A Review on Classes of Anti Diabetic Drugs and Synthetic Methods to Access Them: Classical and Modern Approaches

By

Md. Sakif Shahriyar
ID: 19146095

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/our 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/We have acknowledged all main sources of help.

Md. Sakif Shahriyar
ID: 19146095

Approval

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Examining Committee:

Supervisor:

Dr. Humair Bin Md. Omer
Assistant Professor
School of Pharmacy
BRAC University

Program Coordinator:

Professor Dr. Hasina Yasmin
Assistant Dean and Program Coordinator
School of Pharmacy
BRAC University

Dean:

Professor Dr. Eva Rahman Kabir
Dean
School of Pharmacy
BRAC University

Ethics Statement

This study involve no animal and human trial.

Abstract

Diabetes mellitus (DM) is a global health problem that threatens and hurts a lot of people every year. Most people with diabetes have type 2 diabetes, and diabetic care relies heavily on oral anti-diabetic medication. Oral anti-diabetic drugs include sulfonylureas, thiazolidinediones, meglitinides, sodium glucose co-transporter (SGLT2), a-glucosidase inhibitors, dipeptidyl peptidase-(IV) inhibitors, and biguanides. Due to the increasing prevalence of type-2 diabetes, researchers have been trying to develop safer and more environmentally friendly methods of producing anti-diabetic medications. This is to avoid a possible public health crisis. This review looks at the different ways that anti-diabetic drugs in the above classes are synthesized. The purpose of the review article is expected to help synthetic and medicinal chemists who are entering the field of diabetic treatments to provide state of the art knowledge in make DM drugs and its synthetic procedures in the literature.

Keywords: Anti-diabetic drug; Synthetic Route; Diabetes mellitus; Synthesis; Type-2 diabetes mellitus; Alternative Route

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List of Acronyms

DM	Diabetes Mellitus
SGLT	Sodium glucose co transporter
SAR	Structure Activity Relationship
GLP	Glucagon like Peptide
TZD	Thiazolidinedione
DPP	Dipeptidyl Peptidase
ATP	Adenosine Triphosphate
FDA	Food and Drug Administration
SNAr	Nucleophilic Aromatic Substitution
DCC	Dicyclohexylcarbodiimide
CDI	Carbonyldiimidazole
DCU	Dicyclohexylurea
US	United States
HOBt	Hydroxybenzotriazole
EDC	Ethylcarbodiimide
EMA	European Medicines Agency
BF	Boron Trifluoride
MSA	Meglumine Sodium Amidotrizoate
NaBHCN	Sodium Cyanoborohydride
TLC	Thin Layer Chromatography
HMDS	Hexamethyldisilane
PPh3	Triphenylphosphine
TMEDA	Tetramethylethylenediamine
DBQ	3, 5-Di-tert-butyl-1, 2-benzoquinone
DMF	Dimethylformamide
THF	Tetrahydrofuran
NMM	N-Methylmorpholine
MW	Microwave
TFAA	Trifluoroacetic anhydride

NMP	N-Methyl-2-pyrrolidone

CHAPTER 1

Introduction

1.1 Diabetes and its types:

Diabetes is a long-term medical illness that hinders our bodies' ability to turn food into usable energy. Carbohydrate-based foods are broken down by the body into glucose, which is subsequently absorbed into the bloodstream. When our blood sugar levels go too high, our pancrea responds by producing insulin. Insulin acts as a key, unlocking the door for glucose in the blood to enter cells in the liver and muscles, where it may be used for energy (Sagandira et al., 2021).

Diabetes occurs when the body either does not create enough insulin or is unable to use the insulin it does make properly. When there isn't enough insulin or when cells become resistant to insulin, too much glucose (sugar) stays in the circulation. In the long run, this could cause severe complications with one's health, such as renal disease, vision loss, and heart problems.

Unfortunately, there is no known way to completely reverse diabetes at this time; however, making healthy changes to one's lifestyle, such as decreasing weight, eating better, and increasing physical activity, can have a significant impact. And, of course, the most essential part: taking diabetes pills. Type 1, type 2 diabetes, and gestational diabetes are the three most common forms of the disease (diabetes during pregnancy) (International Diabetes Federation, 2020).

It is widely believed that the autoimmune response is the major cause of type 1 diabetes (the body attacks the pancreatic B cells by mistake). The production of insulin is blocked by this reaction. Around 5-10% of diabetics have type 1 diabetes. Symptoms of type 1 diabetes often manifest suddenly. It is most commonly diagnosed in young people (children, teenagers, and

young adults). You need to take insulin every day if you have type 1 diabetes. There is presently no known cure for diabetes type 1 (Chatterjee et al., 2017).

Type 2 diabetes makes it challenging to maintain normal glucose levels due to inadequate insulin use. Ninety five to ninety five percent of people with diabetes have type 2 (Chatterjee et al., 2017). Typically diagnosed in adults, it develops over many years (but more and more in children, teens, and young adults nowadays). If anyone are at risk for diabetes, then should get regular blood sugar checked even if they don't have any signs of the condition. Modifications to one's lifestyle, such as those listed below, can help prevent or delay the onset of type 2 diabetes.

I. Weight reduction
II. Healthy food consumption.
III. Exercising and taking antidiabetic drugs

It is possible for women who have never had diabetes before to develop gestational diabetes when they are pregnant. If you have gestational diabetes, there is a chance that your unborn child will have a higher risk of developing certain health problems. Diabetes that was caused by pregnancy normally disappears after delivery of the baby. On the other hand, it increases the likelihood that a person may develop type 2 diabetes later in life. In addition to this, there is a greater likelihood that the child would be obese as a child or adolescent and will, as a result, go on to acquire type 2 diabetes later in life.

1.2 Anti Diabetic Drugs and Its Types

The many categories of diabetes medications are going to be the topic of conversation throughout this essay. Antidiabetic medications were developed in order to stabilize and control the levels of glucose in the blood of diabetic patients. Diabetes is treated with a variety of

different medications. Insulin, pramlintide (Amylin), GLP-1 receptor activators (such as Byetta and Victoza), and glucose-lowering medications that are taken orally are all examples of different types of diabetes medications. Insulin is used to treat type 1 diabetics, while pramlintide (Amylin) and GLP-1 receptor activators are used to treat type 2 diabetics (tablets). There are only a few different categories of diabetes medications. Biguanides, sulfonylureas, meglitinide, thiazolidinedione (TZD), dipeptidyl peptidase 4 (DPP-4) inhibitors, sodium-glucose cotransporter (SGLT2) inhibitors, and -glucosidase inhibitors are the oral antidiabetic medication types that are used the most frequently (American Diabetes Association, 2015) (Sola et al., 2015).

1.2.1 Type 1 Diabetes Anti-Diabetic Medications:

In order to maintain good health, people with type 1 diabetes must take insulin injections every day. Additionally, type 1 diabetics need to eat healthy, control blood glucose levels, and monitor their sugar levels (Sola et al., 2015).

1.2.2 Type 2 Diabetes Anti-Diabetic Medications

Blood glucose levels in some patients with type 2 diabetes may be manageable with dietary and physical activity changes alone. If diet and exercise stop working, however, anti-diabetic medication may be recommended. Oral hypoglycemics, which are tablets, will be taken orally, or an injection will be used (insulin and GLP-1 receptor agonists). Study more about it, commonly prescribed as the first anti-diabetic drug are biguanides like Metformin.

We may receive an alternative medication in place of or in addition to biguanides if biguanides are ineffective when used alone. Given that various medications have varying benefits and drawbacks the kind of medication we are prescribed may be based on a number of variables.

There are categories that include a variety of branded and generic anti-diabetic medications:

i. Biguanides, which include metformin, are extremely prevalent (Glucophage)
ii. Glipizide (Glucotrol), glyburide (Glynase, Micronase), chlorpropamide (Diabinese), and tolbutamide are examples of sulfonylureas (Orinase)
iii. Inhibitors of alpha-glucosidase include acarbose (Precose) and miglitol (Glyset)
iv. Thiazolidinediones, including exenatide (Byetta), vildagliptin (Galvus), saxagliptin (Onglyza), and pioglitazone (Actos), as well as DPP-4 inhibitors and GLP-1 receptor agonists include sitagliptin (Januvia), vildagliptin (Galvus), saxagliptin (Victoza)

Additionally, some medications combine several of these medication categories (Sagandira et al., 2021). For example, Vildagliptin and metformin are two such drugs that are combined in the medication Eucreas.

Orally active antidiabetic drugs are currently prescribed to treat type II diabetes. These drugs are complex, small molecules that have intricate chemical structures that are synthetically challenging. These structures contain novel functional groups that are embedded in them and are connected in complicated bond connections that are difficult to synthesize for synthetic and medicinal chemists. However, over the course of time, chemists have devised fresh and original solutions to such issues as a means of gaining access to anti-diabetic medications. This article's goal is to introduce and summarize a selection of synthetic methods that can be used to synthesize different classes of anti-diabetic medicines. In the following review article.

1.2.3 Methodology

The data was collected from research papers, studies, and research articles that could be accessed through a variety of online databases. These online databases include PubMed,

Frontiers, MDPI, ScienceDirect, and Google Scholar, among others. For the purpose of drawing the structures of the anti-diabetic medications, ChemDraw was utilized. Important search terms such as “anti-diabetic medication,” “synthetic route,” “diabetes mellitus,” “synthesis,” “type-2 diabetes mellitus,” and “alternative route,” amongst others, were used to look up papers. On the basis of the problem, articles that were pertinent and useful were gathered, and more background was investigated. After the subject had been decided upon, an outline comprising relevant headings and subheadings was drafted. Both the bibliography and the intext citation were provided by Mendeley Desktop. The entirety of the essay was rephrased, and there were citations included in the composition.

PubMed: PubMed is a free resource that primarily searches the MEDLINE dataset of sources and articles in the biomedical and biological sciences. This database is part of the Entrez information retrieval system and is maintained by the United States National Library of Medicine at the National Institutes of Health.

Frontiers: Frontiers Media publishes scholarly journals in the fields of science, technology, and medicine, all of which are open access and subject to peer review.

MDPI: The journals published by MDPI are freely available online.

Google Scholar: Google Scholar is an easy-to-use tool for searching across a wide body of academic papers.

ScienceDirect: ScienceDirect gives users access to their extensive bibliographic collection of scientific and medical articles.

ChemDraw: ChemDraw was a very useful tool for drawing the structures of this article.

Mendeley: Mendeley is a resource management and scholarly social network that has assisted me in arranging my review, creating citations, working with others online, and learning about the most recent findings.

CHAPTER 2

Synthesis

The synthesis of anti-diabetic drugs requires several starting materials that include reagents, solvents which must be of analytical grade. Many different classes of anti-diabetic drugs are available, including sulfonylureas, thiazolidinediones, meglitinides, sodium glucose co-transporter (SGLT2) inhibitors, -glucosidase inhibitors, dipeptidyl peptidase-(IV) inhibitors, and biguanides. Scientists are working hard to create more effective and long-lasting synthetic solutions for these anti-diabetics in order to head off a major public health emergency. This chapter will cover a variety of reported synthetic methods for the aforementioned classes of anti-diabetic medications. Each of these drugs has different synthetic methods to access and these methods will be assessed in terms of purity, yield of the products, use of toxic metals, other hazardous reagents, reaction conditions. They are explained below.

2.1 Sulfonylureas

Sulfonylureas have been widely used to treat type 2 diabetes since they were first discovered by Janbon and colleagues in 1942. Although there are a variety of diabetes drugs available, sulfonylureas are among the most commonly given due to their low cost and convenience as a once-daily dose. According to a recent study (Sola et al., 2015) (Chemistry & Biology Interface, 2023 n.d.). Sulfonylureas are a class of diabetic drugs that act as insulin secretagogues and are used singly or in conjunction with other diabetes drugs such gliclazide, glipizide, tolbutamide, chlorpropamide, glibenclamide, and glimepiride. Insulin secretion following meals and after eating is increased by sulfonylureas. Sulfonylureas increase basal insulin secretion and as well meal-stimulated insulin release. Many people with diabetes are now taking sulfonylureas from the second generation since they are more effective and have fewer negative side effects (Sola et al., 2015). In the 1950s, the first sulfonylureas were introduced to the market. Some of these drugs' synthetic routes are discussed below.

2.1.1 Gliclazide

Gliclazide is a Sulfonylurea antidiabetic medicine which is used to treat type II diabetes mellitus. Gliclazide medicines are usually taken as tablets and modified-release (MR) tablets. Gliclazide is available in the market with brand names such as Dacadis MR, Diamicron, Edicil MR, Glydex, Laaglyda MR, Lamzarin, Nazdol MR, Zicron, Ziclaseg etc (Gliclazide Side Effects and Other Gliclazide Info at Patient, 2022 n.d.). An interesting fact about Gliclazide is it can be classified in two different ways. They have a sulfonamide group present in their chemical structure, which is able to release a proton, besides they have an aromatic group present in their structure too. And these properties make them defined as first generation anti diabetic drugs. But unlike the other first generation anti diabetic drugs (Sulfonylureas) they have higher potency, shorter half-life. And these pharmacological efficacies make them defined as 2nd generation sulfonylureas or anti diabetic drugs (Gliclazide Side Effects and Other

Gliclazide Info at Patient, 2022 n.d.). Gliclazide is actually a secretagogue, and it functions by facilitating β cells of the pancreas to circulate insulin. So basically, Gliclazide binds to the β cell sulfonylurea receptor which results in blocking the potassium channels which are ATP sensitive. The binding closes the channels which heads to the diminution in potassium efflux and causes depolarization of the β cells. This allows for the opening of voltage-gated calcium channels in the cell, which activates calmodulin and causes the exocytosis of secretory granules carrying insulin (Proks et al., 2002). Consequently, this is how Gliclazide improves insulin dynamics and release of insulin in type II diabetic patients.

