing expenses. With the goal of enhancing the yield or purity and lowering the overall expense of the product, researchers have been working more on optimizing the reaction conditions of current synthetic methods. A liquidphase synthesis technique was discovered recently that contain a hydrophobic support. The hydrophobic support is poorly soluble in polar solvents; hence dilution of the reaction mixtures using poor solvents will result in the desired product precipitation. Following filtering, the precipitated product is simply obtained, and any unwanted contaminants, like extra amino acids, or coupling agents, may be washed off. Nearly every type of peptide, including cyclic peptides and peptides containing disulfide bonds, may be synthesized using this soluble hydrophobic-support-assisted liquid-phase synthetic approach, making it potential high-efficiency peptide synthesis procedures.

First by identifying the structure of semaglutide it is divided into six fragments. Then the six fragments were completely synthesized separately. To effectively complete the whole synthesis of semaglutide soluble hydrophobic-support were incorporated. Following the sequential coupling of these fragments, semaglutide was produced by simply removing the protective groups and the tag support (deprotection).

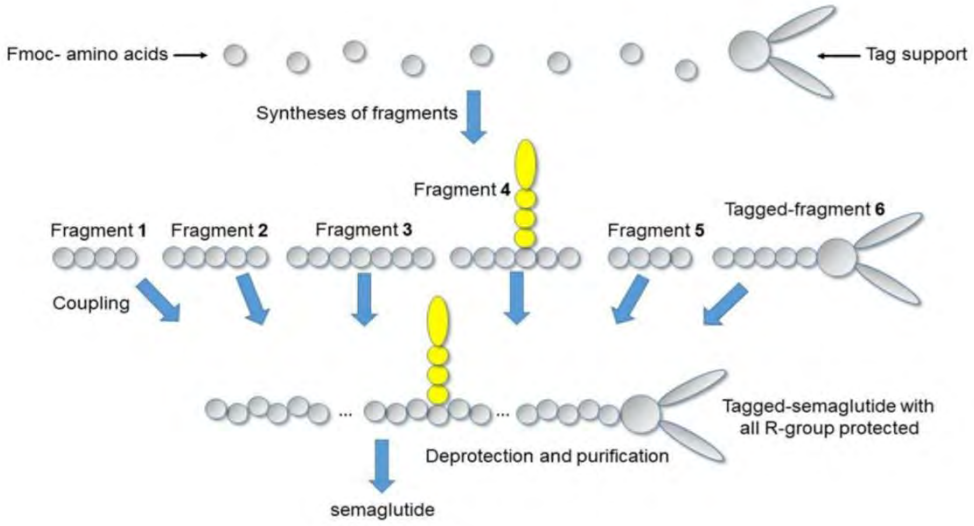


Figure 21: Synthesis of Semaglutide

(Liu et al., 2020), [55]

3.6.2 Synthesis of Danuglipron by lead optimization

A novel high throughput screening (HTS) strategy identified a series of leads, which are small-molecule fluoropyrimidine-based GLP-1R agonists, which can be used to develop potent compound danuglipron. The lead chemical series was optimized to produce strong small-molecule agonists that signal similarly to peptide agonists while activating the GLP-1R in a novel binding mechanism. Researchers demonstrate strong preclinical effectiveness and oral bioavailability in healthy human volunteers for the clinical development candidate PF-06882961 (danuglipron) (Griffith et al., 2022).

The piperidine ring, the benzyl ether, the 5-fluoro-pyrimidine, and the benzimidazole were the four structural areas that were thought to boost the GLP-1R agonist activity of the original hit (2). Though other six-membered rings (such as piperazine, cyclohexane, etc.) also showed GLP-1R agonism, the piperidine ring was shown to be the most effective in structure-activity relationship (SAR) tests. The receptor might also be activated by the 4-chloro-2-fluoro-

