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An outline of antidiabetic medications and their synthetic pathways

Bhushan Popatkar, Shweta Tiwari, Satish Manjare, Ramchandra Thorat and Vikas V. Borge*

Department of Chemistry, University of Mumbai, Vidyanagari, Kalina, Santacruz (E), Mumbai, Maharashtra 400098

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Abstract: One of the most common chronic illnesses and a major cause of death in recent years is diabetes mellitus (DM). As a result, strategies for identifying, stopping, or delaying this illness and its co-morbidities have long been debated. Patients with diabetes mellitus (DM), especially those with type 2 DM, are now recommended to modify their diet and exercise routines and to gradually go from monotherapy, dual therapy, and multi-agent therapy to insulin delivery as the disease progresses. While there have been advancements, the search for the "ideal" diabetes medication is currently ongoing. There is still much disagreement on the molecular pathways that regulate DM. Since each drug has different risks, drawbacks, side effects, and modes of action, selecting the best course of treatment requires careful consideration. In this article, many classes of anti-diabetic medications were reviewed that are on the market, their uses, and their modes of action. This study will focus especially on the more recent and/or commonly prescribed classes. Since these medications influence the pathways in various cellular systems and organs, encouraging metabolic modifications responsible for either favorable or detrimental consequences, special attention will be paid to how they affect cellular metabolism. It is imperative to thoroughly examine this essential attribute before recommending an antidiabetic. The most common kind of diabetes is type-2, and oral anti-diabetic medications are essential for managing it. Sulfonylureas, thiazolidinediones, meglitinides, sodium glucose co-transporter (SGLT2), a-glucosidase inhibitors, dipeptidyl peptidase-(IV) inhibitors, and biguanides are some of the classes of oral anti-diabetic medications that are marketed today. To avert a possible public emergency, the scientific community has been working hard to create better and more sustainable synthetic methodologies towards these anti-diabetics as the burden of type-2 diabetes continues to rise. The several documented synthetic approaches for anti-diabetic medications in the aforementioned classes are summarized in this article. We hope that this compilation will provide organic and medicinal chemists with an invaluable comprehensive basis and reference source for the continued development of DM medicines.

Keywords: Diabetes mellitus; antidiabetic drugs classification; type-2 diabetes; multistep synthesis; mechanism of action; medicinal chemistry. ©2025 ACG Publications. All right reserved.

1. Introduction

Diabetes is a severe, multifactorial, long-term metabolic condition with severe acute and long-term effects[1]. Commonly referred to as diabetes, this condition poses a significant financial burden to individuals in both developed and developing nations because to its repercussions. This disease is thought to afflict 25% of the global population[2]. Diabetes develops mostly because of both environmental and genetic factors[3]. When diabetes develops, the body's cells are unable to properly digest sugar because of insufficient or absent insulin, a peptide hormone that controls blood glucose levels, acting on target tissues. When the pancreas does not create enough insulin or when the body does not use the insulin that is produced properly, insulin is unable to metabolize sugar. This causes the body

*Correspondingauthors: E-Mail: vikas.borge@chem.mu.ac.in

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to break down its own fat, protein, and glycogen to make sugar, which results in elevated blood sugar levels and the liver producing extra by-products known as ketones[4,5]. Diabetes causes long-term damage, dysfunction, and failure of various organ systems (heart, blood vessels, eyes, kidneys, and nerves), leading to disability and premature death[6]. The severity of damage triggered on the respective organ systems may be related to how long the disease has been present and how well it has been controlled. Several symptoms such as thirst, polyuria, blurring of vision, and weight loss also accompany diabetes[7]. There are several forms of diabetes, the two most mentioned are Diabetes mellitus and Diabetes Insipidus and for the Diabetes mellitus the types being type 1 diabetes (T1DM) and type 2 diabetes (T2DM). Insulin-dependent diabetes is another name for type 1 diabetes. It is characterized by insufficient insulin synthesis in the body and is mostly caused by the death of pancreatic islet beta cells[6,7]. Individuals with type 1 diabetes require daily insulin injection to regulate blood glucose levels because they are susceptible to ketoacidosis. Children and adolescents account for the bulk of T1DM cases[5]. However, T2DM, often referred to as non-insulin-dependent diabetes, causes hyperglycaemia and is due to the body's inefficient use of insulin[8,9], and it affects the great majority of diabetics worldwide. Reduced target tissue response to normal circulating insulin levels is the cause of insulin resistance[9]. Most diabetics (90%) have type 2 diabetes, which typically affects adults almost exclusively but is now becoming more common among youngsters[5].

Gestational diabetes (GD or GDM) is a type of diabetes that develops exclusively in pregnancy when blood sugar levels get too high (hyperglycaemia). It happens when the hormones from the placenta block the ability to use or make insulin. Insulin helps the body maintain the right amount of glucose in your blood. Too much glucose in the blood can lead to pregnancy complications. GD usually appears during the middle of pregnancy, between 24 and 28 weeks. Gestational diabetes often has no symptoms, or they may be mild, such as being thirstier than normal or having to urinate more often. Gestational diabetes is sometimes related to the hormonal changes of pregnancy that make your body less able to use insulin. Genes and extra weight may also play a role[10]. Since 1980, the adult population's overall prevalence of diabetes has increased from 4.7% to 8.5%, almost doubling. Furthermore, it has been discovered that the prevalence of diabetes has been rising over the past three decades, with low- and middle-income countries seeing a greater increase in diabetes prevalence than high-income ones. An increase in related risk factors, such as being overweight or obese, corresponds with a rise in the prevalence of diabetes. Diabetes can lead to blindness, renal failure, lower limb amputation, and other long-term complications that have a major negative influence on quality of life if it is not effectively treated or controlled[11].It's interesting to note that diabetes is predicted by WHO to rank seventh among all causes of mortality in 2030[12].Despite extensive study, the incidence and prevalence of diabetes have continued to rise globally, placing an increased burden on tropical developing nations[13,14]. According to demographic estimates, developing nations will have more adults over 64 years old with diabetes (≥82 million) by 2030 than developed countries (≥48 million). Sub-Saharan Africa, India, and the Middle East crescent are predicted to experience the largest relative increases[15,16]. Out of all the instances of diabetes, T2DM makes up 90% of cases and is readily preventable and treatable, whereas T1DM is not preventable with current understanding. The complicated and multidisciplinary nature of diabetes management calls for primary prevention through the encouragement of a balanced diet and active lifestyle. In the treatment of type 2 diabetes, dietary management and exercise are critical pillars of care that may be sufficient to achieve and maintain therapeutic targets of either normoglycemia ornormolipidemic.

Antidiabetic drugs, also known as oral hypoglycemic medications, help manage blood sugar levels in people with diabetes. There are many different types of antidiabetic drugs that work in different ways, including: Metformin: a biguanide that reduces the amount of glucose the body produces, sulfonylureas help the body produce more insulin, Glitazones strengthen the effect of insulin produced by the body, Glinides which include drugs like nateglinide and repaglinide, Gliptins also known as dipeptidyl peptidase-4 inhibitors, are drugs that stimulate insulin production, Gliflozins: also known as SGLT2 inhibitors, are drugs that include dapagliflozin, empagliflozin, ertugliflozin, and canagliflozin. Other types of antidiabetic drugs include Alpha-glucosidase inhibitors, Bile acid sequestrants, Dopamine agonists, and Thiazolidinediones.

Antidiabetic drugs and their synthetic pathways

Table 1. A synopsis of some anti-diabetic medications, including their primary benefits and drawbacks and mode of action with their API compounds: (Active Pharmaceutical Ingredients)

Antidiabetic class	Anti diabetic Drug (API)	Mechanism of action	Advantages	Disadvantages
α-glucosidase inhibitors	Acarbose Miglitol Voglibose	Inhibit the breakdown of carbohydrates in the Intestinal villi.	Weight neutral.	Adverse effects on the stomach. little impact on cholesterol. Potential elevations in liver function tests.
Biguanides	Metformin	Halt gluconeogenesis in the liver. Enhances the absorption of glucose by skeletal muscle. Reduces the intestinal mucosa's ability to absorb glucose. Raises GLP-1 plasma levels.	Extended safety. Loss or neutral weight. Minimal chance of low blood sugar.	Adverse effects on the gastrointestinal tract. Lactic acidosis Probability. Having heart or liver failure.
Sulfonylureas	Gliclazide Glibenclamide Glimepiride	To enhance insulin secretion, by stimulating beta cells SUR 1.	Long-term safety.	Hypoglycaemia risk. Possibility of gaining weight.
Meglitinides	Nateglinide Repaglinide	Binds to Beta-cell SUR 1.	Accelerated insulin reaction.	Possibility of gaining weight. Hypoglycaemia risk.
GLP-1 receptor agonists	Exenatide Liraglutide	Causes increased insulin secretion, delayed stomach emptying, and satiety by binding to the GLP-1 receptor.	Loss of weight. Minimal chance of hypoglycaemia.	Adverse effects on the stomach. Injection administered subcutaneously.
DPP-4 inhibitors	Sitagliptin Saxagliptin Alogliptin	Boost incretin concentrations (GLP-1 and GIP). Boost the release of insulin. Reduce the release of glucagon.	Weight neutral.	Adverse effects on the stomach.
Thazolidine dione	Pioglitazone Rosiglitazone	Activators of the PPAR-Gamma. Improves pre-adipocyte development, boosts muscle's sensitivity to insulin, fat and hepatic tissue. Increases peripheral glucose uptake.	Minimal chance of hypoglycaemia.	Possibility of gaining weight. Possibility of oedema Heart failure risk.
SGLT2 inhibitors	Dapagliflozin Canagliflozin	Restricts the reabsorption of glucose in the kidneys.	Loss of weight. Minimal chance of hypoglycaemia.	Genitourinary tract risk of infections.
Exogenous insulin	Rapid acting Short acting Intermediate acting Long acting	Makes the insulin receptor active. Enhances the liver's production of glucose.	Several delivery techniques and simulations.	Possibility of gaining weight. Hypoglycaemia risk. Administration by subcutaneous injection.

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon like peptide 1; GIP, glucose-dependent insulinotropic polypeptide; PPAR-gamma, peroxi some proliferator activated receptor gamma; SGLT2, sodium dependent glucose co-transporter 2; SUR 1, sulfonylurea receptor 1. Some examples of Antidiabetic drugs[17] are listed in Figure 1.