Structure of Gliclazide

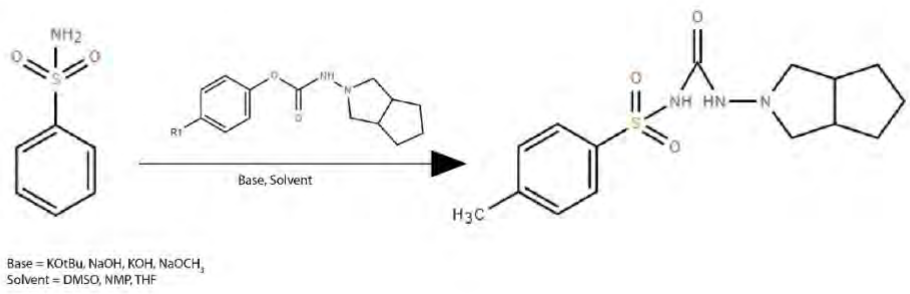


Figure 1: Synthesis of Gliclazide (Al-Omary, 2017)

Three stages are involved in the synthesis of gliclazide. Initially, carbamate is produced when aryl haloformate interacts with an amino heterocyclic molecule. Following the preparation of the p-toluene sulfonamide salt with metal hydroxide or metal alkoxide, this sulfonamide salt will finally combine with carbamate to produce Gliclazide (Figure: 1) (Ambulgekar et al., 2018).

2.1.2 Glipizide

Glipizide is a sulfonylurea which is used to treat type 2 diabetes. It basically functions by increasing the sensitivity of beta cells and so stimulating the secretion of insulin. Glipizide is actually a hypoglycemic agent which is taken orally and is basically a second-generation

sulfonylurea drug class. Glipizide is available in the market named as Glucotrol. The drug was first introduced in 1984 and approved by FDA in 1994 (Glipizide, 2020 n.d.). According to Diabetes Canada's 2018 Clinical Practice Guidelines, sulfonylurea medications are regarded as a second-line therapy for decreasing blood sugar after metformin. Sulfonylureas are more frequently utilized for early-stage type 2 diabetes when there is no advanced pancreatic failure since they need intact pancreatic beta cells for their therapeutic effectiveness (Ivers et al., 2019). Glipizide carries more non polar side chain in their chemical structures, and this increase their hypoglycemic potency and make them better than many other first-generation sulfonylureas. Not only that, but the advantage of glipizide over many other 2nd generation sulfonylurea pharmaceuticals is that it has the quickest half-life and duration of action, which reduces the risk for long-lasting hypoglycemia that is frequently found with blood glucose-lowering medications (Chemistry & Biology Interface, 2023 n.d.). Like all other sulfonylurea medications, glipizide is an insulin secretagogue that acts by promoting the secretion of insulin by pancreatic beta cells, leading to increased insulin levels in the blood. For this reason, the principal therapeutic impact of the medication requires the presence of functional beta cells in the pancreatic islets. When sulfonylureas bind to the sulfonylurea receptor on the plasma membrane of pancreatic beta cells, they inhibit the ATP-sensitive potassium channel and decrease potassium conductance (De Wet & Proks, 2015). This causes the pancreatic beta cell to depolarize and the voltage-sensitive calcium channels to open, facilitating calcium ion inflow. Beta cell production of insulin granules, or exocytosis, is stimulated by elevated intracellular calcium ion concentrations. In addition to this primary mode of action, glipizide also decreases the glucose levels in blood by increasing the number and sensitivity of insulin receptors, boosting hepatic gluconeogenesis, and enhancing peripheral glucose uptake. Less than 10% of the medicine's initial dose can be found in the urine and feces as unmodified glipizide, which is how the drug is primarily removed from the body by hepatic

biotransformation. The urine excretes around 80% of the metabolites of glipizide, whereas the feces excretes about 10% (PubChem, 2022 n.d.). The average terminal elimination half-life of the drug glipizide is two to five hours (An Overview of the Synthetic Routes to Essential Oral Anti-Diabetes Drugs, 2023 n.d.).

Structure of Glipizide

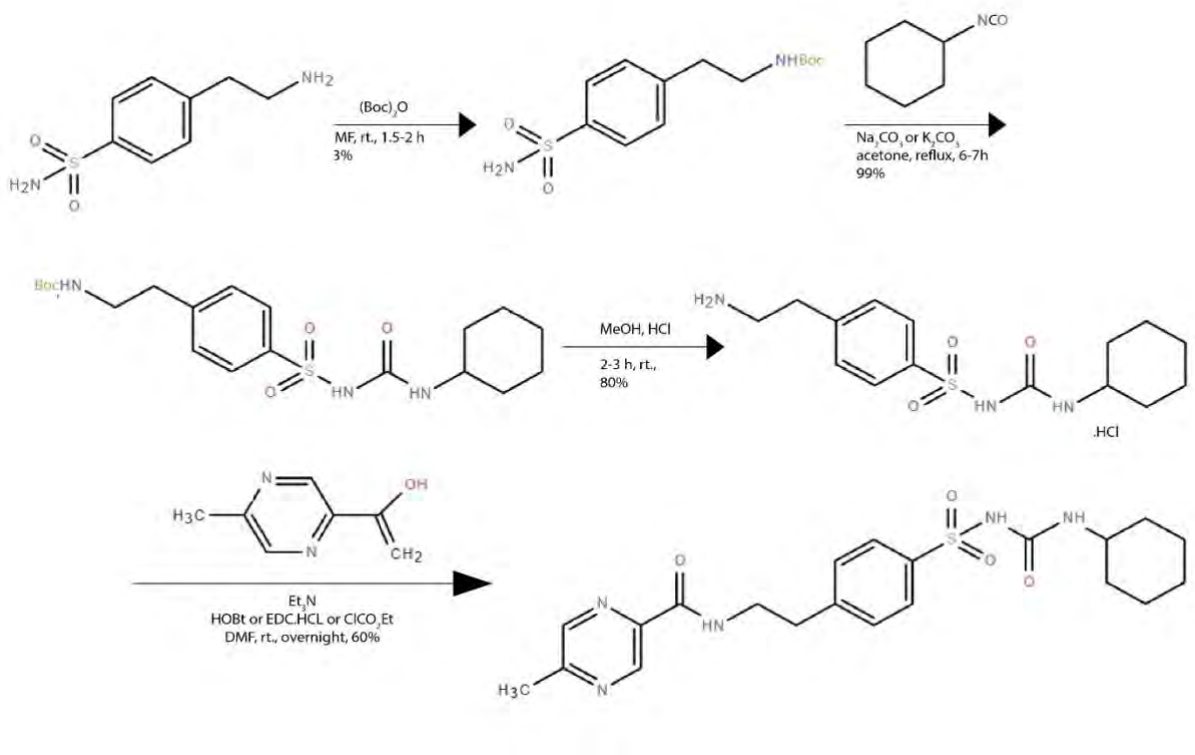


Figure 2: Synthesis of Glipizide (Furman, 2007)

The synthesis of glipizide can be broken down into four phases. Boc protection of the amino acid is the first step in the procedure to produce **14**, which is subsequently treated with isocyanate **15** to produce sulfonylurea **16**. After **16** was deprotected, **17** was produced, and after that, **18** was reacted to produce Glipizide **12**.

2.2Thiazolidinediones

For the treatment of type 2 diabetes, the thiazolidinediones (TZDs), also known as glitazones, were discovered in the late 1990s. In individuals who need insulin, they are taken in combination with other oral anti-diabetic drugs like sulfonylureas, metformin, and acarbose. Citiglitazone, englitazone, darglitazone, troglitazone, rosiglitazone, and pioglitazone are all examples of medications in this category (Cantello et al., 1994) (Jermendy & Csermely, 2001). Rosiglitazone and pioglitazone are the most often prescribed diabetes medications, and their synthetic pathways will be discussed below (Diabetes Medicines DIABETES TIPS, 2021 n.d.).

2.2.1 Rosiglitazone

Rosiglitazone, is available in the market as AvandiaR, was approved by the FDA in 1999 and was later approved in Europe, Japan, and New Zealand, as well as a few other nations (Cantello et al., 1994). High blood sugar in individuals who have type 2 diabetes can be managed with rosiglitazone along with a nutritious diet and regular exercise. Kidney disease, blindness, nerve damage, limb loss, and problems with sexual function can all be avoided by maintaining healthy blood sugar levels. Without enhancing the stimulation and release of insulin by the pancreatic beta cells, it can lower blood sugar levels through improving target cell responsiveness to insulin. Most often reported adverse reactions to rosiglitazone include upper respiratory tract infection; headache; back pain; high blood sugar; lethargy; sinusitis; diarrhea; and low blood sugar (Side Effects of Avandia (Rosiglitazone Maleate), Warnings, Uses, 2021 n.d.). Heart failure, heart attacks, liver damage, and bone fractures are examples of unfavorable effects that are severeunfavorable effects that are severe (Silvestrini, 2017). The synthesis of rosiglitazone, began with the SNAr reaction of 2-chloropyridine with 2- N-methylamino) ethanol to yield alcohol. Alcohol was treated with aldehyde to produce benzaldehyde, which is then condensed with thiazolidinedione to produce alkene. Following alkene reduction,

rosiglitazone had a 26% total yield. Despite the fact that it is a four-step technique, it requires hazardous reagents like NaH and piperidine and takes 36 hours to complete the entire process. This method employs a series of sophisticated chromatographic separation and purification steps.

Structure of Rosiglitazone

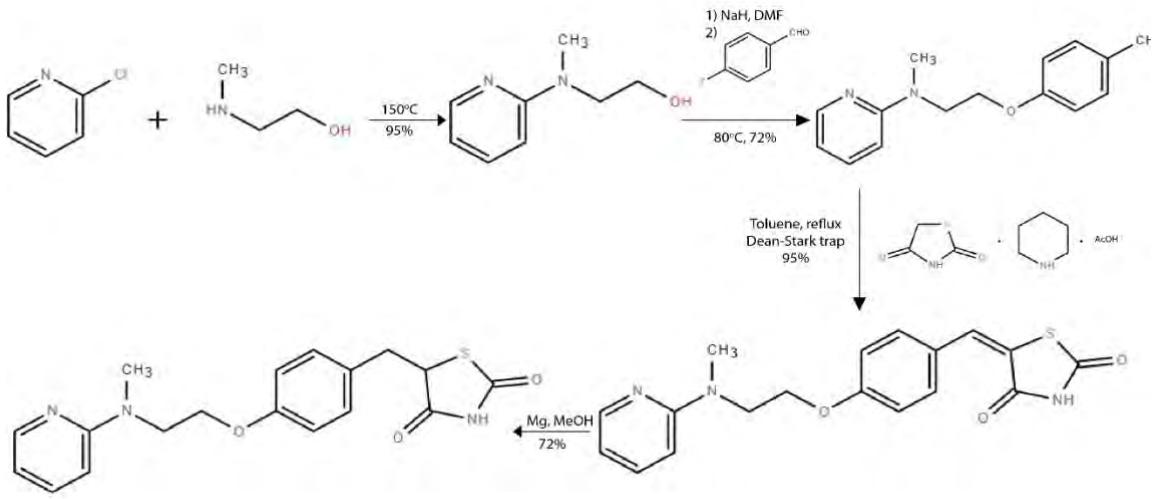


Figure 3: Synthesis of Rosiglitazone (Jawale et al., 2012)

2.2.2 Pioglitazone

The FDA approved pioglitazone, marketed as Actose, in 1999, and it has since been approved in 45 countries, including Europe, India, Canada, and Japan (Shodhganga: A Reservoir of Indian Theses @ INFLIBNET, 2023). When insulin is present, the thiazolidinedione ACTOS is able to exert its beneficial effects on diabetes (Pioglitazone, 2017). Increased insulin-dependent glucose disposal and lower hepatic glucose production are the results of

pioglitazone's reduction of insulin resistance in the periphery and the liver (Vardanyan & Hruby, 2016). Pioglitazone also does not have any known severe interactions with other drugs (Pioglitazone, 2017). It is synthesized pioglitazone by treating with fluoronitrobenzene to produce nitro compound. Following nitro group reduction, amine was produced, which was then diazotized and Meerwein arylated to provide alpha promo ester. Following -bromo ester cyclization with thiourea, imino-thiazolidine was obtained, which was then hydrolyzed to produce pioglitazone in a 24% total yield.

Structure of Pioglitazone

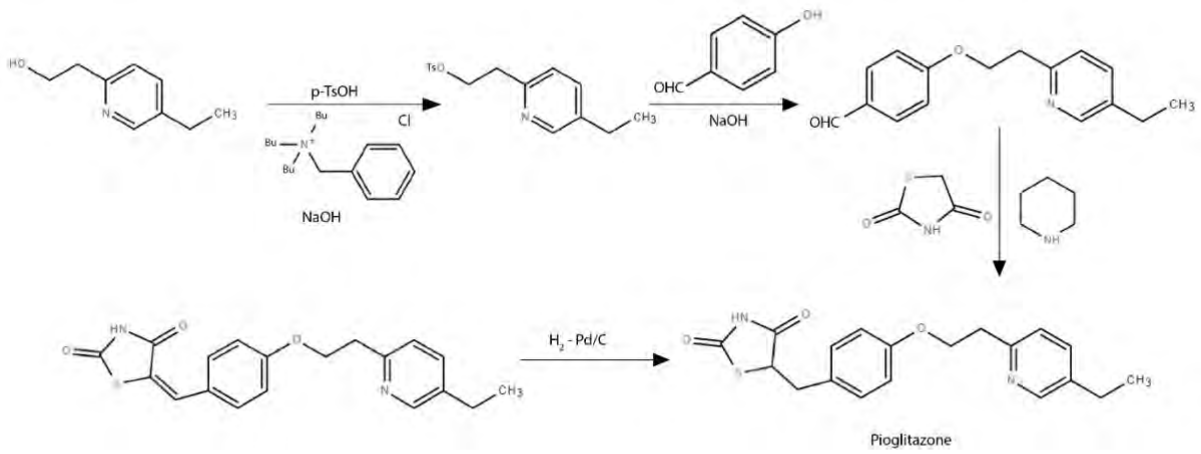


Figure 4: Synthesis of Pioglitazone (Vardanyan & Hruby, 2016)

2.3 Meglitinides

Meglitinides, commonly referred to as glitinides, are an oral medicine used to treat type 2 diabetes mellitus. They are insulin secretagogues with brief half-lives, similar to sulfonylureas

(White et al., 2014). The two main analogues of this class are nateglinide and repaglinide. The FDA initially approved repaglinide, the first drug in the class, in 1997. Nateglinide received FDA approval two years later, in 2000 (White et al., 2014). Here, synthetic approaches to repaglinide and nateglinide are reviewed.