benzyl ether substitute. The most effective substitutes were those with a small molecular size at position 4 (such as chloro, fluoro, cyano, etc.). By adding a pyridyl group in place of the 5-fluoro-pyrimidine, it was possible to significantly boost the potency of the compound. This was likely accomplished by influencing the pendent benzyl ether's preferred conformation through the attraction of the oxygen and nitrogen lone pairs. The optimal torsion angle between the aromatic and piperidine rings is probably favored by the removal of fluorine. Pyridyl alteration was coupled with a more polar 6-aza-benzimidazole to produce 3, which was >100-fold more powerful than HTS hit 2. However, small molecule 3 has a high metabolic intrinsic clearance (CLint) in human liver microsomes due to its high lipophilicity (log D7.4 = 5.7). The high lipophilicity was also linked to off-target pharmacology, such as the blockage of the hERG ion channel (IC50 = 5.6 M).

Additional adjustments were made to lower lipophilicity, lower metabolic clearance, and enhance the off-target profile. To enhance both potency and physiochemical qualities, an acid substituent was added. When a carboxylic acid-containing substituent was added to the benzimidazole at position 7, it produced 4. The potency of compound 4 was equivalent to that of compound 3 (EC50 = 4.6 M), but it had significantly reduced lipophilicity (log D7.4 = 2.3), suggesting that the acid was probably having a useful interaction. The best efficacy was found with a carboxylic acid immediately linked to position 6 of the benzimidazole. For instance, 5 was more effective than 3 as a powerful GLP-1R agonist [SA EC50 = 95 nM]. In HLM (29 mL/min/kg) and human hepatocyte [31 μL min−1 (million cells)−1] metabolic stability experiments, compound 5 showed a moderate CLint and high selectivity against the hERG channel. Small molecule 5 was still a complete agonist but 20-fold less powerful [CS EC50 = 2.1 M] indicating that more potency advancements will be needed. Smaller, more polar groups were favored as a means of optimizing the substituent on the benzimidazole

nitrogen, which was successful in increasing potency without adversely affecting physiochemical characteristics. For instance, PF-06882961 (danuglipron), a complete agonist (EC50 = 13 nM in the CS cAMP test), was discovered as a result of a methylene-linked oxetane's potency increasing by almost 100 times compared to that of the methyl substituent in compound 5. Danuglipron also has a nitrile substitution for the chloride in the benzyl ether region, which reduces CLint in human hepatocytes (6.9 L/min/million/cells) and HLM (<10 mL/min/kg) (Griffith et al., 2022).

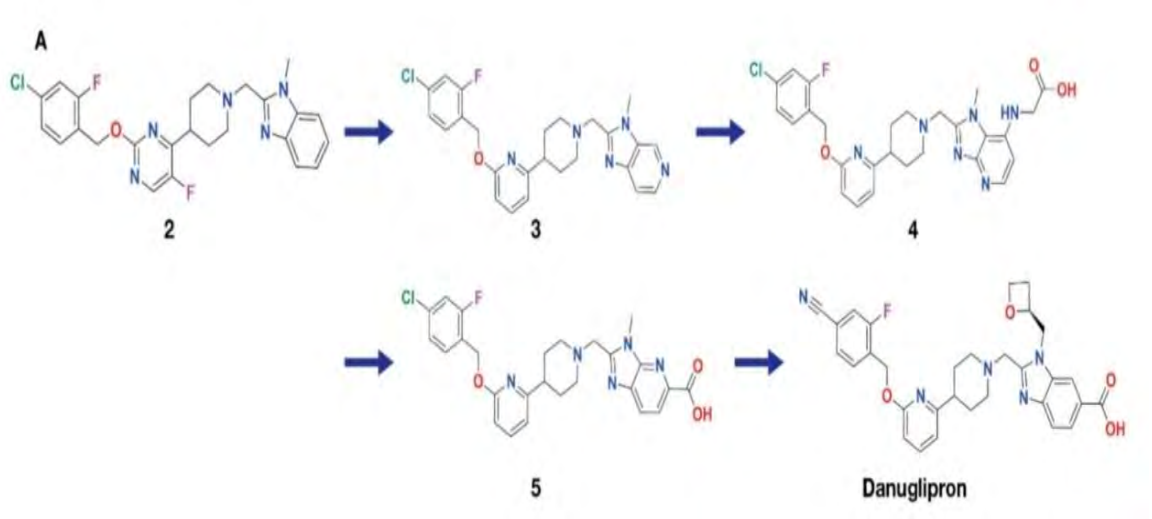


Figure 22: Optimization of small molecule 2 for the identification of the clinical candidate danuglipron