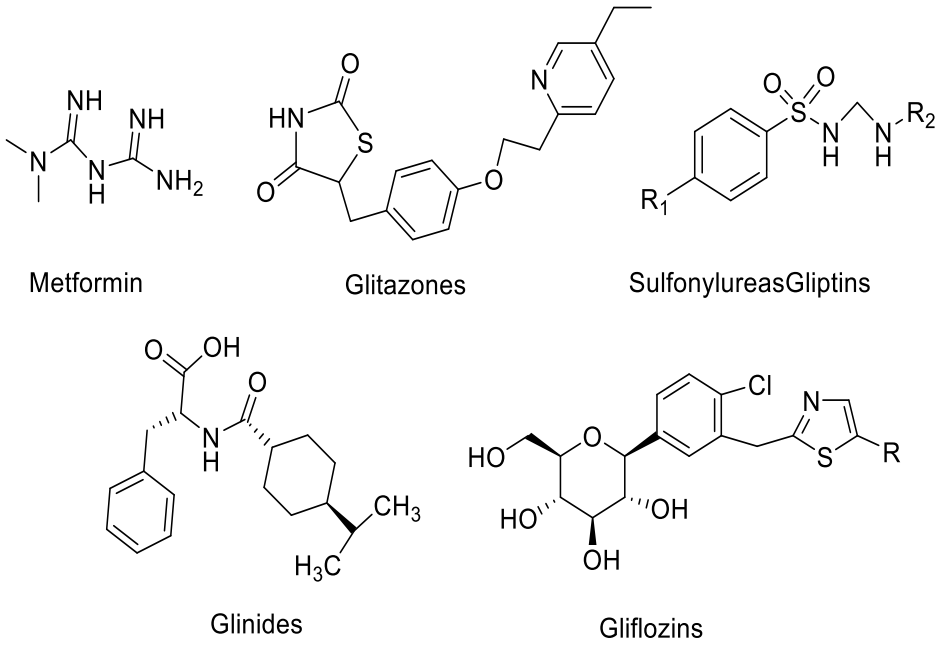


Figure 1. Few Examples of Antidiabetic Drugs.

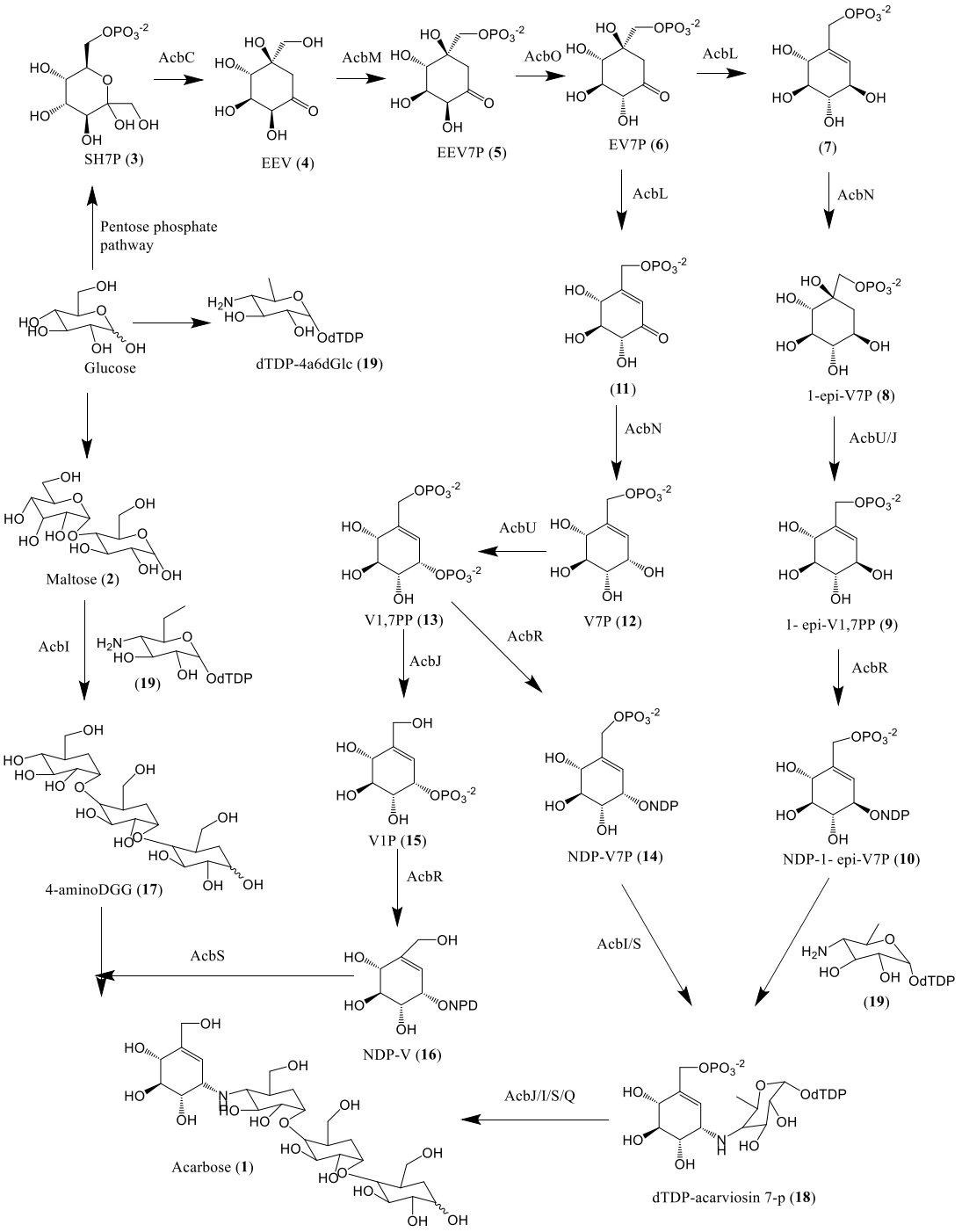
2. Study Design

A comprehensive literature review was conducted to gather relevant information on Antidiabetic medications and their synthetic pathways. Multiple databases including Google Scholar, PubMed, Science Direct and Scopus were searched. Publications mostly from last 20 years included to ensure synthetic methods and drug development. Studies included detailing classifications of antidiabetic drugs

2.1. Methods for the synthesis of API Compounds

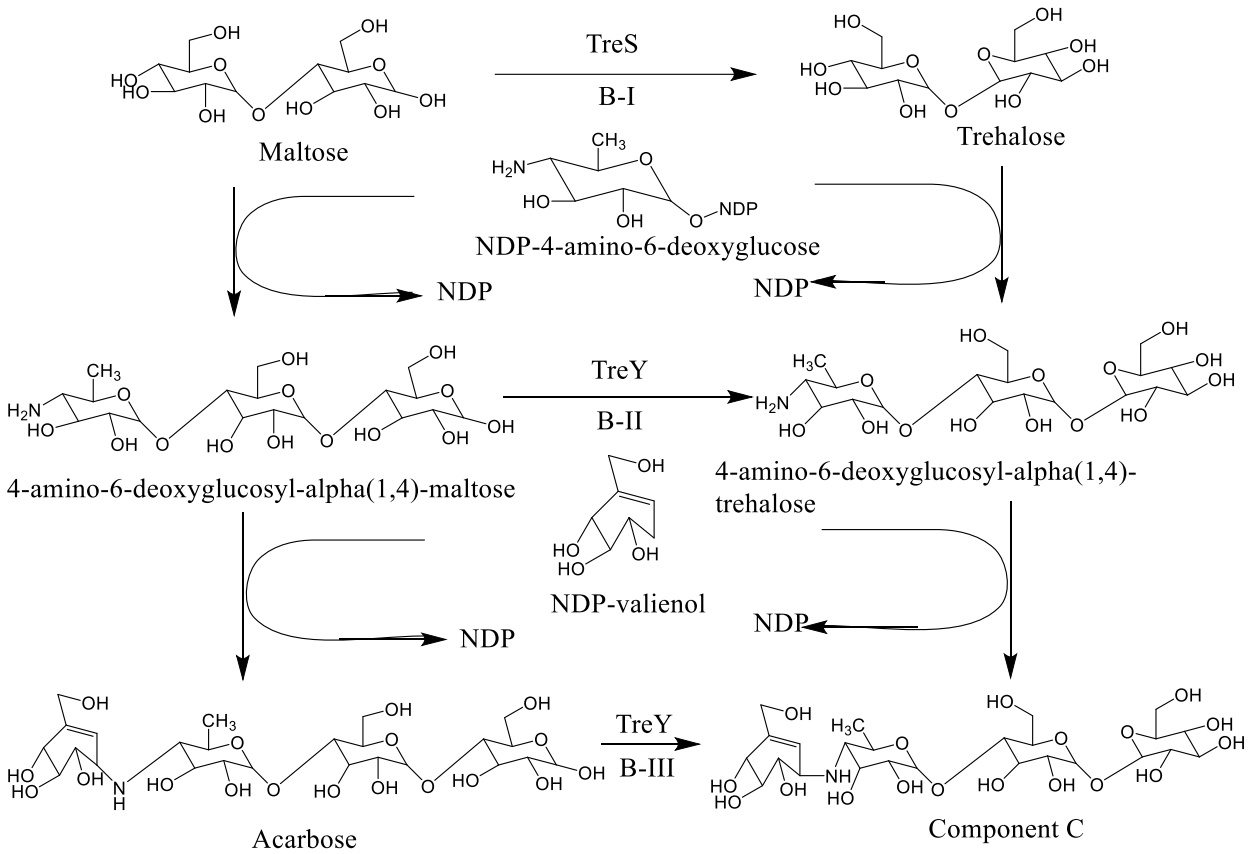
2.1.1. Acarbose

The two components that make up acarbose (**1**) are maltose (**2**) and a pseudosugar (C7-cyclitol), which is joined to an amino-deoxyhexose by a C-N bond[18] (Scheme 1). Only the first half of the route has been clarified, even though the production of acarbose has been investigated over the past forty years using isotope incorporation, gene inactivation studies, biochemical tests, and comparative genomic, transcriptomic, and proteomic analysis. 2-*Epi*-5-epi-valiolone (EEV-4), a cyclization product of the pentose phosphate pathway intermediate andsedoheptulose 7-phosphate (SH7P-3), is the source of the C7-cyclitol unit of acarbose. The enzyme AcbC, which resembles dehydroquinate synthase (DHQS), catalyses this cyclization process. The ATP-dependent KinaseAcbM strain converts EEV (**4**) to 2-epi-5-epi-valiolone 7-phosphate (EEV7P-5), which is then transformed into 5-epi-valiolone 7-phosphate (EV7P-6) by the epimerase AcbO. It was proposed that the product is reduced to 5-epi-valiolol 7-phosphate (**7**) by the putative cyclitol dehydrogenase AcbL, and then NDP-1-epi-valiolol-7-phosphate (**10**) is produced by dehydration, phosphorylation, and nucleotidylation processes. A more recent study, however, revealed that AcbL converts 5-epi-valiolone-7-phosphate (**6**) to valienone-7-phosphate (**11**) while AcbN reduces it to valienol-7-phosphate (V7P-12). It's unclear what is down the pathway farther. It has been suggested that (**12**) is phosphorylated by the putative kinase AcbU to give valienol-1,7-diphosphate (V1,7PP-13) and then modified by the putative nucleotidyl transferase AcbR to give NDP-valienol-7-phosphate (NDP-V7P-14) based on the putative functions of enzymes encoded by genes present in the biosynthetic gene cluster of acarbose. dTDP-Acarviosin-7-phosphate (**18**) is produced by coupling the latter molecule with dTDP-4-amino-4,6-dideoxyglucose (dTDP4a6dGlc-19). Lastly, the phosphatase AcbJ and the probable glycosyltransferases AcbI, AcbS, and/or AcbQ convert (**18**) to acarbose (**1**). Despite its attractiveness, the above-proposed pathway is not supported by any biological evidence.