2.3.1 Nateglinide

In 1989, Toyoshima and his team found two methods for producing nateglinide starting with cumic acid and perillic acid (SHINKAI et al., 1989). The drug nateglinide helps the body control how much sugar is in the blood. It makes the pancreas make more insulin, which lowers the amount of glucose in the blood. Beta cells in the pancreas have an ATP-sensitive potassium (K+ATP) channel that Nateglinide can interact with. When a beta cell's membrane potential drops, a calcium channel opens, allowing calcium into the cell and triggering insulin secretion (Hu, 2002). STARLIX (nateglinide) is an oral blood sugar-lowering drug in a group called "glinides." In their first method, they hydrogenated cumic acid in the presence of PtO to make a mixture of equal parts cis-trans acids and carboxylic acids. The combination of cis-trans carboxylic acids was esterified with VeOH to make cis-trans esters, then isomerized with NaH to make a mixture of 1:6 cis-trans-methyl esters. The trans-cis-methyl esters were then broken down by water by crystallizing the trans-acid isomer. After activating the trans-acid with DCC, the methyl ester was added to make nateglinide ester. By breaking down the nateglinide ester with water, 21% of nateglinide was made in the end. Without using chromatography, recrystallization was used to clean up nateglinide and its intermediates. This method has a number of problems, such as the fact that it takes a long time and has many steps, the use of pyrophoric NaH, which makes the reaction hard to handle on a large scale, the dissolution of methyl ester under vacuum environment distillation during purification, using DCC, a very hydroscopic and acute irritating compound, which is difficult to manage on a big scale, and

combining hydrogen with Adams catalyst, which is very dishonorable and leads to toxic byproducts, are both examples of bad practice (Figure: 05).

Structure of Nateglinide

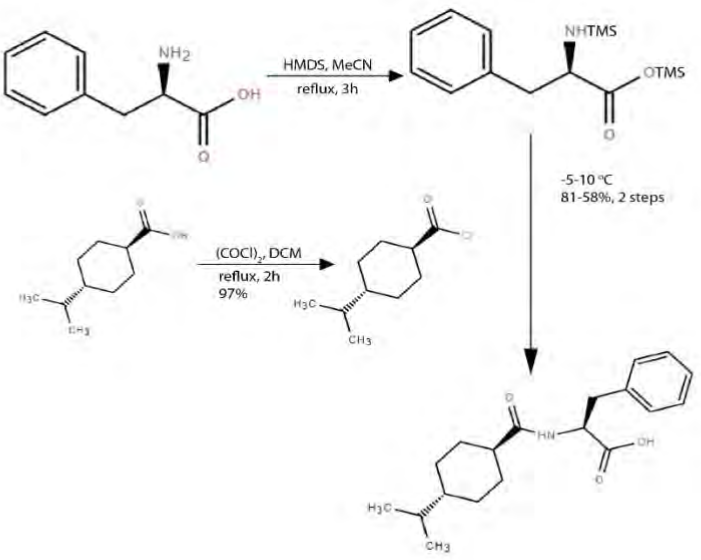


Figure 5: Synthesis of Nateglidin (Sagandira et al., 2021)

2.3.2 Repaglinide

It takes two steps to prepare repaglinide (Sagandira et al., 2021). Alternative acid-activating agents, such as DCC and CDI, are utilized in the first step in place of PPh3 to produce phenyl acetic acid amidation starting with organocatalytic PPh3/CCl4-mediated amidation to produce amide. Following acidification and ethoxycarbonyl group hydrolysis, repaglinide was produced in a 75% overall yield. The method has flaws, including the use of a pricey, poisonous, and very moisture-sensitive DCC, and the creation of the by-products DCU and Ph3PO, which necessitates time-consuming product purification. Furthermore, CCI4 is undesirable for large-scale production since it is harmful to ecosystems and human health. A cost-effective and commercially viable synthetic method for repaglinide was developed in

2003. (Sagandira et al., 2021) It is similar to the one below with the exception of the use of PivCl for carboxylic acid activation during the amidation step. Repaglinide is available with a 99.5% purity total yield of 67% (Sagandira et al., 2021).

Structure of Repaglinide

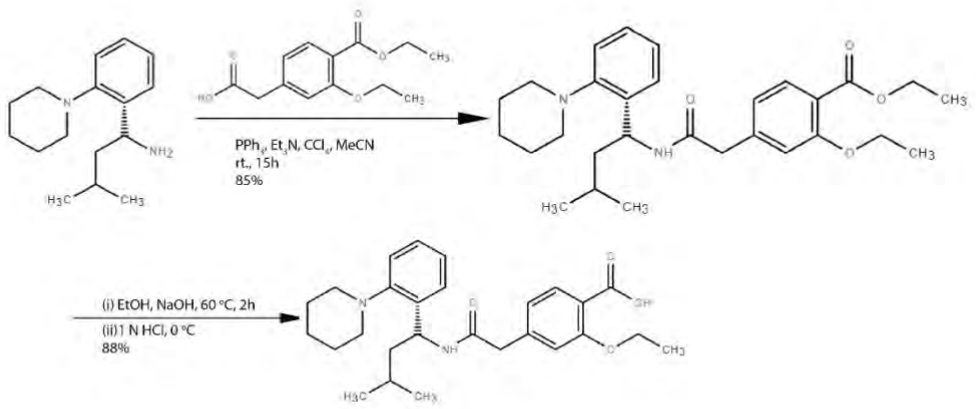


Figure 6: Synthesis og Repaglidine (Sagandira et al., 2021)

2.4 Dipeptidyl Peptidase 4 (DPP-4) Inhibitors

Gliptins, sometimes referred to as DPP-4 inhibitors, are a type of orally taken anti-diabetic medications that were initially developed in 1998 for the purpose of treatment of type-2 diabetes (Alcántara & Alcántara, 2017). These medications provide a number of advantages over conventional anti-diabetic medications, including no weight gain and fewer hypoglycemic spells (Hansen et al., 2009). There are now 17 gliptins that have been found and received FDA approval for use (Alcántara & Alcántara, 2017). The most popular medications for treating type-2 diabetes are sitagliptin, vildagliptin, saxagliptin, linagliptin, and alogliptin; two of their synthetic methods will be discussed here (S et al., 2019).

2.4.1 Sitagliptin

The first medicine under the gliptins to receive US FDA approval was sitagliptin, which is marketed as Januvia and Janumet (Alcántara & Alcántara, 2017). With compound lithiation as the first step, the 2, 4, 5-trifluorobenzyl bromide treatment follows to complete the sitagliptin synthetic process. Providing a compound ring opening with HCI and then Boc-protection. Following homologation to produce B-amino acid, ester hydrolysis of the molecule produced Boc-protected amino acid (Biftu et al., 2007). When HOBt and EDC were present, the ß-amino acid was coupled to produce compound. Fumarate salt of sitagliptin was produced with a yield of 11% after the product underwent boc-deprotection and fumaric acid treatment (Figure: 07). The usage of corrosive, combustible, and pyrophoric n-BuLi and protective group chemistry are among the disadvantages of the method. This process uses a number of chromatographic treatment processes, posing a challenge to its industrial scale applicability (Biftu et al., 2007).

Structure of Sitagliptin

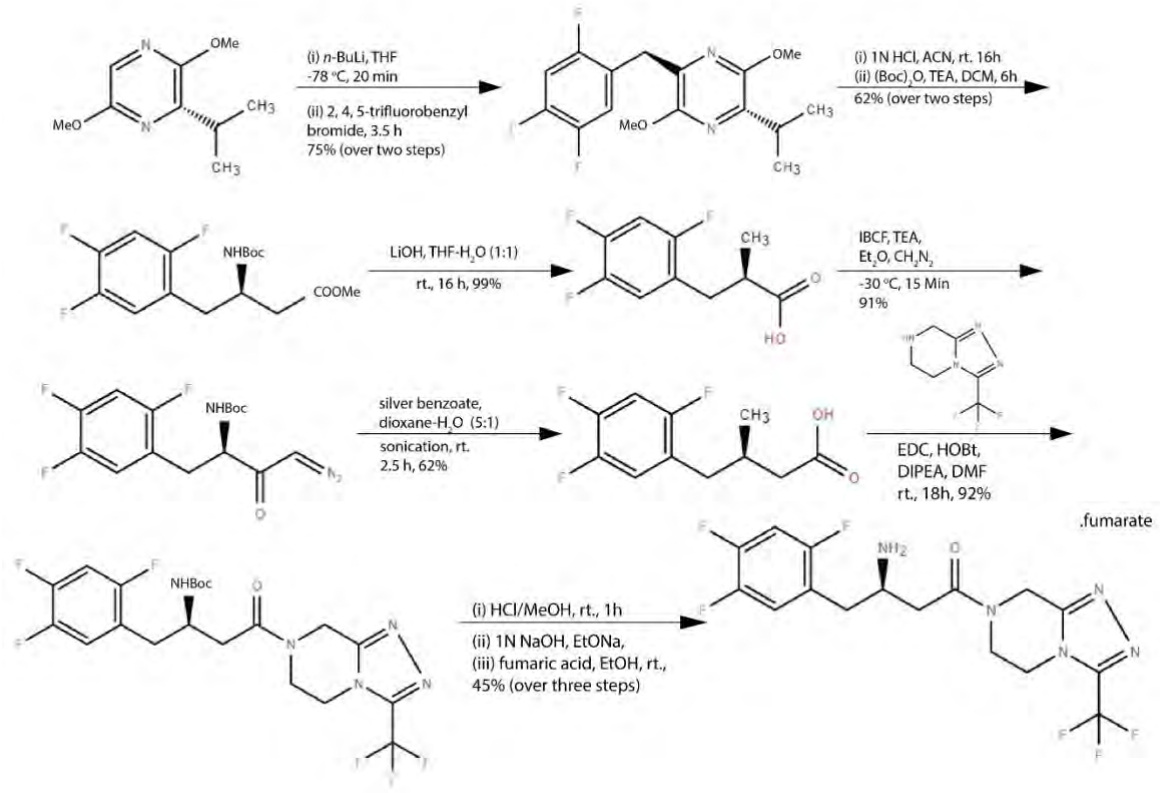


Figure 7: Synthesis of Sitagliptin (Biftu et al., 2007)

2.4.2 Vildagliptin

Vildagliptin, sold under the brand names Zomelis and Galvus, was the first gliptin in the cyanopyrrolidine class to gain FDA approval for the treatment of type 2 diabetes. In 2008, the European Medicines Agency (EMA) authorized the medication that Novartis had first found (Alcántara & Alcántara, 2017).

L-prolinamide is acylated to carboxamide during the initial stage of the drug's synthesis (Villhauer et al., 2003). The resultant dehydration of carboxyamide yields nitrile. Finally, using the molecule produced a 23% total yield of vildagliptin (Figure: 08). Without the use of chromatography, all four intermediates can be achieved. The method, however brief, employs chloroacetyl chloride, which is air and moisture sensitive (Villhauer et al., 2003).

Structure of Vildagliptin

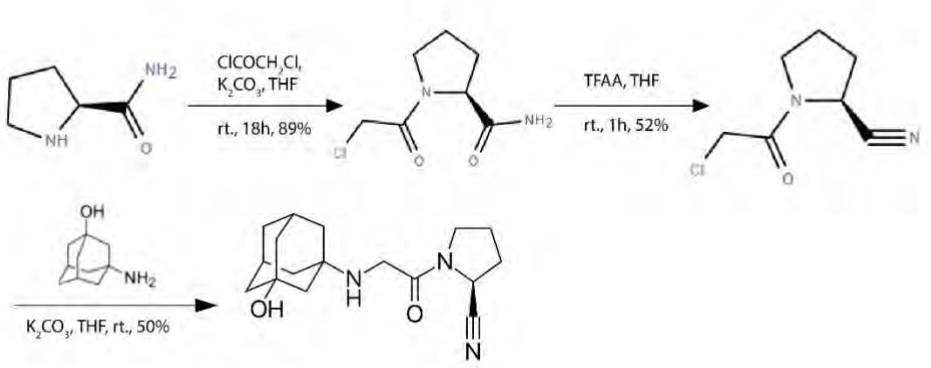


Figure 8: Synthesis of Vildagliptin (Villhauer et al., 2003)

2.5 Sodium Glucose Transporter Inhibitors

Anti-diabetic drugs called sodium glucose transporter-2 inhibitors work by obstructing the transfer of glucose from the kidneys back into the blood stream. Dapagliflozin, canagliflozin, ipragliflozin, ertugliflozin, and empagliflozin are five of the gliflozins that have been licensed for prescription use and are discussed here. The three processes involved in the chemical synthesis of gliflozins are the building of the aryl substituent, glycosylation of the aryl substituent, and final step of deprotection and anomer-center alteration of the arylated sugar to achieve the desired result (G.L Larson, 2015).

2.5.1 Dapagliflozin

From commercially available 5-bromo-2-chlorobenzoic acid, dapaglilozin is synthesized (Sagandira et al., 2021). To afford, carboxylic acid was first acylated with (COCI)2, then Friedel-Crafts acylated with phenetole. Reduction of carbonyl groups with Et_3SiH/BF_3. Et2O was produced next, and the intermediate was treated with the iron gluconolactone silylation that was acquired before being treated with MSA to produce the result of the second stage. Following treatment with Et3Si3F3.Et_2O and acetylation, the founded product produced tetraacetylated beta-C glucoside. Dapagliflozin was created by compound deacetylation and

was 94% pure. Dapagliflozin was successfully synthesized, however the approach had a number of problems, including very long reaction durations, the use of a strong base for deacetylation (LiOH), which causes product degradation, and the use of hazardous (COCI)2. Additionally, the method is undesirable on an industrial scale due to the employment of protective groups (Sagandira et al., 2021) (Figure: 09).