Figure 23:

(Griffith et al., 2022), [33]

Chapter 4

Discussion:

The rate and prevalence of T2DM is rising day by day and it has a direct association with hyperglycemia and other serious conditions like obesity, chronic liver diseases, and a number of different cardiovascular problems. Several antihyperglycemic drugs for the treatment of diabetes were authorized and withdrawn by the FDA after the very first discovery of insulin. A variety of anti-diabetic drugs can control normoglycemia in the human body by a variety of processes. Each of them belongs from different drug class that possesses distinct mechanism of action, degree of glycemic control, and side effects.

In order to offer current up-to-date information about the present developments of antidiabetic drugs, this review provides a comprehensive study of the most prevalent categories of antihyperglycemic products. Several antihyperglycemic compounds are now currently being used extensively, for example insulin, insulin secretagogues; sulfonylureas, incretin-dependent therapies; SGLT2 inhibitors, and GLP1 receptor agonist, DPP-4 inhibitors, and thiazolidinediones (Rosiglitazone). There are already approximately 60 prescription drugs that have received FDA approval as therapy choices for T2DM. In addition, there are now over 100 more antidiabetic medications undergoing clinical studies.

Modern novel drugs including GLP-1 receptor agonists (semaglutide, liraglutide, danuglipron), DPP4 inhibitors (Sitagliptin, Omarigliptin), and SGLT2 inhibitors (dapagliflozins, canagliflozin, Ipragliflozin) have acquired favor in the pharmaceutical market. In this paper, different synthetic ways for the production of several insulin analogues, sulfonylureas, Gliflozins, gliptins, thiazolidinediones were reviewed and discussed.

Additionally, fluorine chemistry by Zhang et al., 2020 has been studied which was used to synthesize a new DPP-4 inhibitor, fluorinated omarigliptin, along with other very potent compounds. A novel GLP-1 agonist danuglipron synthetic route was mentioned Griffith et al., 2022, which is basically done through lead optimization and it is now under development. New efficient routes for synthesizing semaglutide using soluble hydrophobic-support-assisted liquid-phase process were discussed by Liu et al., 2020. An effort can be made to develop more individualized and accessible therapies which can be driven by the existing and novel pharmacological therapies.

Conclusion

Diabetes is a metabolic disorder that may be considered an influential cause of significant financial loss, as well as hampering the growth of society. In addition, untreated diabetes leads to a variety of chronic health issues. In order to overcome this frightening condition, it is crucial to develop research on innovative hypoglycemic and potential anti-diabetic medications.

Numerous studies have demonstrated that dietary restrictions and lifestyle changes together are effective in helping diabetic patients to manage their glycemic index. However lifestyle changes alone are rarely sufficient to meet the necessary glycemic target. Also, single-medication therapy is not a guaranteed effective approach for achieving long-term glycemic control. From the middle of the 1950s through the middle of the 1990s, the only treatments available were insulin, sulfonylureas, and biguanides. After 1995, new types of DM treatments were identified and established. As a more effective approach and method for reducing hemoglobin A1C (HbA1c) and blood glucose levels, multi-target medicines are continually gaining acceptance and growth. The efficacy and safety characteristics of many second-line anti-diabetic medications, as well as various innovative synthetic approaches, are described in this review. Further advances in understanding the nature of existing drugs and the genetic root cause of the disease expected to result in the development of potential therapies, such as personalized medicine, that could take full advantage of these newly developed, commercially available drugs. By the modifications of the current available drug more potent drugs can be found that may have improved synthetic procedures, right dosage, with lesser adverse effect. The review has highlighted a number of unique modifications that result in potent drugs, which might serve as a starting point for future studies on the synthesis of anti-diabetic drugs.

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