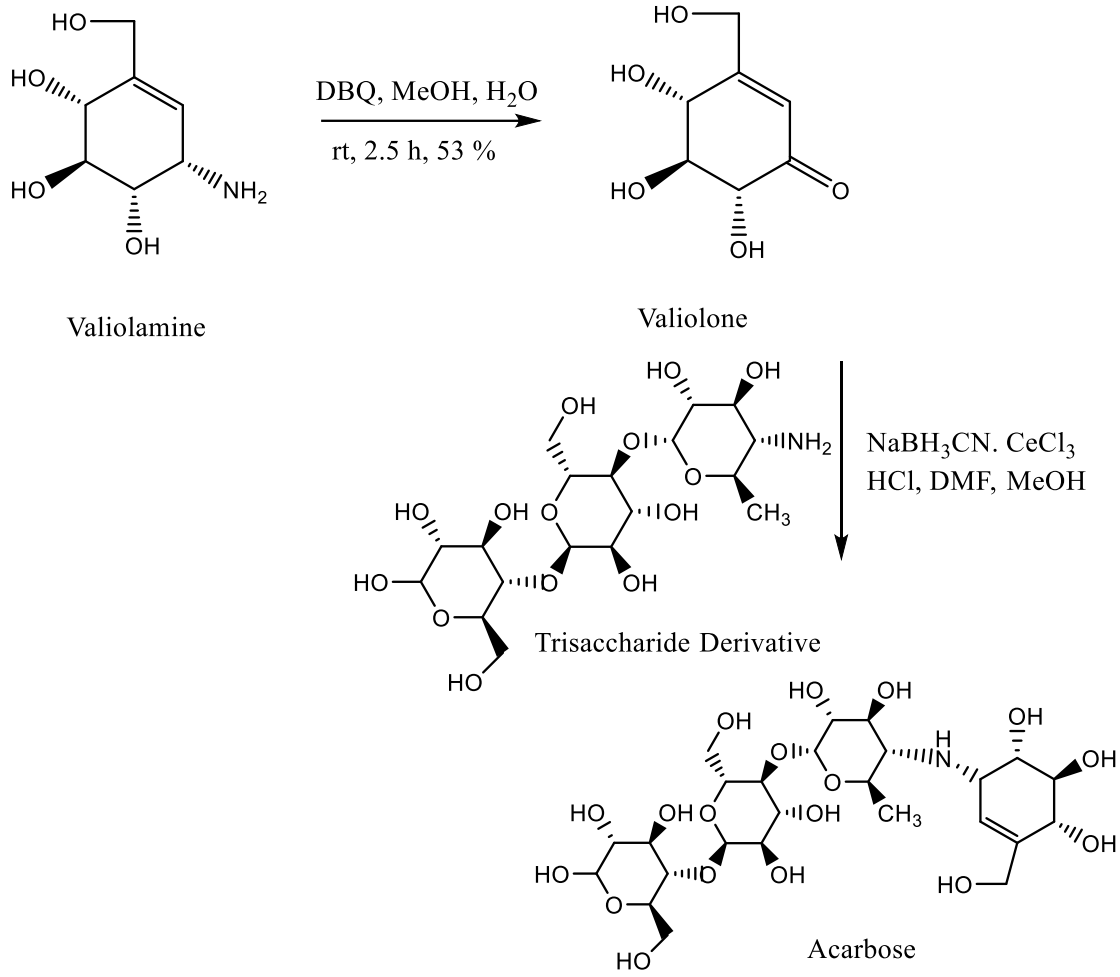
Scheme 1. Synthesis of Acarbose from carbohydrates.

Maltose in the cell can either mix with activated 4-amino-6-deoxyglucose (NDP-4-amino-6-dG) to generate an intermediate 4-amino-6-dG-(α-1,4)-maltose or convert it straight to trehalose by TreS (B-I step)[19](Scheme 2). The latter saccharide is either indirectly transformed to acarbose by coupling with NDP-valienol or directly converted to a trehalose derivative *via* TreY at step B–II. The two products are then bioconverted *via* the extra processes TreYcatalysesstep B–III, to produce the acarviosyl Component C.



Scheme 2. Synthesis of Acarbose from maltose.

Acarbose was synthesized in two steps using a different method[20], who obtained aminocyclitol valiolaminefrom *Streptomyces hygroscopicus* fermentations. Using 3,5-di-*tert*-butyl-1,2-benzoquinone (DBQ), oxidative deamination of aminocyclitol valiolamine resulted in valiolone. Acarbose was then produced by reducing theintermediate Schiff base produced from the condensation of valiolone with the amino trisaccharide derivative with $NaBH_3CN$. The overall yield was not reported by the authors, although this approach provided the quickest synthetic route towards the chemical of interest, acarbose (Scheme 3).



Scheme 3. Synthesis of acarbose from baliolamine.

The complex oligosaccharide acarbose is a member of the α-glucosidase inhibitors pharmacological class[21], α-glucosidase are the enzymes that convert complex carbohydrates into absorbable monosaccharide units. They are found on the intestinal mucosa's brush border. Acarbose delays the breakdown of starch, a polysaccharide, and sucrose, a disaccharide, into the monosaccharides, glucose and fructose by competitive, reversible inhibition of glucoamylase, sucrase, maltase, and isomaltose[22]. Additionally, pancreatic α-amylase, which catalyses the initial stage of starch digestion, may be inhibited by acarbose[23]. Since α-glucosidase is not required for the absorption of glucose, lactose, or fructose, acarbose has no effect on their absorption. Because glucose can be bound at both ends of the molecule, carbohydrates that are not absorbed and digested in the upper section of the small intestine are transferred to and absorbed in more distal sections of the gut[24]. Following a meal high in carbohydrates, the effect of acarbose causes the blood glucose concentration to rise less quickly. Colonic bacteria in the large intestine break down small amounts of carbohydrates into the short-chain fatty acids butyrate, propionate, and acetate, which are then absorbed.

When using acarbose, the absorption of the fatty acids stops a considerable loss of calories in the faeces. Acarbose lowers the postprandial hyperglycaemia that people with NIDDM (**n**on-**i**nsulin **d**ependent **d**iabetes **m**ellitus) experience. In the range of 30 to 60 mg/dL, the postprandial blood glucose concentration decrease is moderate in magnitude. Acarbose treatment results in a reduction in glucose absorption as seen by the area under the glucose concentration time curve (AUC). In most, but not all, investigations, the reduction in postprandial blood glucose concentrations has been correlated with minor reductions in glycosylated haemoglobin values. When compared to a placebo, certain clinical trials have shown a modest decrease in the fasting blood glucose concentration (FBG) or fasting plasma glucose concentration (FPG)[25]. When observed, this drop is minor (10 to 20 mg/dL), and the exact

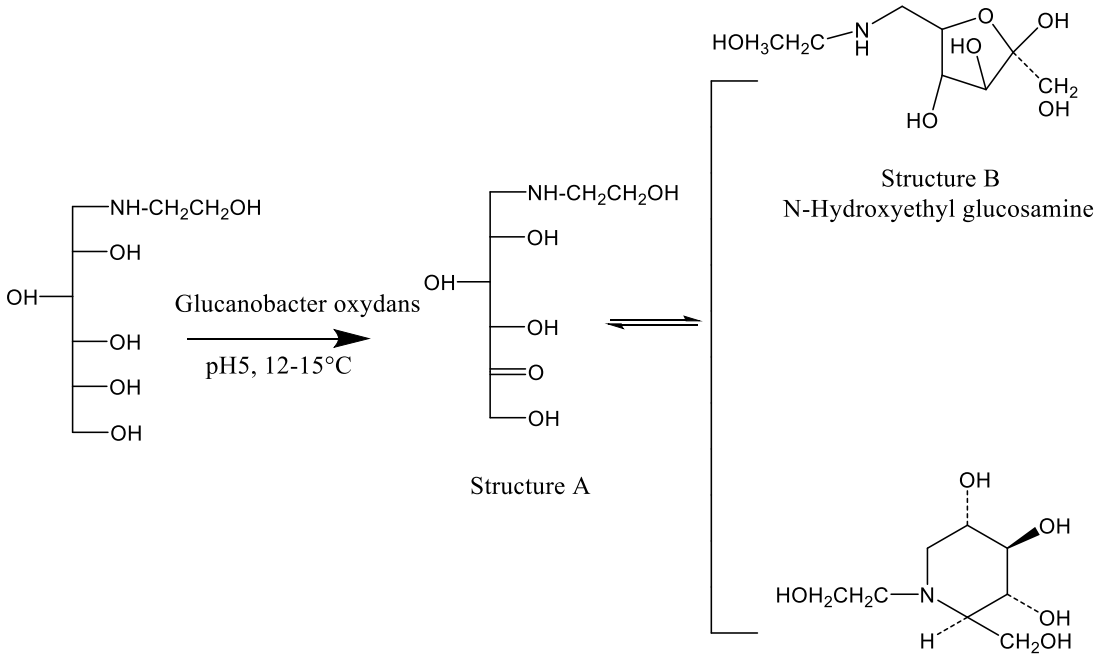
mechanism is unknown. It's probable that a decrease in postprandial glucotoxicity and an increase in beta cell sensitivity to blood glucose are what lead to the reduction in FBG[25].

2.1.2.Miglitol

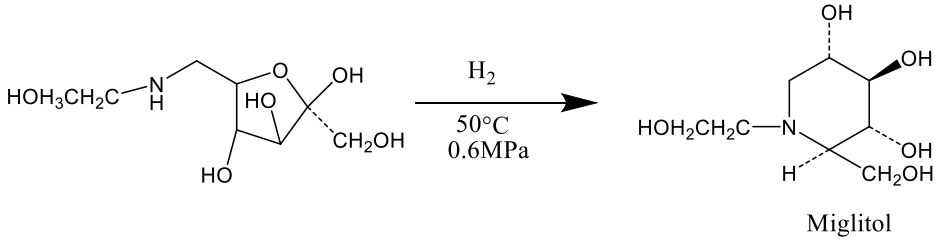
N-2-Hydroxyethyl-glucamine (NHEG) was converted into 6-deoxy-6-hydroxylethyl-amino-L-sorbose (DHES) by the regioselective oxidation by *Gluconobacteroxydans*, and then the generated intermediate of this process was converted to *N*-hydroxyethyl-deoxynojirimycin (Miglitol) by reductive ring closure reaction[26] (Scheme 4). The regioselective oxidation reaction was catalysed by the high activity of sorbitol dehydrogenase of *Gluconobacteroxydans* biomass which was obtained in preliminary studies. The reductive ring closure reaction was carried out under the conditions of 10%Pd/C as catalyst, at 45~55°C and 0.6MPa of hydrogen. The reaction mixture was separated and purified using a strong acidic ion exchange resin column to provide pure Miglitol.