Structure of Dapagliflozin

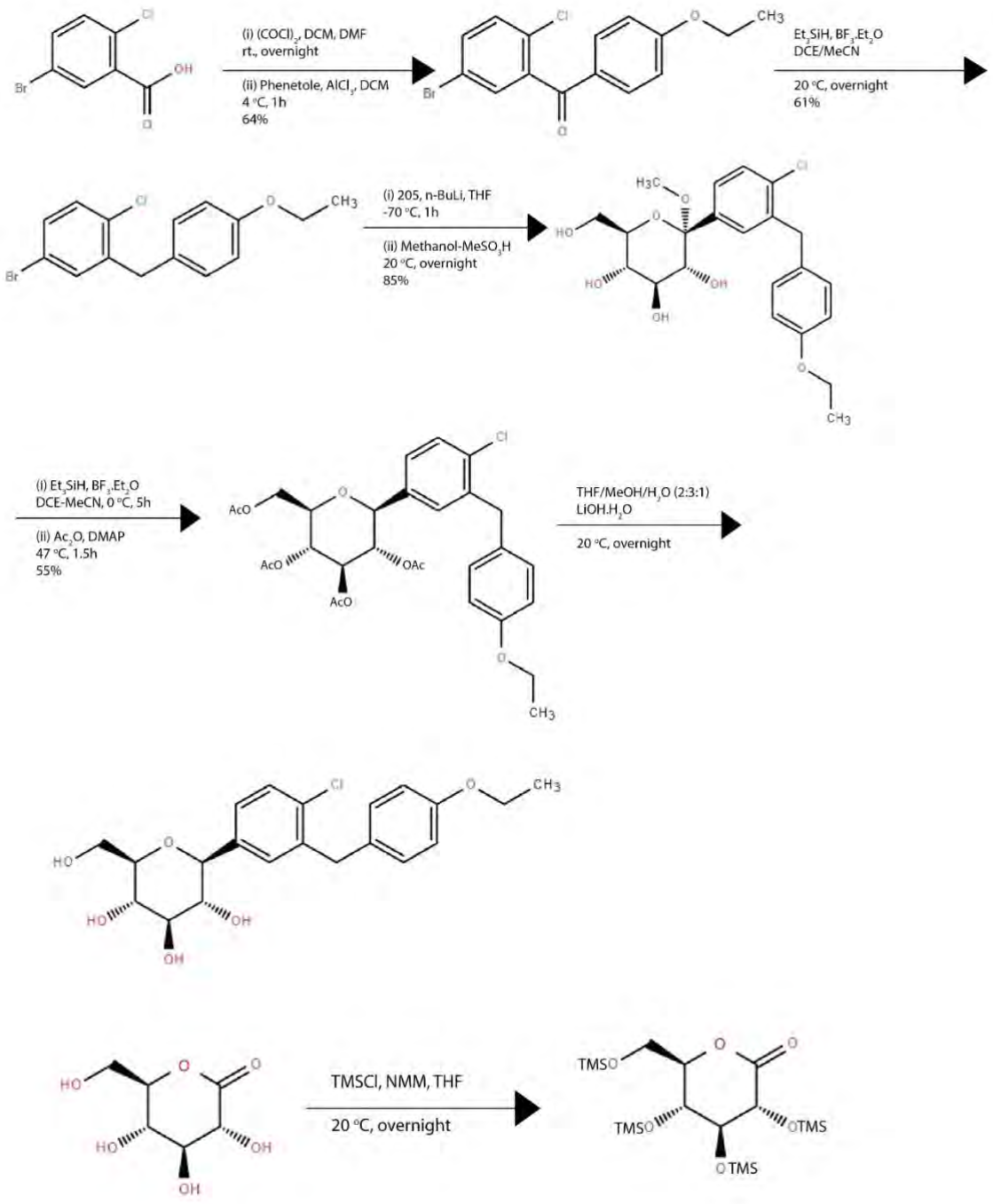


Figure 9: Synthesis of Dapagliflozin ***(Sagandira et al., 2021)***

2.5.2 Canagliflozin

First, benzoic acid was acylated to benzoyl chloride, and then ketone was made by performing a Friedel-Crafts acylation with thiophene (Nomura et al., 2010). Thiophene aglycon was produced by reducing a ketone with Et_3SiH/BF_3OEt_2. Following lithiation, protected

gluconolactone and desilylation were applied to lithiated thiophene aglycor to generate methyl ester. Finally, canagliflozin was obtained in 34% overall yield through the stereoselective reduction of methyl using Et_3SiH/BF_3OEt_2 (Nomura et al., 2010) (Figure: 10).

Structure of Canagliflozin

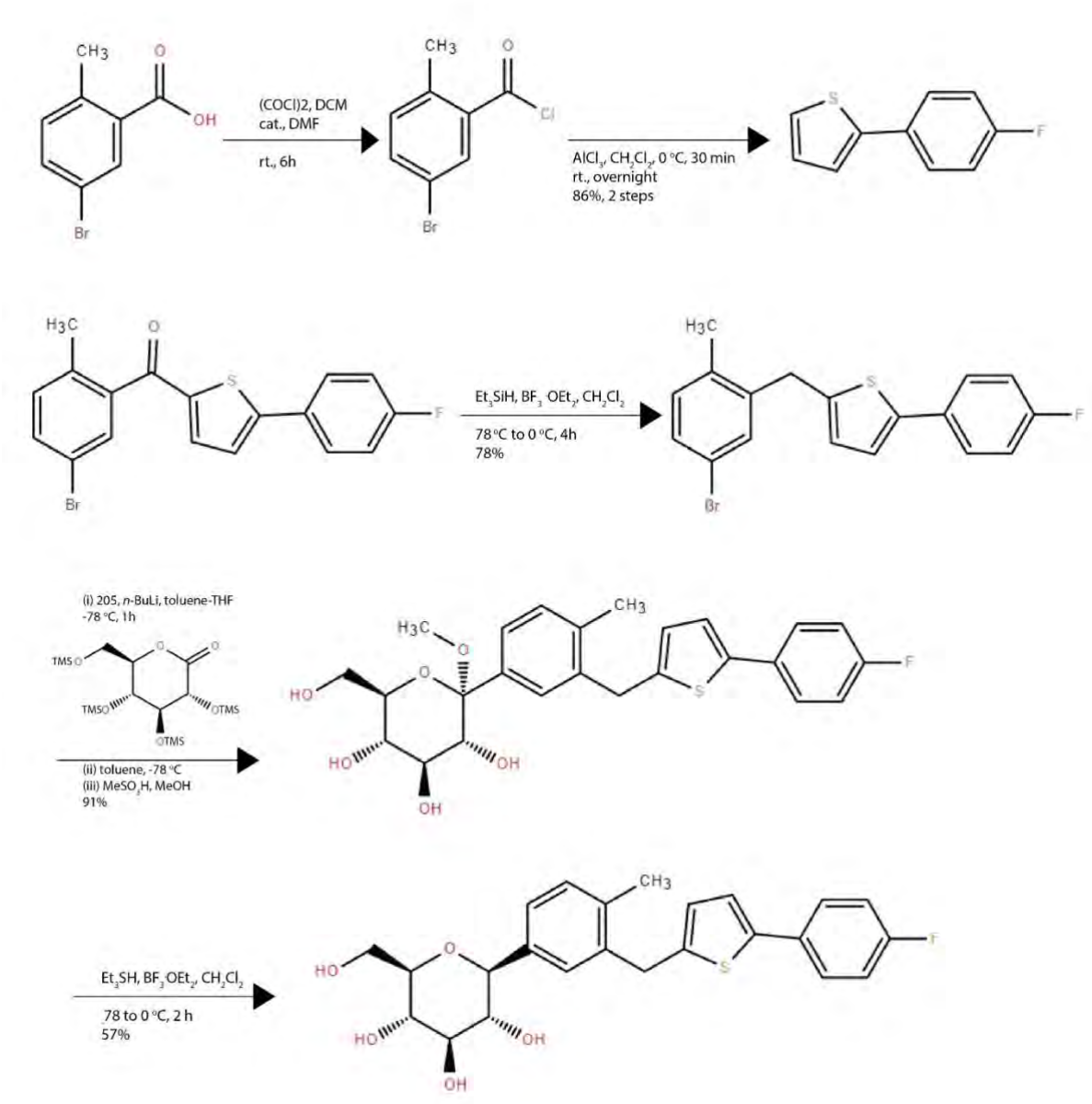


Figure 10: Synthesis of Canagliflozin (Nomura et al., 2010)

2.6 Alpha Glucosidase inhibitors

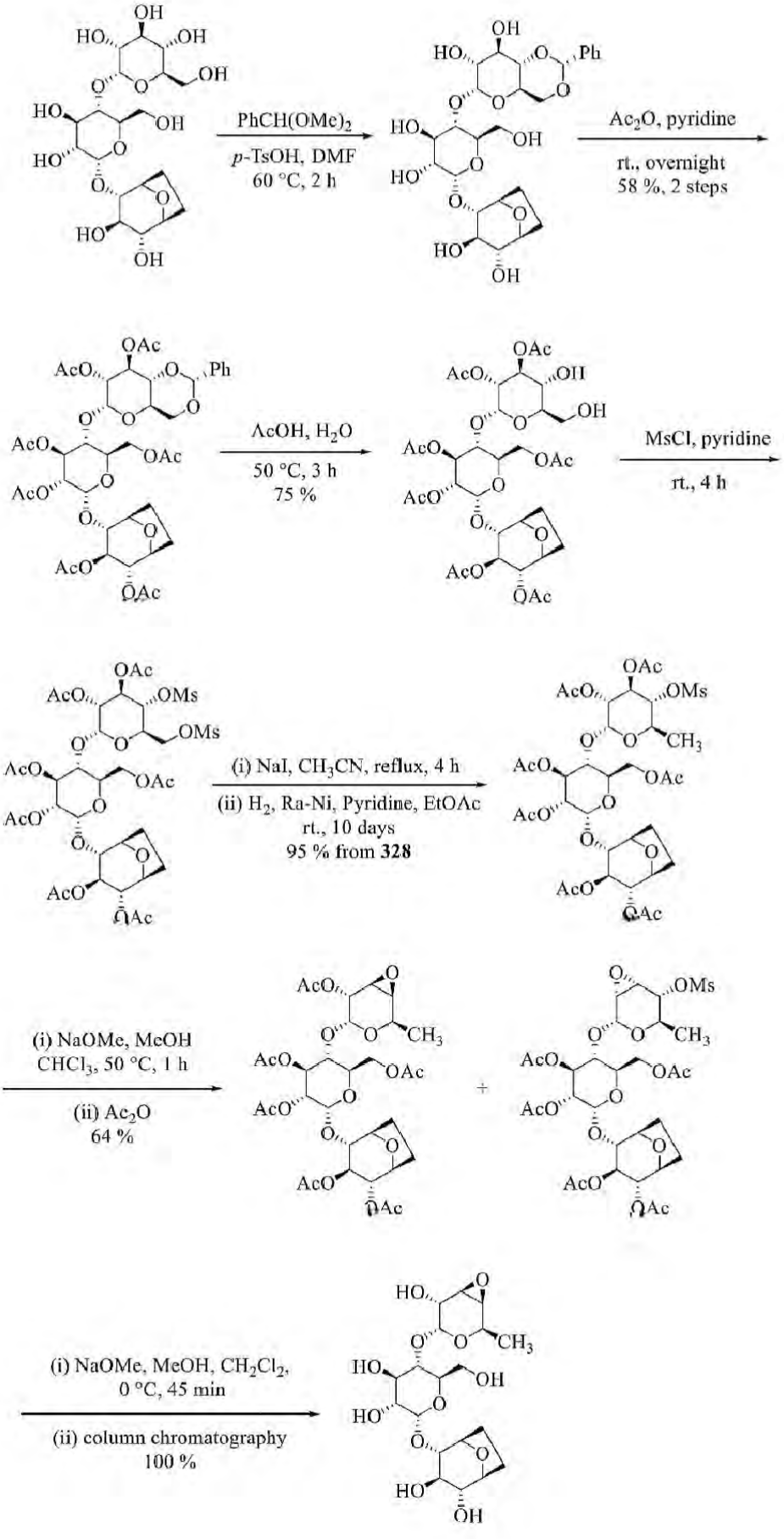
Through the competitive and reversible suppression of intestinal alpha-glucosidase enzyme activity, type 2 diabetes is treated with alpha glucosidase inhibitors (Kumar Thakur et al., 2018), (Patil et al., 2015). Glucoamylase, sucrase, maltase, and isomaltose are examples of alpha glucosidase enzymes that transform complex non-absorbable carbohydrates into absorbable monosaccharides (Kumar Thakur et al., 2018). Therefore, inhibiting these enzymes causes a delay in the digestion of carbohydrates, which lowers postprandial hyperglycemia and insulin levels (Kumar Thakur et al., 2018). This class of medications includes the oral formulations of acarbose, voglibose, and miglitol. Here, a review of two of their synthetic routes is provided.