The synthetic mechanism is given below (Scheme 4). *N*-Hydroxyethyl-glucosamine is prepared according to the procedure of Step 1. Glucose as the initial raw material, is catalysed by *Gluconobacteroxydans* at temperature ranges from 12°C to 15°C, and then may produce the equilibrium mixture structure of substances A, B and C. The structure of B is the most stable; it is simply N-hydroxyethyl-glucosamine. The next synthesis process (Step 2) is that*N*-hydroxyethyl glucosamine is further catalysed and deoxygenated by H_2 gas at 0. 6 MPa pressure and 50°C to produce Miglitol in the end.

Step 1: Synthesis process of N-Hydroxyethyl glucosamine

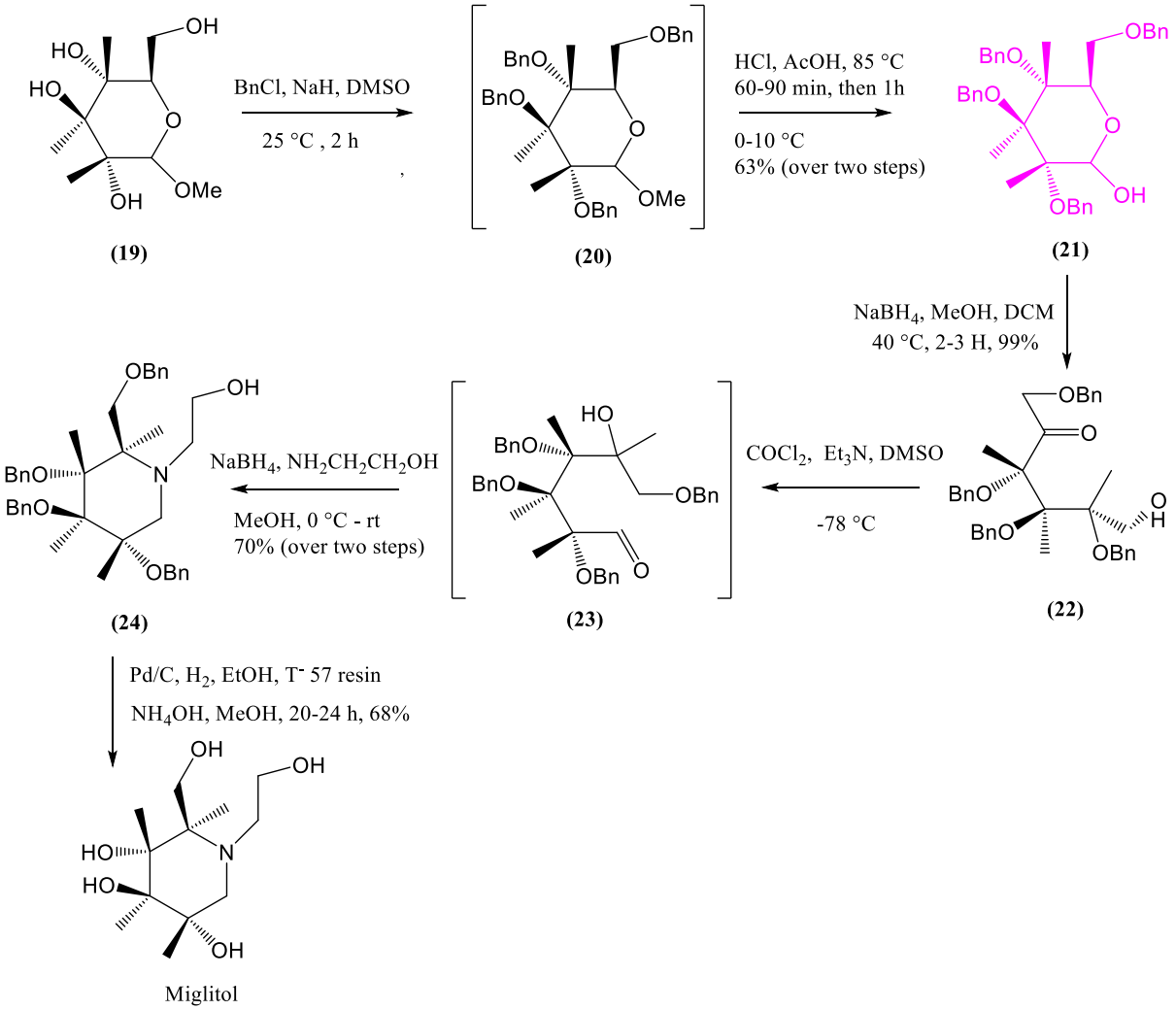


Step 2: The synthesis reaction of Miglitol



Scheme 4. Synthesis of Miglitol from *N*-2-hydroxyethyl-glucamine

A simple method that allows for the quick and safe synthesis of miglitol was described by Tripathi and colleagues[27] (Scheme 5). Compound **19** was first benzylated to create compound **20**, which was then demethylated to produce diol **21**. Compound **23** was obtained by Swern oxidation of intermediate **22**, which was produced by reduction of diol **21**. Following reductive amination of **23**, intermediate **24** was produced. This was hydrogenated in the presence of Pd/C to produce miglitol with a 44% yield. This procedure spares the unstable intermediates **20** and **23** from separation and purification, which prevents related losses.



Scheme **5.** Synthesis of glucosidase inhibitor miglitol

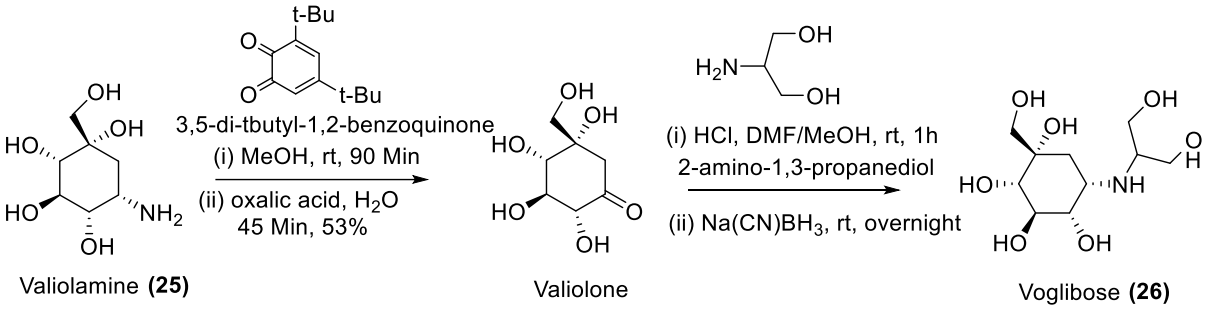
N-desoxy-nojirimycin, also known as N-OH-ethyl nojirimycin, is the source of miglitol. It provides the brushborder-glucosidases with a reversible competitive binding, just like acarbose. The small intestine absorbs practically all the short-acting α-glucosidase inhibitor miglitol. It must be taken with every major meal and reduces the postprandial rise in blood glucose levels in Type 2 diabetics by affecting the digestion of carbohydrates. Miglitol is far less effective than sulphonylurea in decreasing blood glucose levels, however it has little to no effect on fasting blood glucose levels. Three times a day, a maximum permitted dosage of 100 mg is allowed. Both monotherapy and adjunctive usage of miglitol with other hypoglycemic medications are possible. This chemical has been recommended for use by several writers, particularly in the treatment of older people with Type 2 diabetes. Its effectiveness is, however, quite limited; a moderate to average HbA1c reduction of 0.3-0.7% point can be attained[27]. An extra benefit could be the impact on blood insulin levels: miglitol treatment resulted in marginally reduced postprandial serum insulin levels. In patients with Type 2 diabetes, this may theoretically result in less weight gain or perhaps none and a lower risk of hypoglycemia, particularly when the medication

is contrasted with long-actingsulphonylureas like glibenclamide. We have very little long-term experience with patients with Type 1 diabetes. Miglitol may result in less postprandial glucose excursions, a minor decrease in the need for insulin, and potentially a decreased risk of hypoglycemia. To properly evaluate the clinical usage of miglitol in these patients, further extended data are required.

After reading Tormo et al.'s study[29] and learning that miglitol is fully absorbed, there was some discussion as to whether the substance would have systemic effects. Salehi and Lundquist's *in vitro* investigation[30] revealed that miglitol reduced the activity of islet cell α-glucoside hydrolase, which in turn suppressed glucose-induced insulin release. According to Reuser et al.[31], intracellular accumulation of miglitol may cause glycoprotein accumulation by inhibition of non-intestinal α-glucosidase, based on a review of the literature. However, studies using HepG2 and human fibroblasts have shown that the risk of glycogenosis is minimal at the dose that is typically employed. The evidence that acute miglitol treatment reduced postprandial glucose levels in Type 2 diabetic subjects without causing a corresponding fall in insulin or C-peptide levels; this does, in fact, raise the possibility of extra-intestinal effects. According to Joubert et al.[32], there was a systemic effect of this kind in healthy individuals.

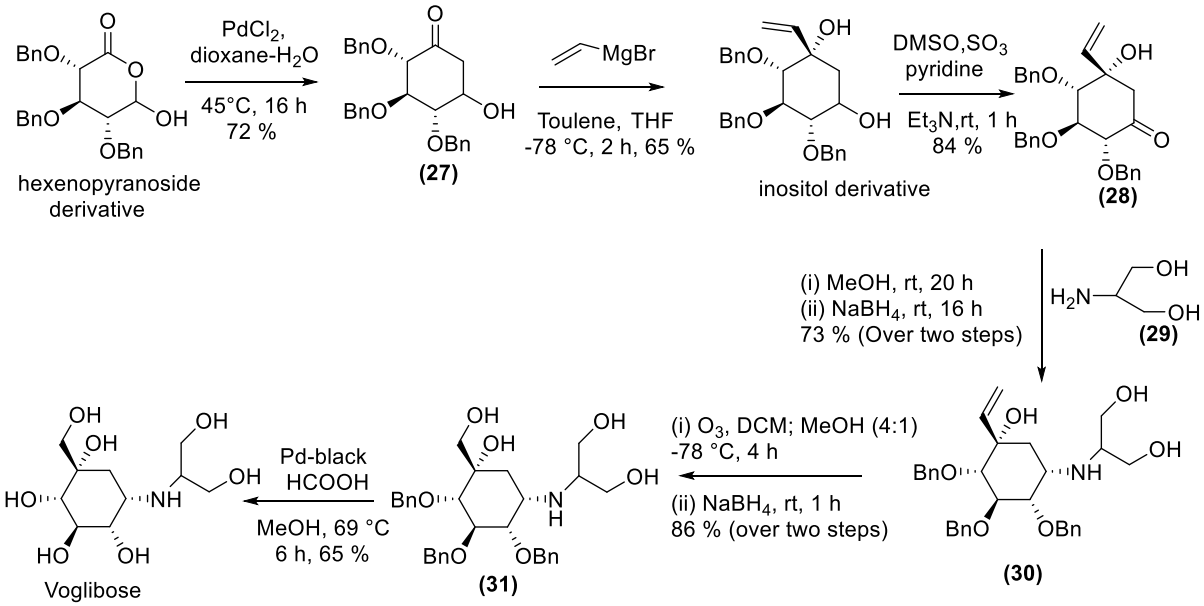
2.1.3. Voglibose

Voglibose **26** was synthesized[33] from valiolamine **25**. Using 3,5-di-*t*-butyl-1,2-benzoquinone, valiolamine is oxidized to produce an imine intermediate, which is then hydrolysed to produce the important intermediate valiolone. Voglibose was produced by treating valiolone with 2-amino-1,3-propanediol in the presence of $NaBH_3CN$; however, the yield was not disclosed. This method only requires two steps, is straightforward, and has extremely quick reaction times. However, it only uses one column chromatographic purification (Scheme 6).



Scheme 6. Synthesis of voglibose from valiiolamine.

To produce cyclohexanone derivative **27**, the hexenopyranoside derivative was made to undergo a Ferrier rearrangement in the presence of a catalyst, as described by Shogaki et al. in their low-cost and safe voglibose synthesis method. The inositol derivative was produced by the addition reaction of cyclohexanone derivative **27** with vinyl magnesium bromide, an alkenylating agent. Compound **28** was produced by oxidizing the inositol derivative later. Compound **28** was subjected to dihydroxyamination using dihydroxyaminating agent **29**. The resultant intermediate was reduced, allowing inositol derivative **30**, a crucial step towards voglibose, to be obtained. After oxidation and reduction of the intermediate **30**, compound **31** was produced. Deprotection then produced voglibose in an overall yield of 16%. This technique makes use of several chromatography purification steps as well as protection group chemistry (Scheme 7**)**.



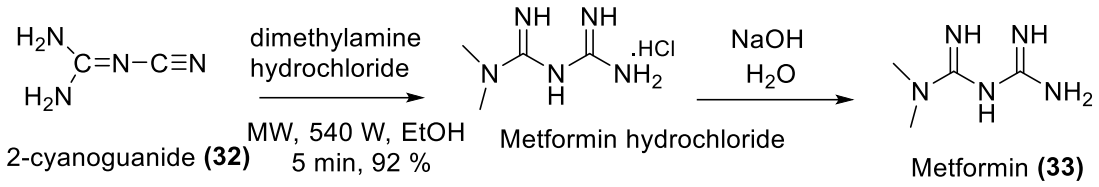
Scheme 7. Synthesis of voglibose from hexenopyranoside derivatives

A derivative of valiolamine, voglibose is made by *Streptomyces Hygroscopicus*. Voglibose is promptly eliminated after being slowly and poorly absorbed, much like acarbose. Voglibose, like the other alpha-glucosidases inhibitors, increases the body's production of GLP-1, an incretin hormone with antihyperglycemic effects[34]. Three times a day, a single oral dose of 0.2 mg of voglibose should be given. If this amount is insufficient, it can be increased to 0.3 mg. Voglibose has an anti-hypoglycaemic effect because it reversibly inhibits the α glycosidase-hydrolysing enzymes in membrane-bound intestines, which hydrolyse oligosaccharides and disaccharides to glucose and other monosaccharides in the small intestine's brush border. Voglibose thus reversibly inhibits the enzymes that break down carbohydrates, such as sucrose, maltose, zomaltase, etc., delaying both the absorption and digestion of dietary polysaccharides. As a result, PPHG (Post prandial hyperglycaemia) is decreased. Additionally, voglibose may promote the release of alpha endogenous glycogen-like peptide 1 (GLP-1), which inhibits glycogen and lowers blood glucose levels while fasting. The administration of voglibose has been observed to cause an increase in the production of GLP-1, an insulinotrophic hormone that is also known to improve insulin sensitivity and secretion[35]. Voglibose does not result in lactose intolerance or diarrhoea since it lacks the inhibitory effect against lactase. When combined with other oral hypoglycaemic agents (OHAs), such as sulfonylurea, it has also demonstrated an addictive effect. It also lessens the impact of sulfonylureas on insulinotropic response and weight gain. In addition to inhibiting α-glucosidase enzymes, voglibose also raises plasma levels of GLP-1 overall by promoting the release of GLP-1 from gut L-cells and lowering plasma DPP-4 action. Therefore, there was a rise in plasma active GLP-1 levels following voglibose therapy[36]. Furthermore, it has been observed that voglibose (1-4 mM) significantly inhibits the synthesis of melanin in melanoma cells by preventing the appropriate N-glycan processing of tyrosinase which is a glycoprotein that is involved in the process of melanogenesis resulting in significant decline in this protein[37]. Notably, voglibose was administered in a case of non-alcoholic steatohepatitis, which improved the patient's hepatitis. The precise mechanisms are yet unknown, but they might have to do with a drop in free radical generation, which would lower the expression of TNF-α both in the liver's mRNA and protein[38].

2.1.4. Metformin

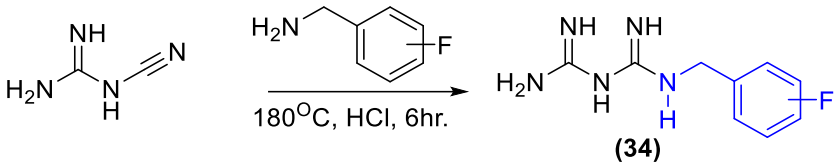
Metformin **33** was prepared using an environmentally friendly microwave-assisted synthetic method on thin-layer chromatography plates, as described by Shalmashi[39] (Scheme 8). After placing a spot solution of 2-cyanoguanide **32** and dimethylamine hydrochloride on TLC and heating it with a microwave, metformin hydrochloride was produced with a 92% yield. Later on by reaction with NaOH and hydrolysis Metformin was obtained. This method's advantages include a straightforward process

setup, quicker reaction times, the use of fewer milligrams of reagents and solvents, and high product purity without the need for chromatography purification.



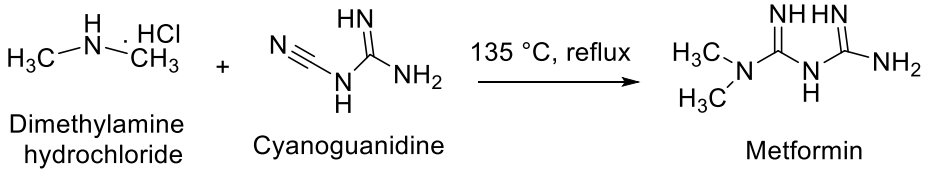
Scheme 8. Synthesis of Metformin from 2-cyanoguanide.

Edson D. Hernández-Velazquez *et. al*[40] synthesized benzyl fluorinated metformin derivatives **34**. *In vitro* enzymatic assay with α-amylase was performed, and then *in vivo* experiment was carried out with streptozotocin-induced CD1 mice using the selected derivatives (Scheme 9). Blood glucose was measured every day. After sacrifice, the lipid profile, serum, and liver γ-glutamyl transferase (GGT) activity determined the biocompatibility. Compounds show enhancement in the activity and higher biocompatibility for blood glucose, lipids metabolism and GGT activity regulation.



Scheme 9. Synthesis of fluorobenzyl metformins.

Dimethylamine hydrochloride reaction with cyanoguanidine and reflux at 135°C provides the metformin (Scheme 10).



Scheme 10. Synthesis of metformin from dimethylamine hydrochloride and cyanoguanidine.

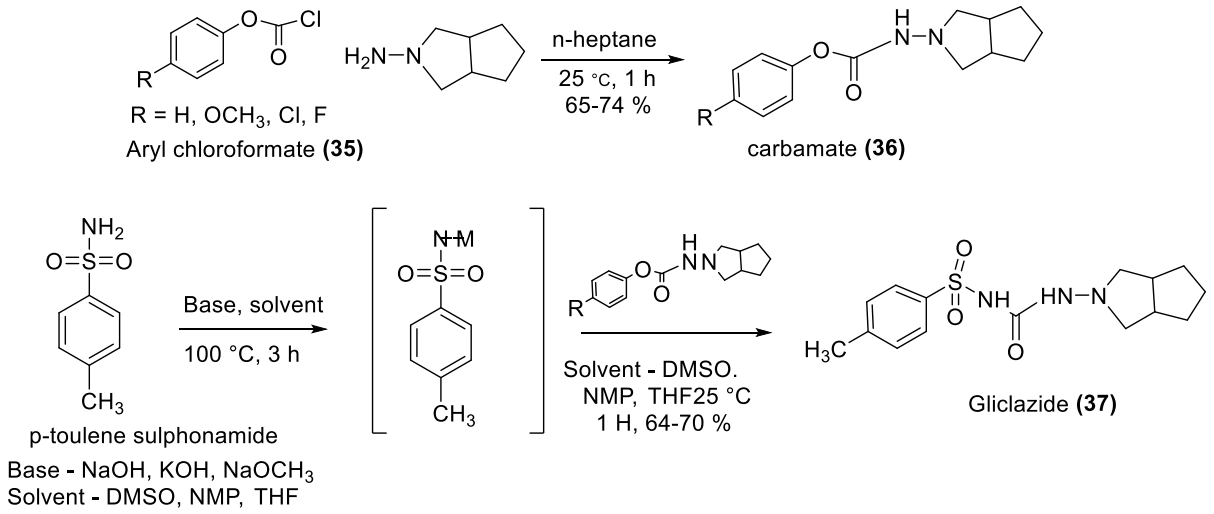
Instead of directly inhibiting the expression of gluconeogenic genes, metformin, an insulin-sensitizing medication, blocks hepatic gluconeogenesis by regulating the gluconeogenic flow[41]. Additionally, it decreases the absorption of glucose in the intestinal mucosa and raises the uptake of glucose in skeletal muscle[42]. The precise mechanisms of metformin's activity have not yet been fully understood, despite over 60 years of research[43]. However, metformin is known to have no effect on pancreatic beta-cell stimulation of insulin secretion. Metformin has been shown in recent years to function as an inhibitor of complex I of the electron transport chain, which activates signalling that is sensitive to AMP-activated protein kinase (AMPK)[44]. Through the phosphorylation of some important proteins, AMPK regulates the metabolism of fats and carbohydrates as well as cellular energy. Increased activity causes several physiological changes, such as increased muscle absorption of glucose, increased liver and muscle fatty acid oxidation, decreased hepatic synthesis of glucose, cholesterol, and triglycerides, and decreased lipogenesis. Metformin may also have the effect of raising plasma levels of GLP-1, an incretin hormone with antihyperglycemic qualities, and triggering the expression of the islet incretin receptor gene *via* a mechanism mediated by the peroxisome proliferator-activated receptor alpha

(PPAR-alpha)[45]. The primary benefit of metformin over other biguanides is its extremely low propensity to induce lactic acidosis. However, there are certain drawbacks, like unfavorable gastrointestinal consequences. Even though this medication is recommended as the first line of treatment for people with type 2 diabetes, many patients require additional medication to achieve glycaemia control after using this medication.

Metformin does not induce the release of insulin or other hormones, such as glucagon, and its therapeutic action depends on the presence of insulin. Metformin inhibits the release of adiponectin, a hormone that increases insulin sensitivity[46]. Without being digested, metformin is eliminated from the body through tubular secretion, which is facilitated by organic cation transporters. It is then eliminated unaltered in the urine.