2.6.1 Acarbose

The pseudo-tetrasaccharide acarbose, which is sold by Bayer under the trade name Precose, was first isolated in the 1970s and received US FDA approval in 1995 (Alanzi et al., 2018). In 17 steps, it can be made from 1, 6-di-O-acetyl-2, 3, 4-tri-0 penzyl-d-glucopyranose. To obtain a mixture of trisaccharide epimers, it was first condensed with the protected 1, 6-anhydromaltose (Shibata & Ogawa, 1989). Debenzylated trisaccharide was produced by hydrogenolysis with Pd/C of the required isomer, which was then converted into 1, 6-anhydromaltotriose via O-deacetylation. With hCH(OMe)2 and p-TsOH, 1,6 anhydromaltotriose was monobenzylidenated to produce 4,6-cyclic acetal, which was then acetylated to hepta-acetate. Nepta-acetate was then hydrolyzed in an acidic solution to produce diol, which was subsequently mesylated to produce bismesylate. Bis-mesylate was converted into a mesylate derivative through primary mesyl group displacement with Nal, followed by hydrogenolysis using a raney nickel catalyst. The intended epoxide was produced as the main by-product of the desired epoxide after the desired mesylate derivative was epoxylated,

reacetylated, and afforded the desired 3, 4-epoxide. The chiral azido cyclohexene derivative was reacetylated in parallel to produce a protected valienamine intermediate. The resulting azido tetraol was then ketalized, and the ketal-protected azide was then reduced with H2S. A mixture of 3- and 4-substituted adducts were produced when 4, 7:5, 6-di-O-isopropylidene-valienamine was reacted with epoxide. These adducts were then subjected to acidic ketal hydrolysis to produce the corresponding pseudo-tetrasaccharide derivatives. The desired regioisomer was obtained by acetylating the resultant adducts and purifying them using column chromatography. Acarbose peracetate ester was produced using acetolysis. The title chemical, acarbose, was produced by further methanolysis of the ester groups and was originally synthesized in a 0.1% overall yield. However, the lengthy synthetic approach and lengthy reaction times, the requirement for chromatography to purify the majority of intermediates, and the need for protective chemicals make it unsuitable for mass production (Shibata & Ogawa, 1989) (Figure: 11).

Structure of Acarbose


PhCH(OMe)2
p-TsOH, DMF
60 °C, 2 h
Ac2O, pyridine
rt., overnight
58 %, 2 steps
AcOH, H2O
50 °C, 3 h
75 %
MsCl, pyridine
rt., 4 h
(i) NaI, CH3CN, reflux, 4 h
(ii) H2, Ra-Ni, Pyridine, EtOAc
rt., 10 days
95 % from 328
(i) NaOMe, MeOH
CHCl3, 50 °C, 1 h
(ii) Ac2O
64 %
(i) NaOMe, MeOH, CH2Cl2,
0 °C, 45 min
(ii) column chromatography
100 %

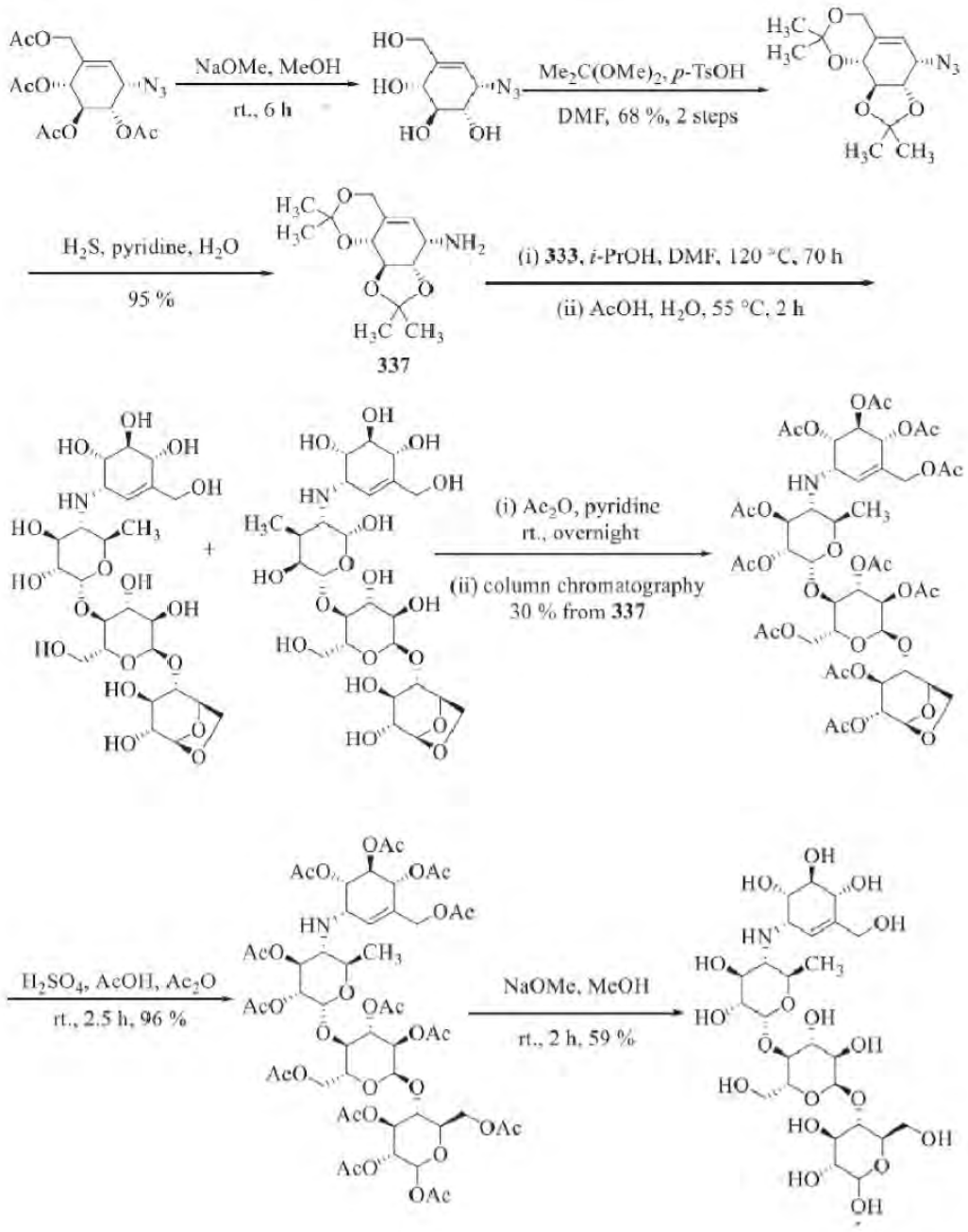


Figure 11: Synthesis of Acarbose (Shibata & Ogawa, 1989)

2.6.2 Voglibose

Voglibose is manufactured from valiol-amine. Using 3, 5-di-t-Butyl-1, 2-benzoquinone, valiolamine is oxidized to produce an imine intermediate, that is hydrolyzed to produce the important intermediate valiolone (Floss & Lee, 2000). The yield was not recorded when valiolone was treated with 2-amino-1,3-propanediol while $Na(CN)BH_3$ was present. This method is quick and just requires two steps. Single column chromatography is used, however the process is straightforward and has quick reaction times (Figure: 12).

Structure of Voglibose

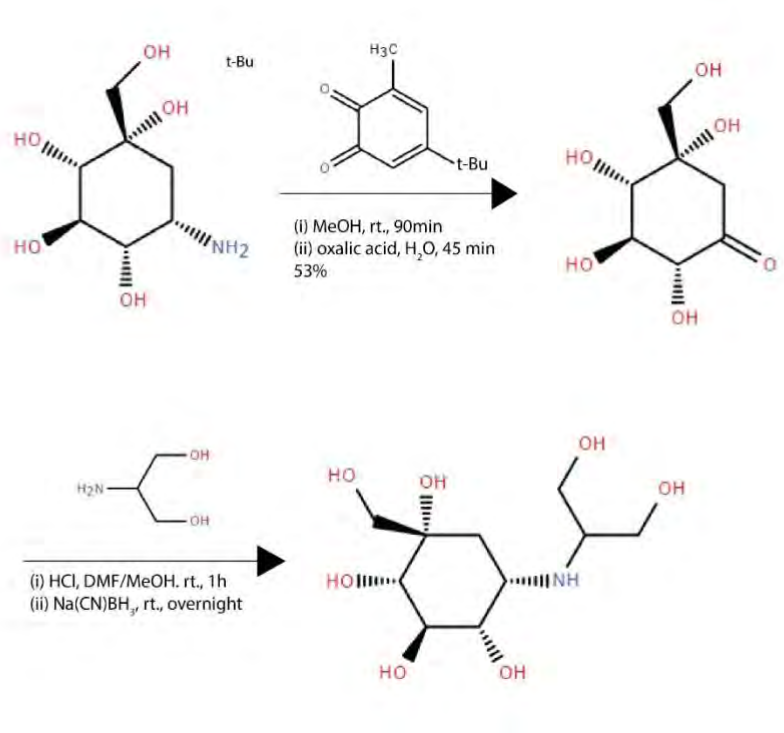


Figure 12: Synthesis of Viglibose (Floss & Lee, 2000)

2.7 Biguanides

Since biguanides can not excite e pancreatic β cells and only rarely result in hypoglycemia, they are regarded as antihyperglycemic rather than hypoglycaemic drugs (Sofer et al., 2014). This class works by enhancing peripheral glucose absorption and decreasing hepatic glucose synthesis (Sofer et al., 2014), (Rosa & Dias, 2014). Stumbled upon in the 1950s, this class of medications includes metformin, buformin, and phenformin. However, because of the high danger of lactic acidosis, phenformin and buformin were later removed off the international market (Rosa & Dias, 2014). I'll go into the chemical production of metformin in this section.

2.7.1 Metformin

A first-line biguanide-class oral antidiabetic medication called metformin is helpful to treat type-2 diabetes. In 1972, the Canadian government gave it the go-ahead for use, and the US FDA followed suit in 1994 (Sekhar et al., 2014). Metformin can be prepared via a green, microwave-assisted synthetic process on thin-layer chromatography plates (Shalmashi, 2008). By microwave irradiating a spot solution of 2-cyanoguanide and dimethylamine hydrochloride on TLC, metformin was produced with a 92% yield. The advantages of this approach include a straightforward process setup, quicker reaction times, smaller (milligram) reagent and solvent quantities, and excellent product purification requiring filter screening (Figure: 13) (Shalmashi, 2008).

Structure of Metformin

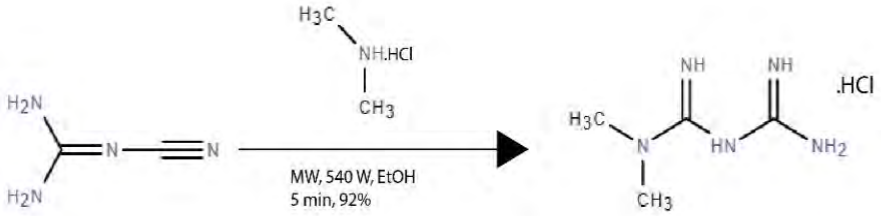


Figure 13: Synthesis of Metformin ***(Shalmashi, 2008)***

CHAPTER 3

Alternative Synthetic Route of Anti-Diabetic Drugs

Biological activity can be predicted from molecular structure using alternative synthetic route with the use of this potent technology, desirable new compounds can be synthesized or purchased, and old molecules can be given additional details. Proper knowledge of alternative synthetic routes of anti diabetic drugs can help finding an alternative and more efficient way to prepare an anti diabetic drug that can have easier synthetic route, better time and cost efficiency in production, better therapeutic effect, fewer side effects etc. Alternative synthetic routes of afore mentioned anti diabetic drugs are discussed below.

3.1 Alternative Synthetic Route of Sulfonylureas

3.1.1 Alternative Synthetic Route of Gliclazide

Through this synthesis method, gliclazide can be obtained in high yield by reacting hydrazide amide with cyclopentane (Sagandira et al., 2021). The high product yield, low environmental impact, and enhanced safety of this approach make it a promising candidate for large-scale industrial synthesis of gliclazide 1. In addition, the usage of an amino heterocycle, which is notoriously vulnerable to oxidation, is not required (Sagandira et al., 2021) (Figure: 14).

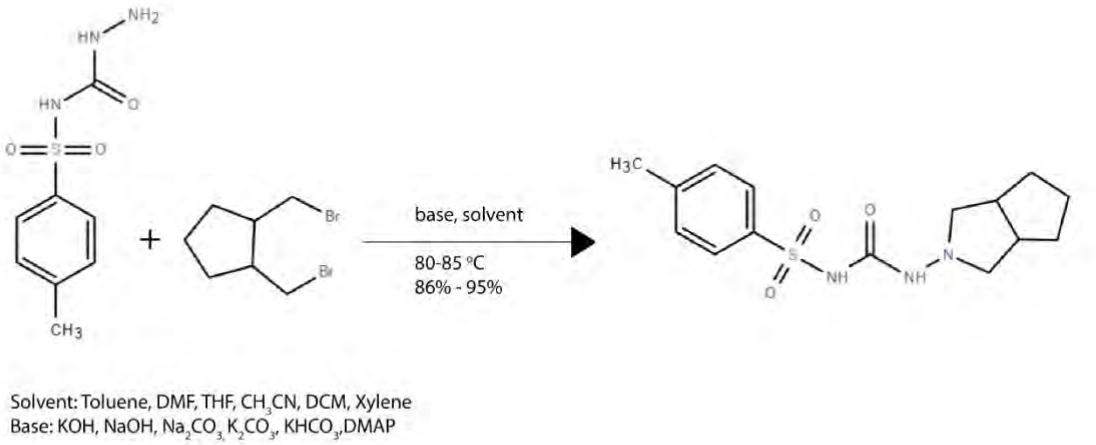


Figure 14: Alternatve synthetic route of Gliclazide *(Sagandira et al., 2021)*

3.1.2 Alternative Synthetic Route of Glipizide

This synthesis approach reveals a practical method for reaching glipizide that does not require the use of a protective group (Furman, 2007). Initial amidation of amino acid with carboxylic acid afforded amide, which was then treated with isocyanate to give glipizide in an overall yield of 82%. This method is preferable because it sidesteps the protection group chemistry and produces a high yield overall. However, it requires the use of a potentially dangerous isocyanate (Furman, 2007) (Figure: 15).