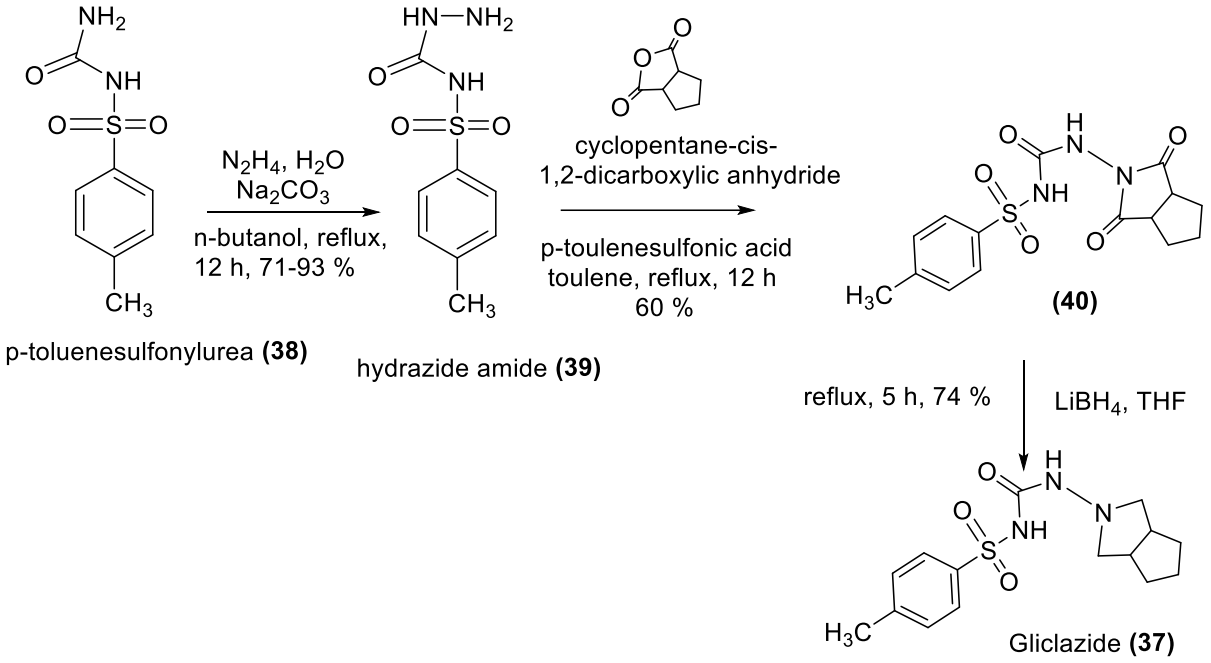
2.1.5. Gliclazide

Gliclazide was synthesized by Ambulgekar *et al.*[47] by condensing various carbamates with *p*-toluene sulphonamide. various aryl chloroformates **35** were used to react with Amine (*cis*-N-amino(hexahydrocyclopentan[c]pyrrole)to produce various carbamates **36**(Scheme 11). Then *p*-toluene sulphonamide reacted with a base in a solvent to form the sulphonamide salt which was further reacted with these various carbamates to produce, Gliclazide and the respective phenols. Gliclazide **37** was thus obtained with a purity of >99% and an overall yield of 43-52%. The authors used materials that are readily available in stores to illustrate an effective synthetic process. Furthermore, the synthetic approach provided excellent yields, purity, and quick reaction times.



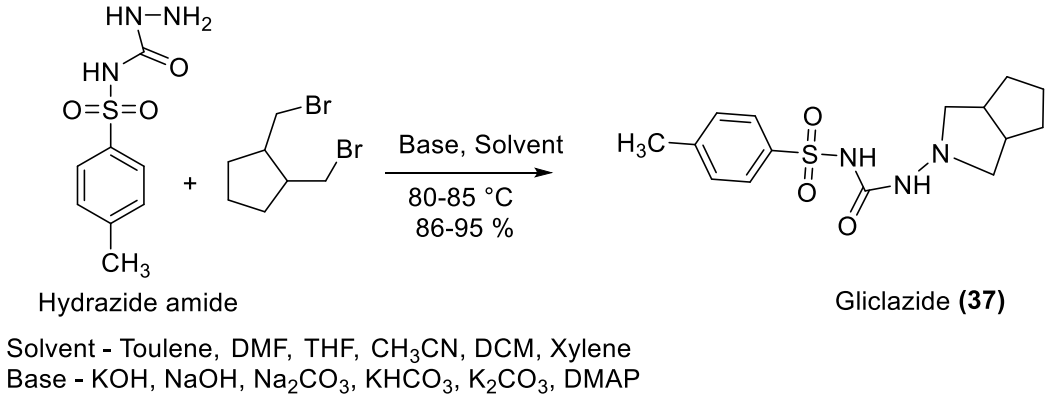
Scheme 11. Synthesis of glicalazide from aryl chloroformates and various amines.

Gliclazide was also synthesized[48] using *p*-toluenesulfonylurea **38**. Following the condensation of *p*-toluenesulfonylurea with hydrazine hydrate to form the corresponding hydrazide **39**, the latter was condensed with *cis*-1,2-dicarboxylic Anhydridein refluxing toluene containing *p*-toluenesulphonic acid as catalyst to yield 60% of **40**. Gliclazide was then obtained by a subsequent $LiAlH_2$ reduction of **40** in 31-41% total yield (Scheme 12). The process only requires three steps; however, it is distinguished by its lengthy reaction times. The problem of raw material oxidation was essentially resolved, and the usage of amino heterocyclic compounds was avoided.



Scheme 12. Synthesis of glicalazide from p-toluenesulfonylurea.

Gliclazide **37** was produced in great yield by treating hydrazide amide with *cis*-1,2-bromomethyl cyclopentane. The industrial synthesis of gliclazide is attracted by this synthetic approach due to its good product yield, environmental friendliness, and enhanced safety (Scheme 13). Furthermore, while amino heterocycles are said to be readily oxidized, the above approach does not employ them[48].



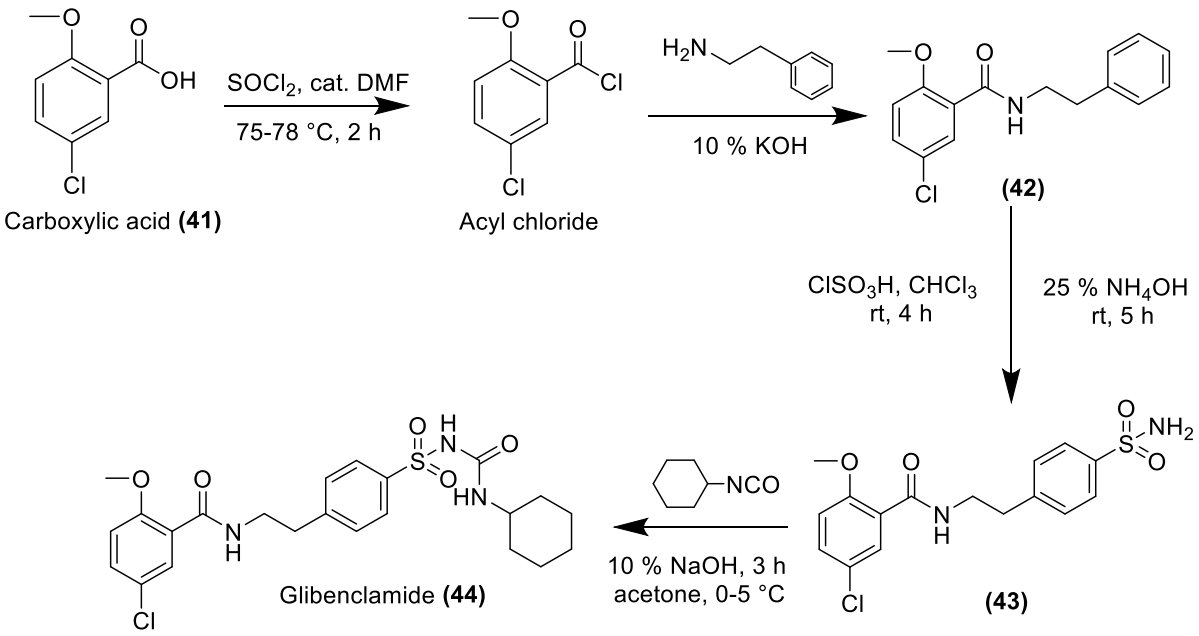
Scheme 13. Synthesis of Glicalazide from the hydrazide amide and *cis*-1,2-bisbromomethyl cyclopentane

The β-cell sulfonyl urea receptor (SUR1) is bound by gliclazide. Subsequently, the ATP-sensitive potassium channels K(ATP) are blocked by this interaction. The binding process causes the channels to close, which lowers potassium efflux and causes the β-cells to depolarize. This causes the β-cell's voltage-dependent calcium channels to open, activating calmodulin and triggering the exocytosis of secretory granules containing insulin. While they are not essential for the upkeep of glycaemic regulation, K(ATP) channels have a well-established role in the stimulus–secretion coupling of β-cells. By demonstrating that β-cells are protected against oxidative stress by genetic or pharmacological deletion of K(ATP) channels, Drews and Dufer[49] explored a novel function for these channels. The pathophysiology of type 2 diabetes is significantly influenced by increased oxidant generation. When β-cells are unable to maintain the increased insulin demand brought on by an excessive fuel intake, type 2

diabetes (T2DM) develops. Rather, β-cell mass is reduced by apoptosis and β-cells begin to release less insulin. K(ATP) channel deletion or blockage prevents oxidative stress-induced reductions in insulin production and β-cell mass. These results might provide fresh perspectives on the early management of T2DM. Sulfonylurea receptor 1 (SUR1) blockers may protect against myocardial ischemia, according to relatively recent research. The effects of gliclazide, a selective SUR1 blocker, on cardiac function and arrhythmia following isoprenaline-induced myocardial damage in obese rats were assessed by Bao *et al*.[50]. Thus, in obese rats, blocking SUR1 protects against isoprenaline-induced myocardial damage. The fact that an SUR1 blocker prevents ischemia suggests that SUR1 has a more important biological role than previously thought in controlling how the cardiovascular system functions under pathological circumstances. Sulfonylurea medications work by blocking K(ATP) channels in the pancreas to provide an insulinotropic effect. Nevertheless, these channels are also expressed in the smooth muscle of the heart and blood vessels, suggesting potentially harmful consequences on the cardiovascular system.

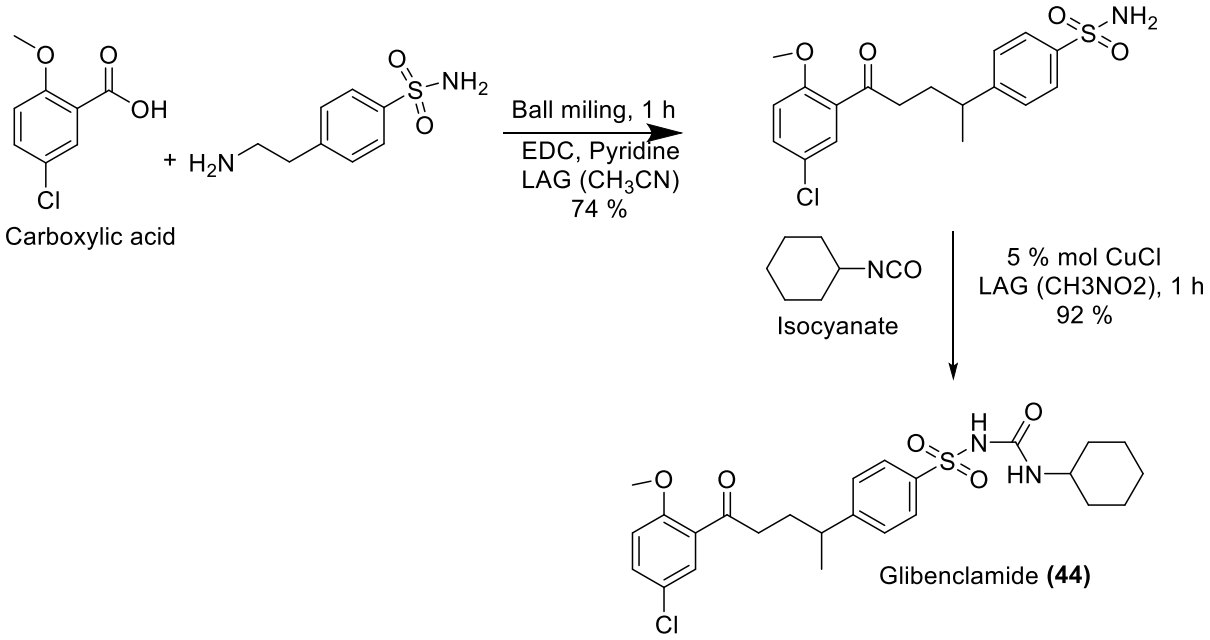
2.1.6. Glibenclamide

A 5-step synthetic method towards Glibenclamidewas disclosed by Velingkar and colleagues[51] (Scheme 14). The activation of 3-chloro-6-methoxybenzoic acid **41** was the first step taken by the authors, who then reacted to the correspondingamidated acyl chloride with β-phenethylamine to produce N-phenethyl 3-chloro-6-methoxybenzamide **42**. Chlorosulphonation of this amide produced the **43** against isoprenaline-induced myocardial damage Glibenclamide **44** by further reaction with cyclohexylisocyanatein 10% NaOH/3h/acetone/0-5ºC. Chromatography was not necessary since recrystallization was used to purify all the intermediates. Regretfully, neither the end product's yield nor its purity was made public. Furthermore, the creation of both ortho-substituted and para-substituted intermediates from chlorosulfonication presented selective issues for the authors during the manufacture of the sulfonamide. These intermediates are difficult to separate and interfere with the aminolysis phase.



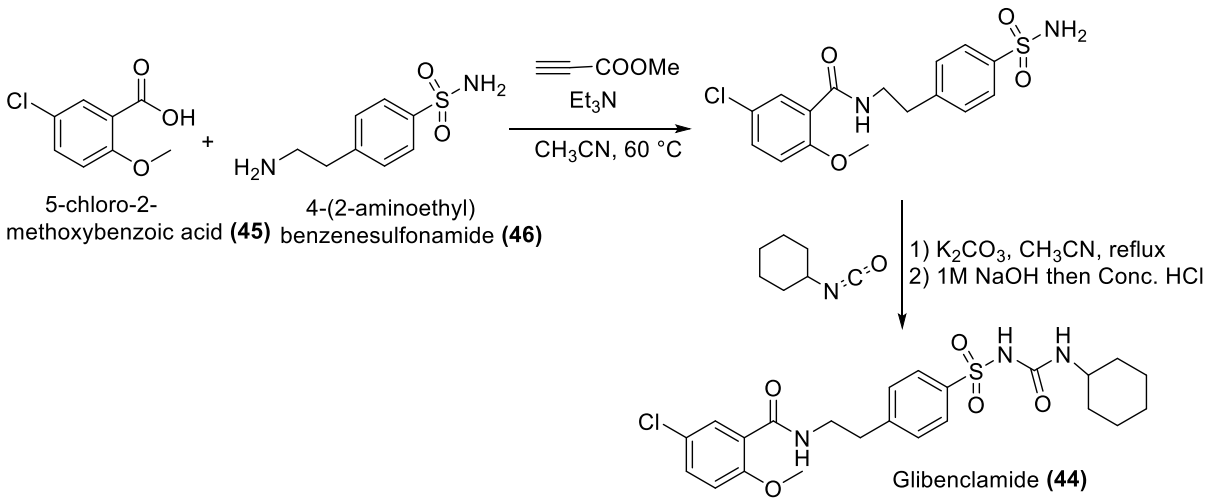
Scheme 14. Synthesis of glibenclamide from 3-chloro-6-methoxybenzoic acid**.**

Tan and colleagues employed mechanochemistry to synthesize Glibenclamide in two steps with an overall yield of 70%. The authors combined carbodiimide-mediated amide mechano synthesis in a ball mill and the Cu-catalysed coupling of the sulfonamide and cyclohexylisocyanate in this process (Scheme 15). The combination of coupling reagent EDC. HCl and mechanochemistry ensured simple reaction workup during the brief operation



Scheme 15. Synthesis of glibenclamide from the 3-chloro-6-methoxybenzoic acid and a sulphonamide derivative.

The process of creating Glibenclamide **44** started with the condensation of 4-(2-aminoethyl) benzenesulfonamide **46** with 3-chloro-2-methoxybenzoic acid **45** in the presence of trimethylamine and methyl acetylenate, yielding amide. Following a 1.5-hour reflux of amide and potassium carbonate in acetone, isocyanatocyclohexane was added, and the combination was refluxed for an additional 16 hours to get Glibenclamide[52] (Scheme 16).



Scheme 16. Synthesis of glibenclamide from the 3-chloro-6-methoxybenzoicacid and a sulphonamide derivative in presence of methyl acetylene and trimethyl amine

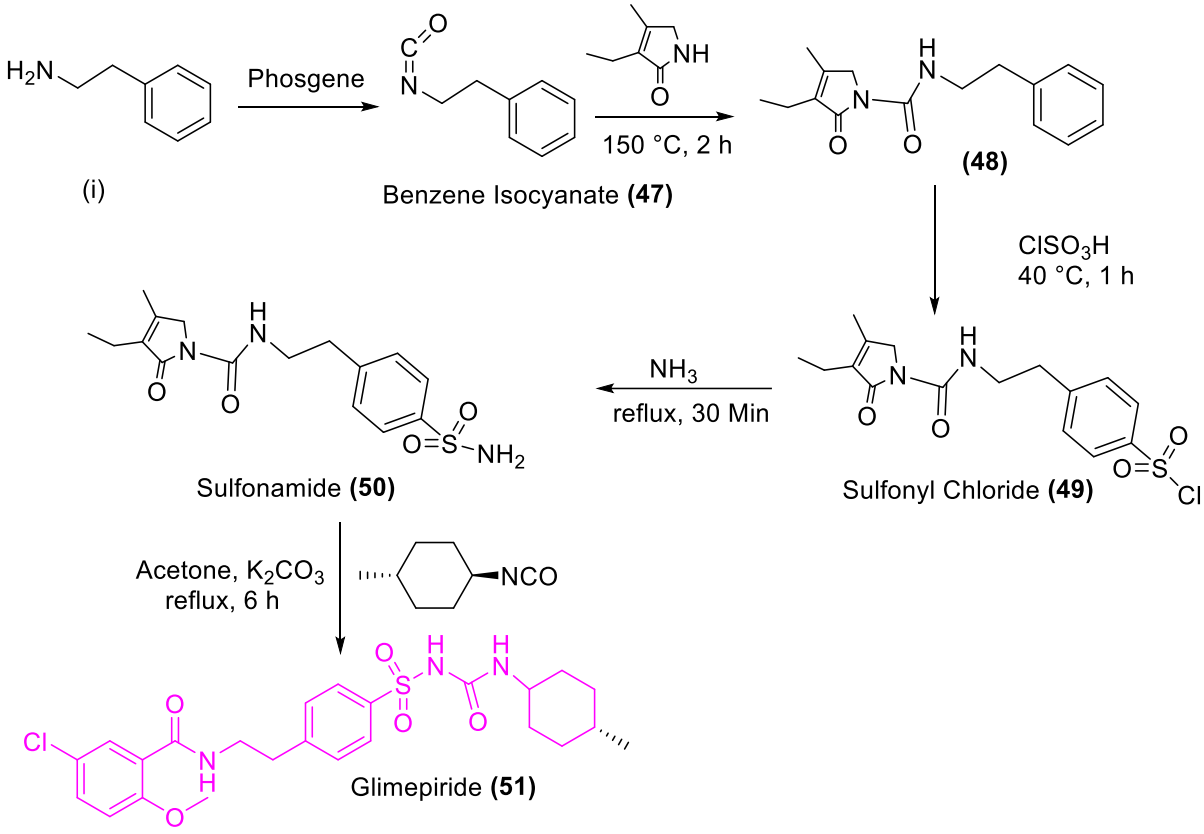
Glibenclamide, a second-generation sulfonylurea, is commonly prescribed to patients who do not respond to the standard initial treatment, metformin. Glibenclamide stimulates insulin secretion by inhibiting ATP-sensitive potassium channels located on β cells, resulting in elevated levels of intracellular potassium and calcium ions. Consequently, the heightened level of calcium within the cell triggers the secretion of granules that contain insulin.

Glibenclamide, also known as glyburide, is an oral medication used to treat type 2 diabetes by increasing insulin secretion from the pancreas[53]. It Binds to sulfonylurea receptors 1 (SUR1) on beta cells. It Inhibits ATP-sensitive potassium channels on beta cells, which prevents potassium from effluxing through the KIR6.2 channel. Glibenclamide depolarizes beta cells which opens voltage-

sensitive calcium channels. It Increases Calcium levels inside the cell, which triggers the secretion of granules containing insulin.