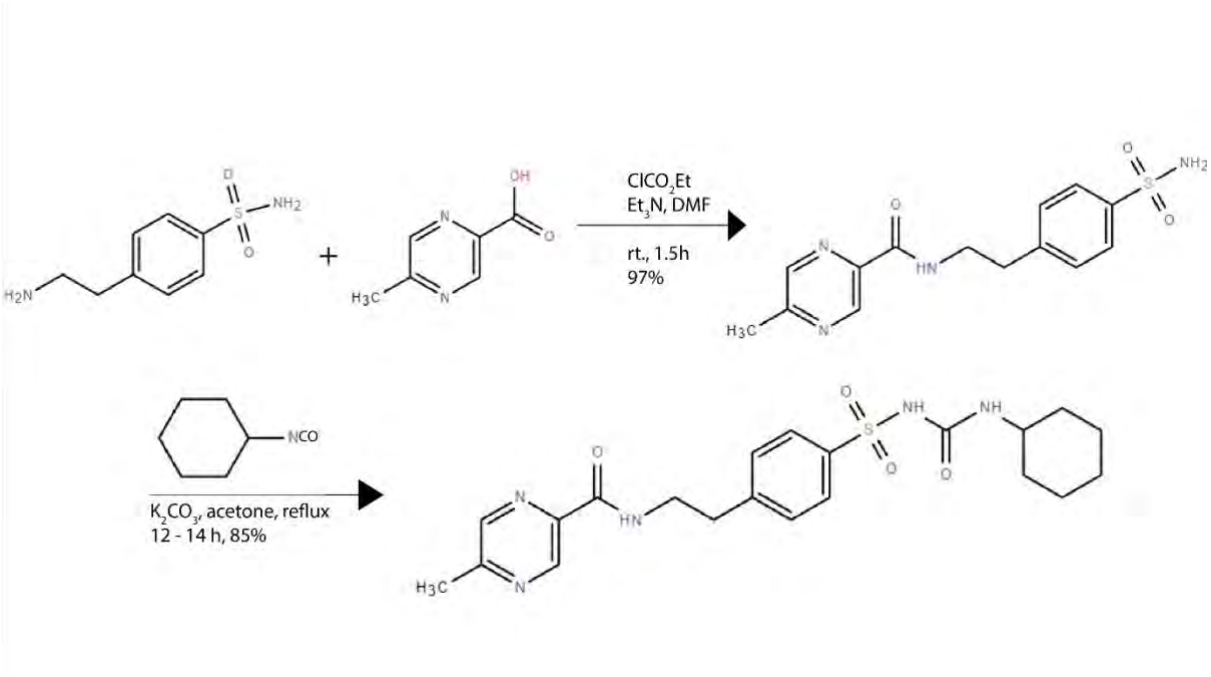


Figure 15: Alternative synthetic route of Glipizide (Furman, 2007)

3.2 Alternative Synthetic Route of Thiazolidinediones

3.2.1 Alternative Synthetic Route of Rosiglitazone

This synthetic method to rosiglitazone is a four-step process designed to be both practical and scalable in order to address some of the shortcomings of the existing routes, such as increased reaction times, scale up issues, product contamination, and decreased yields (Jawale et al., 2012). At first in this process, Knoevenagel condensation of benzaldehyde was initiated. While that was going on, chloropyridine was being converted into alcohol (Jawale et al., 2012). In a 54% total yield without using any chromatographic methods, alcohol was treated with to afford an alkene, which was then reduced to afford rosiglitazone. Compared to a non-microwave aided process, the total reaction time was significantly shorter, which is appropriately 22 hours. Furthermore, toluene and acetic acid were swapped out with recyclable non-volatile deep eutectic solvent for Knoevenagel condensation, and the stronger base sodium hydroxide (NaH) was swapped out for the softer potassium carbonate (K2CO3) (Jawale et al., 2012) (Figure:16).

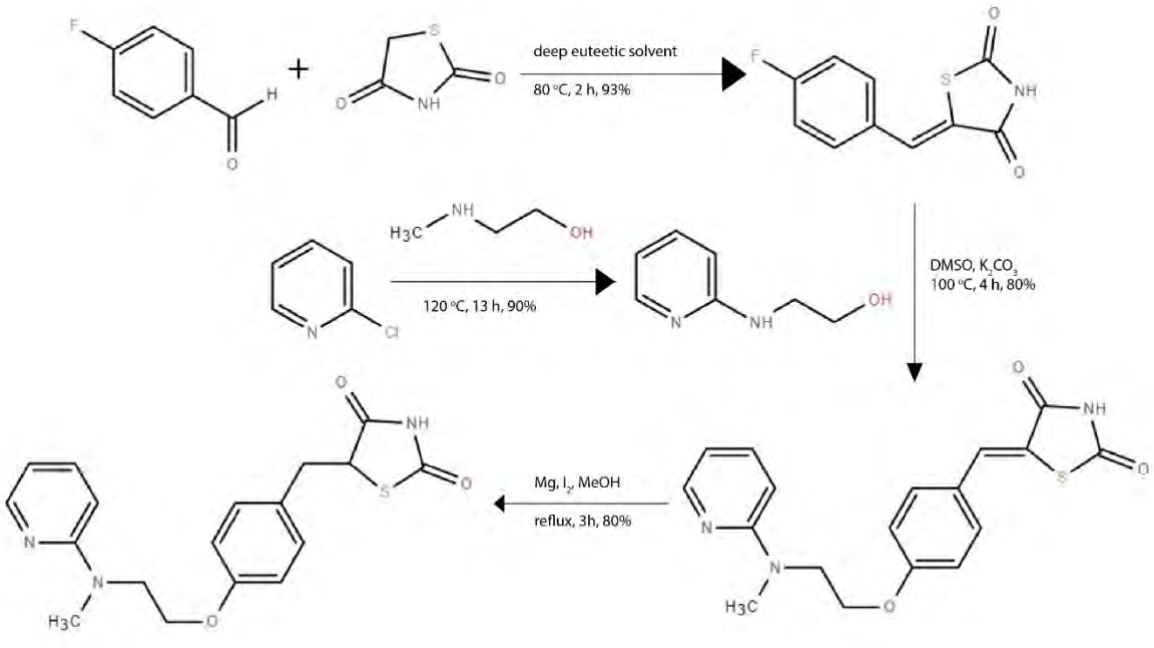


Figure 16: Alternative synthetic route of rosiglitazone (Jawale et al., 2012)

3.2.2 Alternative Synthetic Route of Pioglitazone

Six stages are involved in this synthetic process to produce pioglitazone, beginning with the bromination and hydrolysis of vinyl pyridine to provide bromohydrin. The chemical was obtained by reacting benzaldehyde with bromohydrin (Sagandira et al., 2021). Alkene was produced via a Knoevenagel condensation between the chemical and thiazolidinedione. Pioglitazone was obtained via reductive elimination from an alkene-derived intermediate that had been chlorinated. Without using chromatographic purification procedures, we were able to increase the overall yield of pioglitazone to 19% (Sagandira et al., 2021) (Figure: 17).

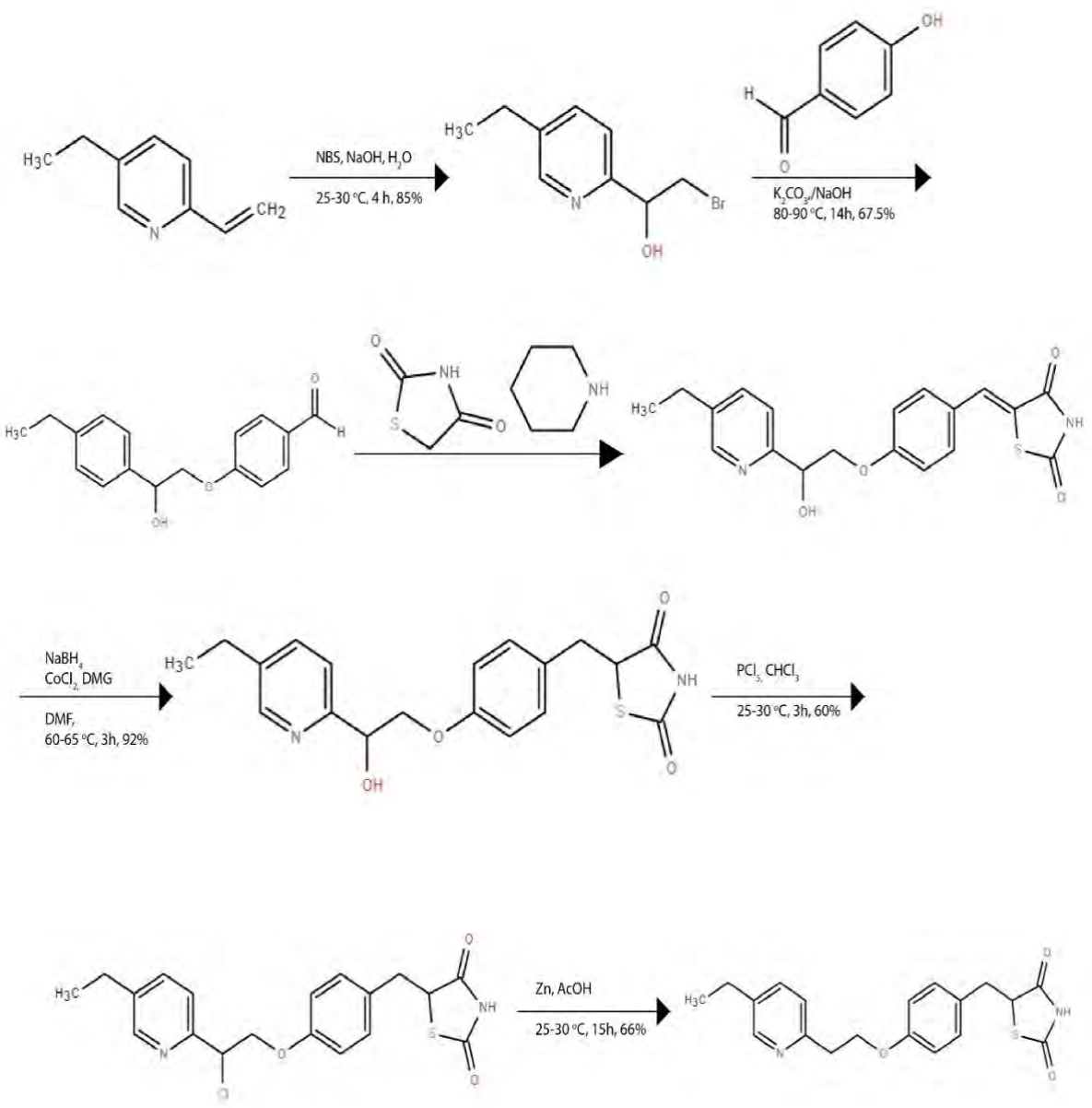


Figure 17: Alternative Synthetic route of Pioglitazone (i) (Sagandira et al., 2021)

A second approach for producing pioglitazone involves first treating with sulfonyl halide, which then allows for the treatment of with the resulting benzaldehyde (Sagandira et al., 2021). A 37% total yield of pioglitazone was obtained after the Knoevenagel condensation of benzaldehyde with thiazolidinedione produced an alkene (Sagandira et al., 2021) (Figure: 18).

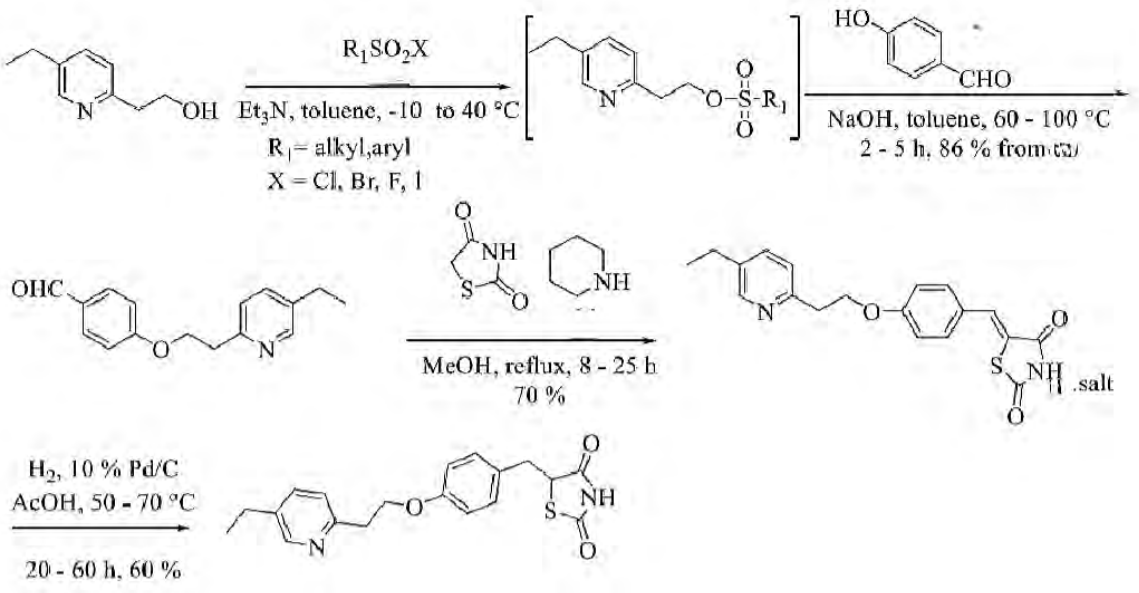


Figure 18: Alternative synthetic route of Pioglitazone (ii) (Sagandira et al., 2021)

3.3 Alternative Synthetic Route of Meglitinides

3.3.1 Alternative Synthetic Route of Nateglinide

Preparing nateglinide with (COCl)2 instead of chlorine dioxide is a time- and cost-effective option. N, O-bis trimethylsilyl D-phenylalanine was produced via silylation of Dphenylalanine with HMDS; this was followed by amidation with acyl chloride derived from carboxylic acid (Sagandira et al., 2021). Overall, a yield of 78%-82% was achieved, with a purity of >99.7% for nateglinide. (COCl)2 is corrosive and sensitive to moisture, just like the other chlorinating chemicals used in the manufacture of nateglinide. Although more transformations were incurred, the utilization of Diphenylalanine in its free amine form was avoided by resorting to the protective group chemical (Sagandira et al., 2021) (Figure: 19).

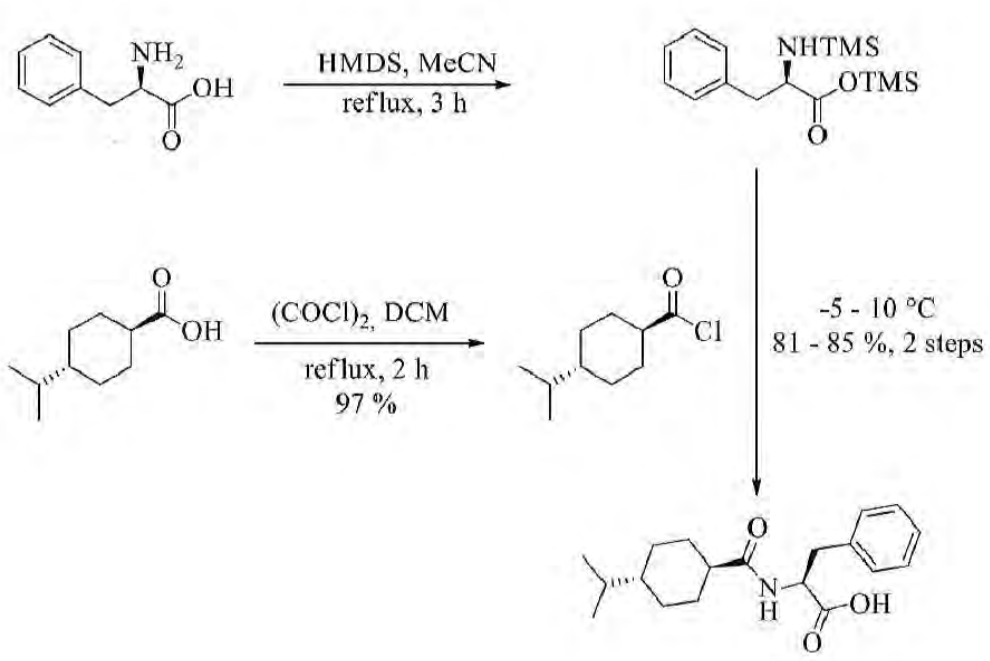


Figure 19: Alternative Synthetic route of nateglinide (Sagandira et al., 2021)

3.3.2 Alternative Synthetic Route of Repaglinide

The two-step synthetic technique using boric acid for the amidation is a less expensive option for producing repaglinide while still providing a useful and effective procedure (Sagandira et al., 2021). Avoiding the laborious purification normally associated with chemicals like DCC and PPh3 is achieved here (Sagandira et al., 2021). As a whole, we were able to produce 74% pure repaglinide, with a concentration of 99.8%. The intended product was obtained in good yield and purity using this method, and the capacity building processes, which include filtering and precipitation, were straightforward (Figure: 20) (Sagandira et al., 2021).

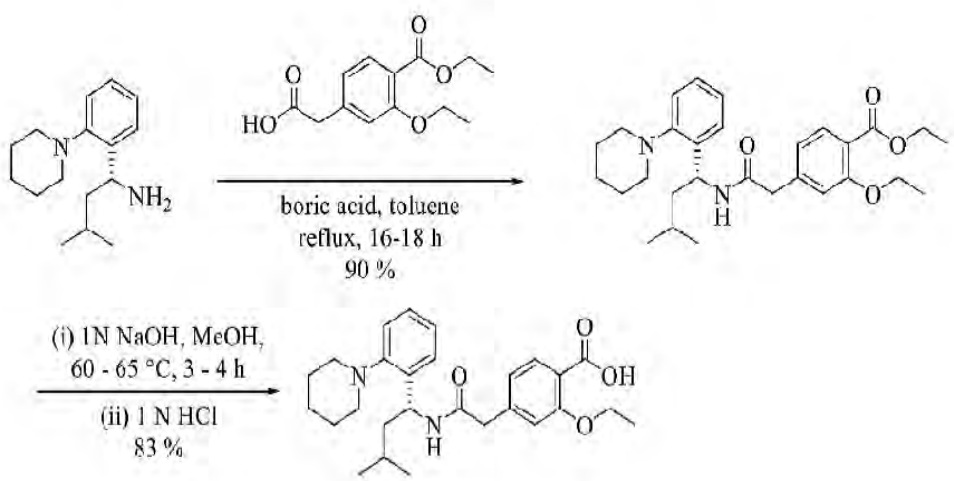


Figure 20: Alternative synthetic route of Repaglinide (Sagandira et al., 2021)

3.4 Alternative Synthetic Route of Dipeptidyl peptidase 4 (DPP-4) inhibitors

3.4.1 Alternative Synthetic Route of Sitagliptin

The safest and most eco-friendly synthetic pathway for sitagliptin, with higher yields, better chemical purity, and higher optical purity, is the one that has been developed for industrial manufacture of the drug sitagliptin. Combining triazolopiperazine with a BOC-protected molecule made it more cost-effective (Sagandira et al., 2021). In a two-step process including no chromatographic purification steps, BOC-deprotection of the molecule yielded sitagliptin with a 92% total yield. Consequently, the simplicity of the process makes it applicable to widespread synthesis. The addition of boronic acid, a cheap and widely accessible "green" catalyst, boosts the method's appeal (Sagandira et al., 2021) (Figure: 21).

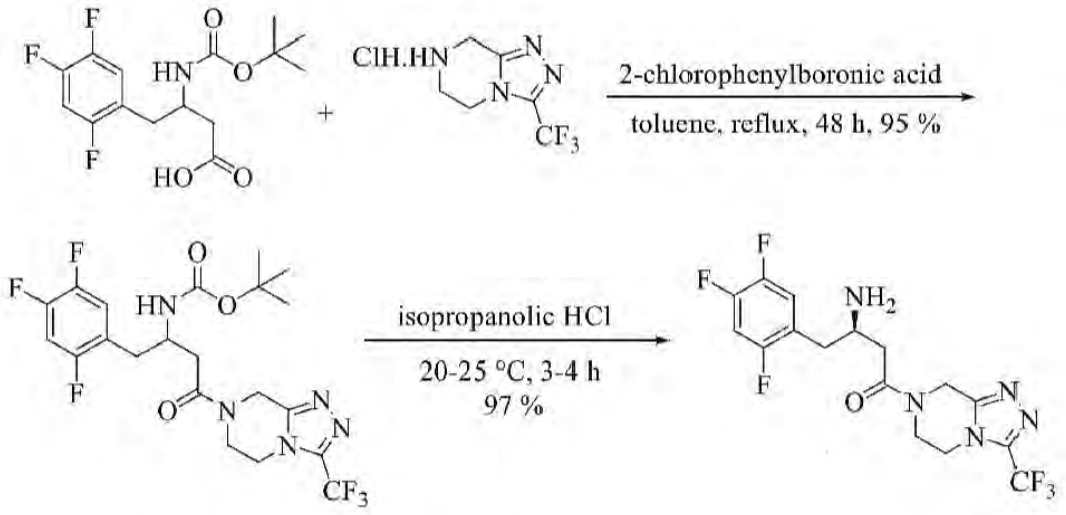


Figure 21: Alternative synthetic route of Sitagliptin ***(Sagandira et al., 2021)***

3.4.2 Alternative Synthetic Route of Vildagliptin

The first step in the synthesis of vildagliptin is the tosylation of hydroxy acetic acid to generate p-toluenesulfonate (Sagandira et al., 2021). After L-prolinamide amidation, amide was obtained, and cyanuric chloride dehydration led to nitrile. Finally, vildagliptin was made more affordable by consolidating it with nitrile. The total yield for it though 4-step, quick synthetic method was 42%. The final product was able to afford vildagliptin because of the decrease in di-substituted contaminants. This even helps cut down on di-substituted impurities, thus a highly pure chemical and visual product can be obtained without resorting to chromatography (Sagandira et al., 2021) (Figure: 22).

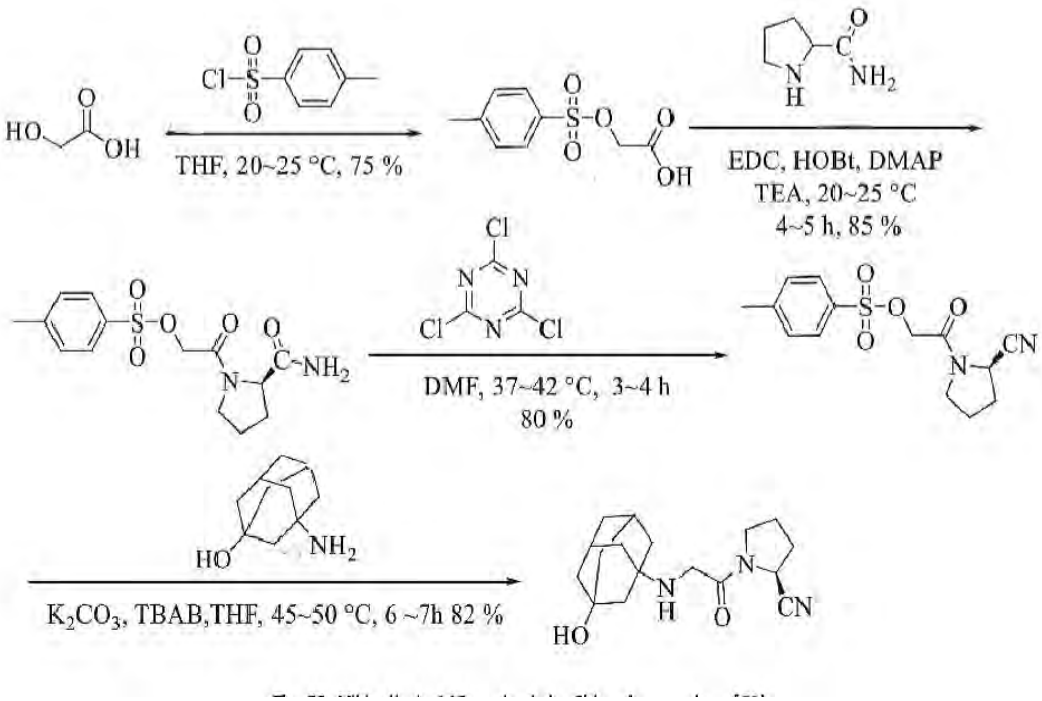


Figure 22: Alternative Synthetic Route of Vildagliptin (Sagandira et al., 2021)

3.5 Alternative Synthetic Route of Sodium Glucose transporter inhibitors

3.5.1 Alternative Synthetic Route of Dapaglifloz

In this section, I will discuss a practical synthetic approach to dapagliflozin. When gluconolactone is silylated, it is converted to lactol via a two-step process involving gluconolactone, lithiated aryl bromide, and desilylation (Yu et al., 2019). MSA is used to convert lactol into the more affordable C-aryl glucoside. By combining n-propanol and n-heptane, we are able to crystallize the crude oil and obtain intermediate as a crystalline n-propanol solvate with a purity of >98.5%. Finally, Et_3SiH/BF_3 is used for direct reduction of the molecule. High diastereoselective (b:a > 99:1) in the production of crude b-C-aryl glycoside was achieved using Et_2O. After crystallization with an ethyl acetate and n-heptane mixture, pure dapagliflozin is obtained with an overall yield of 62% and a purity of >99.7% (Yu et al., 2019). By minimizing the amount of water and n-propanol used in the process, the synthesis of dapagliflozin on a kilogram scale was successfully optimized. Additional benefits include the elimination of the need for column chromatography in the purification of intermediates. Unfortunately, protective group chemistry and extremely lengthy reaction times are insurmountable obstacles (Figure: 23).

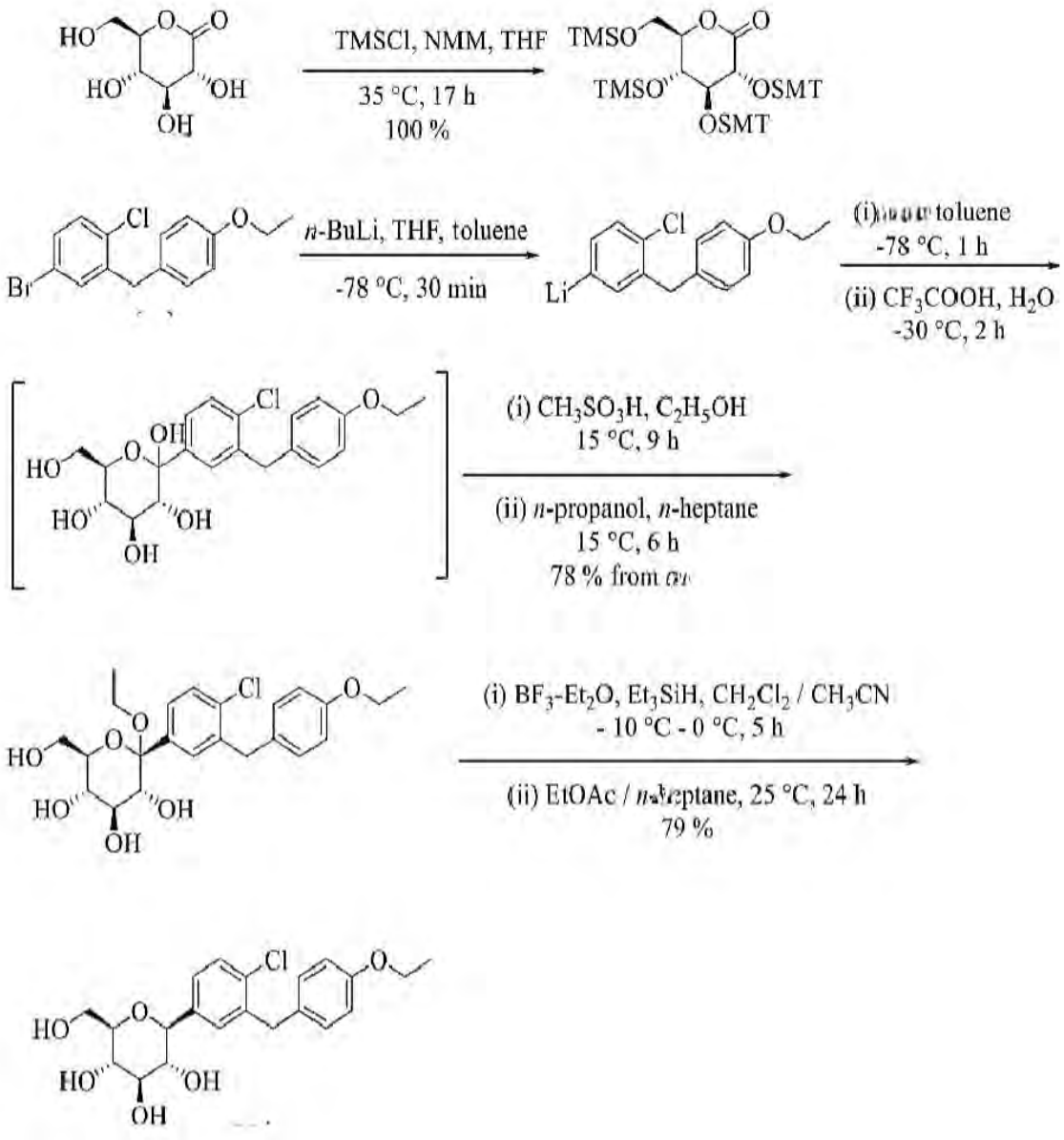


Figure 23: Alternative Synthetic Route of Dapagliflozin ***(Yu et al., 2019)***

3.5.2 Alternative Synthetic Route of Canagliflozin

Iron catalyzed cross coupling of glycosyl halide with aryl metal reagent is a very effective synthetic approach towards canagliflozin synthesis. The authors began with an aryl metal reagent, Ar_2Zn, to cross-couple glycosyl bromide (TMEDA) (Adak et al., 2017). The chemical can be obtained by reacting 2MgBrCl with an iron phosphine complex. Canagliflozin was obtained after the acetyl protecting groups were removed using trans-esterification with tin oxide catalyst in an overall yield of 58%. The method was notable for its great inhibitory activity and satisfactory yields. Iron catalyst is both cheap and nontoxic, thus the procedure can be scaled up without issue (Adak et al., 2017) (Figure: 24).

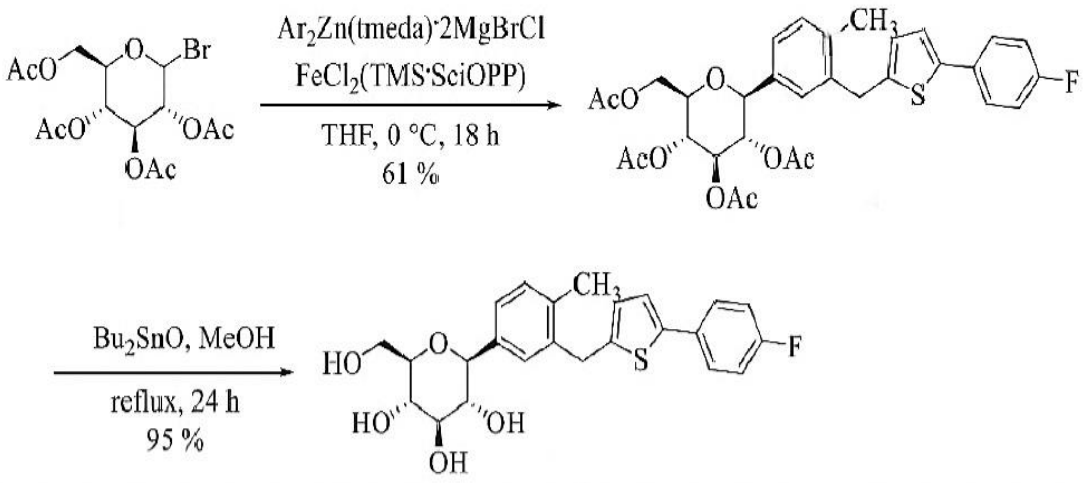


Figure 24: Alternative Synthetic Route of Canagliflozin (Adak et al., 2017)

3.6 Alternative Synthetic Route of Alpha Glucosidase inhibitors

3.6.1 Alternative Synthetic Route of Acarbose

In this article, I will discuss an alternative synthesis approach for acarbose that is both shorter and more time-efficient. There are two steps involved in this production of acarbose from aminocyclitol valiolamine, which was previously obtained from Streptomyces hygroscopicus fermentations. Using 3, 5-di-tert-butyl-1, 2-benzoquinone (DBQ), valiolamine in aminocyclitol was oxidatively deaminated to valiolone (Floss & Lee, 2000). To get acarbose, the ketone was reductively aminated with the amino trisaccharide derivative in the presence of NaBH3(CN). This method provided the quickest synthetic path to the target molecule, acarbose, however the productivity as a whole remains unclear (Floss & Lee, 2000) (Figure: 25).

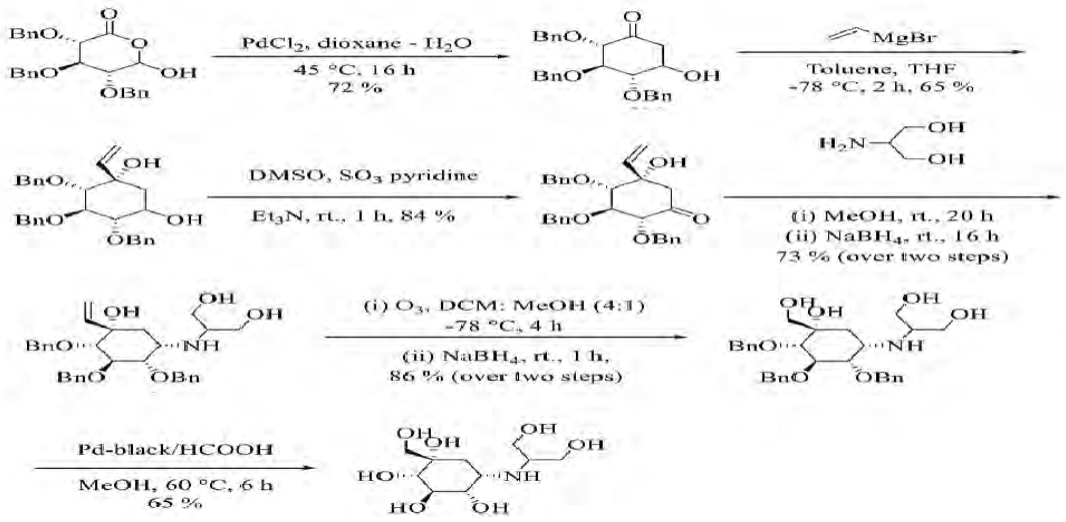


Figure 25: Alternative Synthetic Route of Acarbose; ***(Floss & Lee, 2000)***

3.6.2 Alternative Synthetic Route of Voglibose

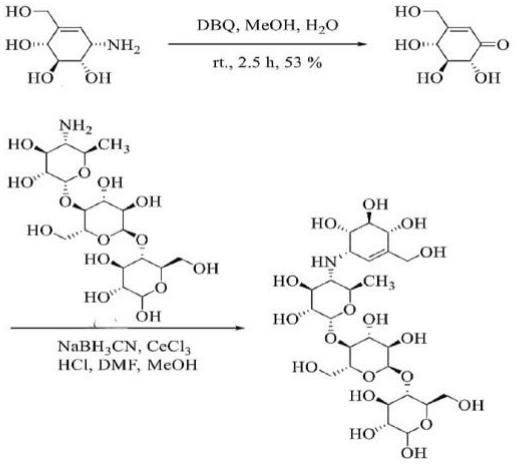


Figure 26: Alternative Synthetic Route of Voglibose *(Sagandira et al., 2021)*

A catalyst-aided, low-cost, and secure method of synthesizing voglibose involves the ferrier rearrangement of a hexenopyranoside derivative to afford a cyclohexanone derivative. The inositol derivative was obtained through an addition reaction of a cyclohexanone derivative with the alkenylating substance vinyl magnesium bromide (Sagandira et al., 2021). The inositol derivative was subsequently oxidized, yielding the final product. An inositol derivative was obtained via dihydroxyamination of the starting chemical with a dihydroxyaminating agent, and further reduction of this intermediate led to the production of voglibose. An oxidation step, a reduction step, and then deprotection produced voglibose in a yield of 16% from the intermediate. Such process makes use of safeguard group chemistry and several different chromatographic refinement techniques (Sagandira et al., 2021) (Figure: 26).

3.7 Alternative Synthetic Route of Biguanides

3.7.1 Alternative Synthetic Route of Metformin

Metformin can also be made from hydrochloride and dimethylaniline. This is a different way to make the drug. To get dimethylamine hydrochloride, HCl was added to dimethylaniline to make it salty. Then, dimethylamine hydrochloride is added to dicyandiamide to make metformin hydrochloride with an overall yield of 89% (Sagandira et al., 2021). This process is simple and easy to use during production. It also has a high rate of material utilization and doesn't require time-consuming purification steps. But it takes longer for things to happen, costs more to make, and has more side effects (Sagandira et al., 2021) (Structure: 27).

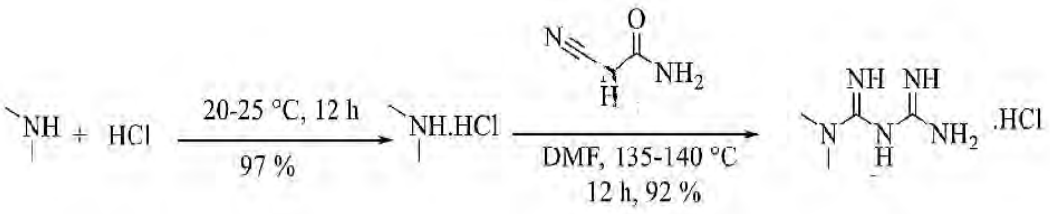


Figure 27: Alternative Synthetic Route of Metformin ***(Sagandira et al., 2021)***

CHAPTER 4

Conclusion

The alarming rise in the number of people diagnosed with type 2 diabetes highlights the need for more effective treatments for this condition. As a result, a lot of oral medications for managing type-2 DM have been made and are now on the market. But it is still important to find more powerful drugs and improve the ways that synthetic drugs are made. Synthetic pathways to several anti-diabetic medicines were investigated in this study. For each route, we talked about its successes, opportunities, and problems. Most of the problems that have been found, like low yields, impurities, low selectivity, and safety concerns, are caused by the fact that batch manufacturing is used. In an interesting turn of events, continuous flow, production technology, the front edge of enabling science is quickly becoming the norm for large-scale pharmaceutical production because it solves most of the problems that come with traditional batch manufacturing technology. New synthetic methods are continuously developed to improve the health and well-being of society as a whole by enabling technologies like continuous flow chemistry, photo catalysis, and artificial intelligence to create more efficient, cost-effective, and environmentally friendly synthetic strategies for anti-diabetic drugs in both academia and industry. Additionally, this review article will act as a valuable resource of knowledge for medicinal chemists and students, enabling them to learn more in-depth

about the many synthetic routes used to make anti-diabetic medications. This article can be of great assistance if you want to use a different synthetic route to make that specific antidiabetic drug if any general synthetic methods for the aforementioned antidiabetic drug do not help with the desired results. The study thus maintains a practical usefulness in the area of antidiabetic medication production. In order to support both small-scale production in lab settings and mass production in industry, the page also provides information on the various production scales of anti-diabetic medications.

4.1 Impact

The continuously improving alternative method that is used in the production of anti-diabetic medications has the potential to solve a wide variety of problems. Features include increasing product purity while simultaneously reducing product time and cost, accelerating production while simultaneously reducing product time, and lowering the cost of the pharmaceutical product. Alternate methods of drug delivery improve drug quality by increasing a medicine's shelf life and decreasing the likelihood of contaminants and degradation. This eliminates or significantly reduces the risk of administering a drug that has degraded while maintaining the safety of the consumer. As a result of advancements in the quality of production on an industrial scale, it is now possible to increase the profit from a medicine simply by modifying its synthetic route. This opportunity was previously unavailable. These alternative pathways have a number of advantages, one of which is that they result in an extremely low amount of industrial waste, which is definitely beneficial to the environment. Anti-diabetic pharmaceutical manufacturers can therefore level up if the synthetic drug pathways that were previously discussed can be correctly applied, and this will have a favorable impact on all aspects. Numerous pharmacological types and specific compounds are being required to treat diabetes, all thanks to years of dedicated study into the sphere of antidiabetic drug manufacturing. This article can contribute to the field by helping researchers discover new therapeutic targets and devise

unique approaches to drug manufacturing. Identifying previously unrecognized drug strategies in the diabetic disease process could be a significant contribution. Targeting the inflammasome, a protein complex involved in inflammation and immunological responses, has been proposed as a potential treatment for diabetes, according to current publications. Treatment for the condition may be improved through the discovery of substances with the ability to regulate inflammasome action. A further potential gain from this work is the introduction of safer and even more environmentally friendly medication manufacturing procedures. The rising demand for antidiabetic medications calls for the development of efficient, eco-friendly manufacturing processes. Better efficient synthetic approaches can be developed by scientists, ones that are less taxing on the environment in terms of energy consumption, trash production, and the use of hazardous chemicals and solvents. Discovering new pharmacological targets, creating unique drug synthesis strategies, and implementing more efficient and sustainable ways for drug production are all examples of novel contributions to the various synthetic processes of antidiabetic medications. Potentially improved and more widely available medicines for diabetes, which impacts millions of people around the world, could result from these studies.

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