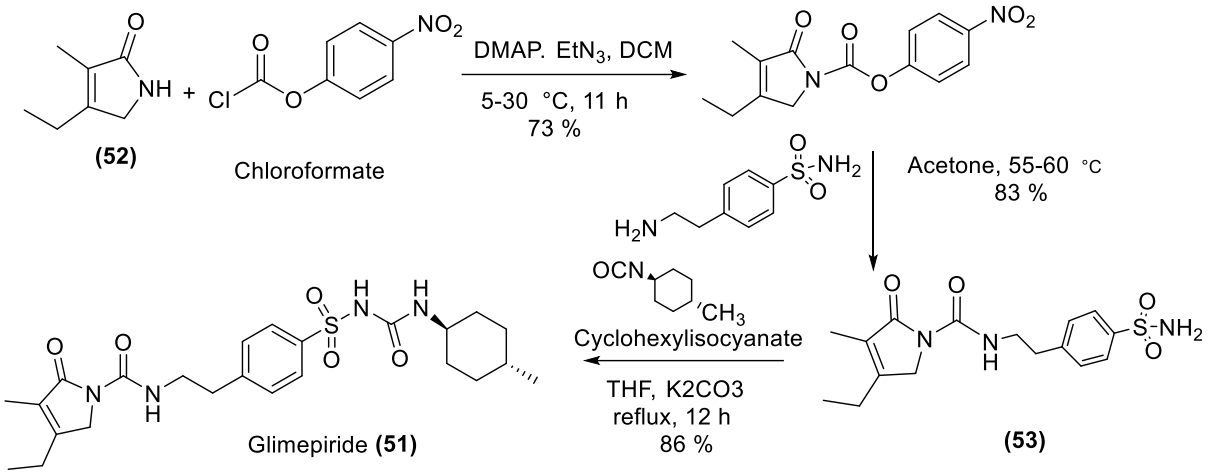
2.1.7. Glimepiride

Weyer and colleagues originally reported Glimepiride in 1983[54] (Scheme 17). The authors began by synthesizing β-phenethylisocyanate **47** using phosgene. A further reaction between the isocyanate and 3-ethyl-4-methyl-2.5-pyrrolidin-2(1H)-oneproduced the di-amide **48**. Chlorosulfonication of diamide **48** produced (Nni*p*-chlorosulphonylphenethyl)- urea sulfonyl chloride **49**, which was then treated with ammonia to produce the respectivesulfonamide **50**. The process of synthesizing Glimepiride **51** involved treating this sulphonamide with *trans*-4-methylcyclohexylisocyanate, which was made concurrently by reacting *trans*-4-methyl cyclohexylamine with phosgene. Moreover, because of difficulties with chlorosulfonication selectivity, the purity of the sulphonamide did not surpass 95%.



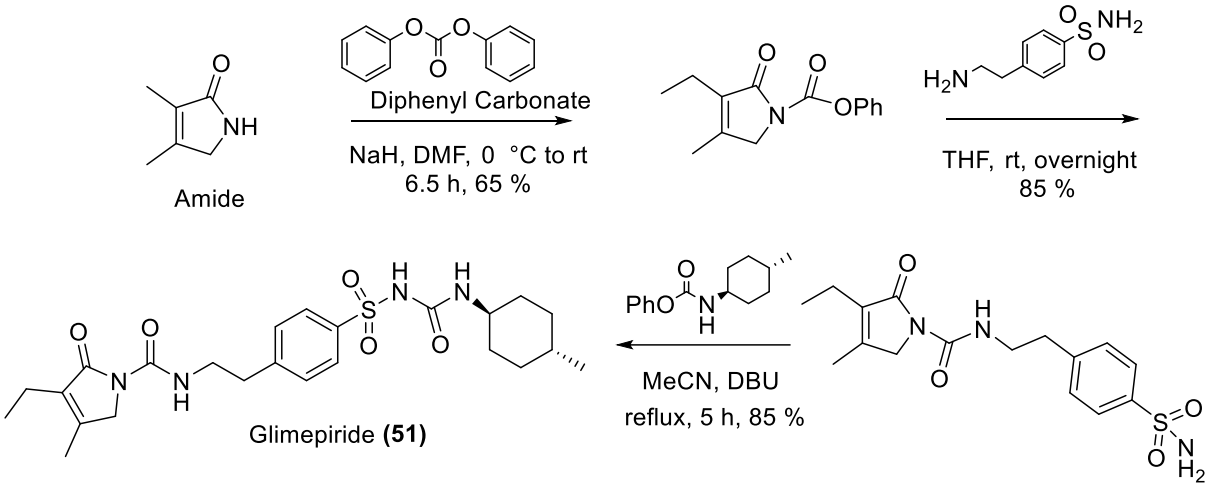
Scheme 17. Synthesis of glimepiride from *trans*-4-methylcyclohexylisocyanate

A three-step synthesis process for Glimepiride was shown by Tanwar *et al.*[55]. After 3-ethyl-4-methyl-2.5-pyrrolidin-2(1H)-one **52** was treated with 4-nitrophenyl chloroformate to create the 4-nitrophenylcarbamate, the latter was reacted with 4-sulphonamidophenylethylamine in acetone at 55-60°C which provided the urea **53** in 83% yield. This urea gave Glimepiride **51** in 83% yield on reaction with *trans*-4-methylcyclohexylisocyanate by refluxing in THF/K_2CO_3 for 12hrs. The selectivity issues related to chlorosulfonation were avoided by the authors by using commercially available sulphonamide, and chromatography was not needed for intermediate purification (Scheme 18).



Scheme 18. Synthesis of glimepiride in three steps

Tanwar and associates[55], used the commercially accessible sulphonamide in order to circumvent the previously described concerns with selectivity associated with its manufacture. Additionally,the approach produced the important intermediate 4-ethylphenyl sulfonyl chloride, achieving a purity level of 99%. Using diphenyl carbonate instead of alternative carbonylation reagents such air-sensitive chloroformates, dangerous phosgene, CO, and CO_2, the authors carried out carbonylation reactions. Using three stages and column chromatography to purify two of the intermediates, Glimepiride**51** was obtained in an overall yield of 39%. The procedure's energy efficiency was increased by doing the first two stages at room temperature (Scheme 19).



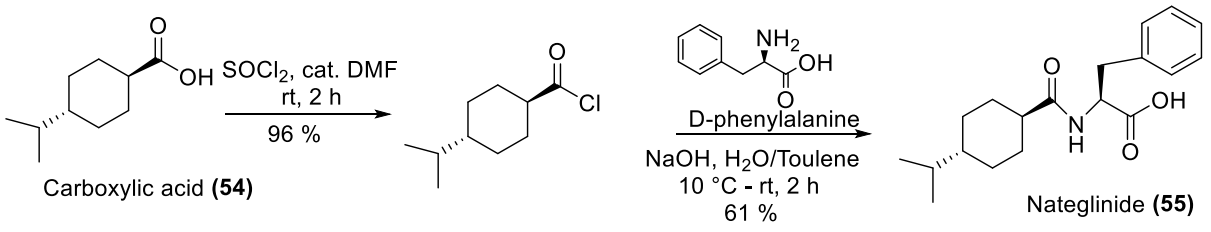
Scheme 19. Synthesis of glimepiride using diphenyl carbonate in the first step.

Glimepiride binds to receptors on the surface of pancreatic B-cells that are dependent on adenosine triphosphate (ATP) for potassium channels, same as other oral insulin secretagogues. Potassium exits the cell, calcium enters the cell, and insulin is released when these channels close and the membrane depolarize[56]. Since Glimepiride is integrated into a 65-kDa protein-binding site on B cells, it seems to be different from the other sulfonylureas[57]. Glyburide and most other sulfonylureas are integrated into a 140 kDa protein[57].

Glimepiride has a significantly lower binding affinity for the B-cell receptor than glyburide. It also dissociates from the receptor site at a rate of eight to nine times faster than glyburide. Theoretically, less fixed-receptor blockage than is seen with the other sulfonylureas, a modification of insulin release, and a reduced ability to induce hypoglycemia come from glimepiride binding at the specific 65-kDa protein-binding region[58].

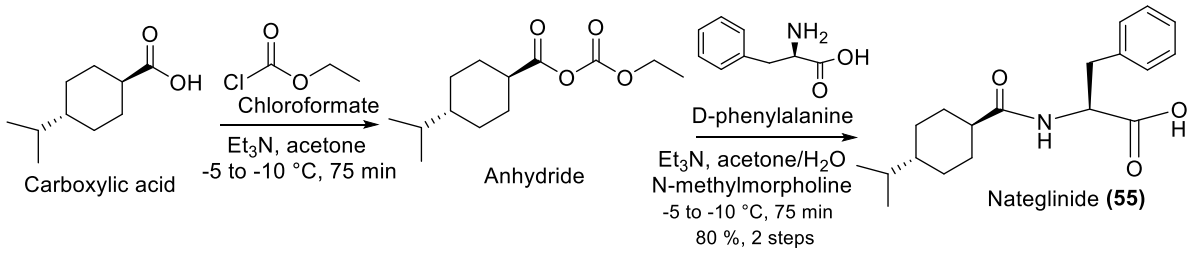
2.1.8. Nateglinide

T*rans*-isopropylcyclohexyl carboxylic acid **54** conversion to its acyl chloride, which was then used to manufacture nateglinide[59] **55**. After amidation of the acyl chloride with *D*-phenylalanine, Nateglinide was produced with a yield of 58% overall (Scheme 20). This two-step process is quick, but using caustic and poisonous $SOCl_2$ is still not ideal. Furthermore, the use of D-phenylalanine in its free amine state led to the production of unwanted side products.



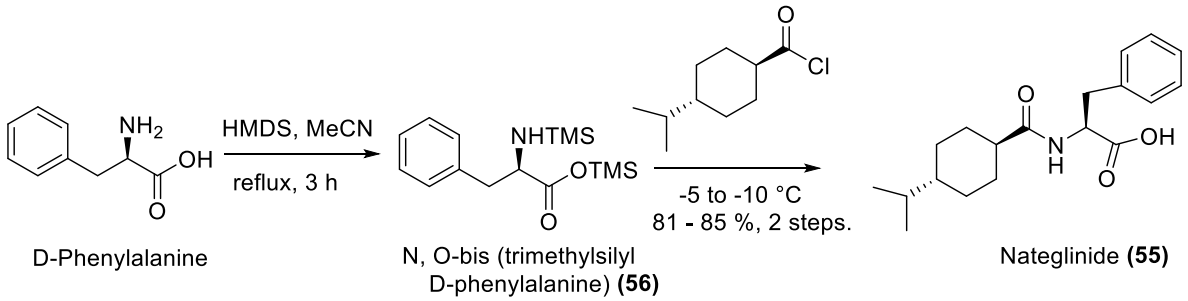
Scheme 20. Synthesis of Nateglinide from *tans*-isopropylcyclohexyl carboxylic acid.

A two-step synthesis of Nateglinide **55** by carbonic anhydride production was described in 2004 by Chandrasekhar *et al*.[60]. Using their method, the acid anhydride was produced by activating *trans*-isopropylcyclohexylcarboxylic acid with ethyl chloroformate. To prevent amino acid racemization, extra ethyl chloroformate and Et_3N had to be used. Nateglinide was produced by reacting to the anhydride with D-phenylalanine, in overall yield of 80% and 94-55% purity. Without the need for intermediary purification, the authors were able to produce Nateglinide at a multigram scale. Precipitation was used to purify the target chemical, Nateglinide, and column chromatography was not necessary. Nevertheless, D-phenylalanine had an unprotected carboxylic acid group which led to undesirable side products. Moreover, ethyl chloroformate is very susceptible to moisture and air (Scheme 21).



Scheme 21. Synthesis of nateglinide from *trans*-isopropylcyclohexylcarboxylic acid derivative and chloroformate

Khamar *et al.* synthesized Nateglinide by employing $(COCl)_2$ as a substitute chlorinating agent[61]. N, O-bis (trimethylsilyl D-phenylalanine) **56** was produced by silylation with HMDS (Scheme 22). This was followed by amidation with *trans*-isopropylcyclohexylcarbonyl chloride, and desilylation to give Nateglinide **55** in >99.7% purity and, 78-82% total yield. Despite causing more transformations, the protective group chemistry was employed to avoid the formation of unwanted side products generated by utilizing *D*-phenylalanine in its free amine form.

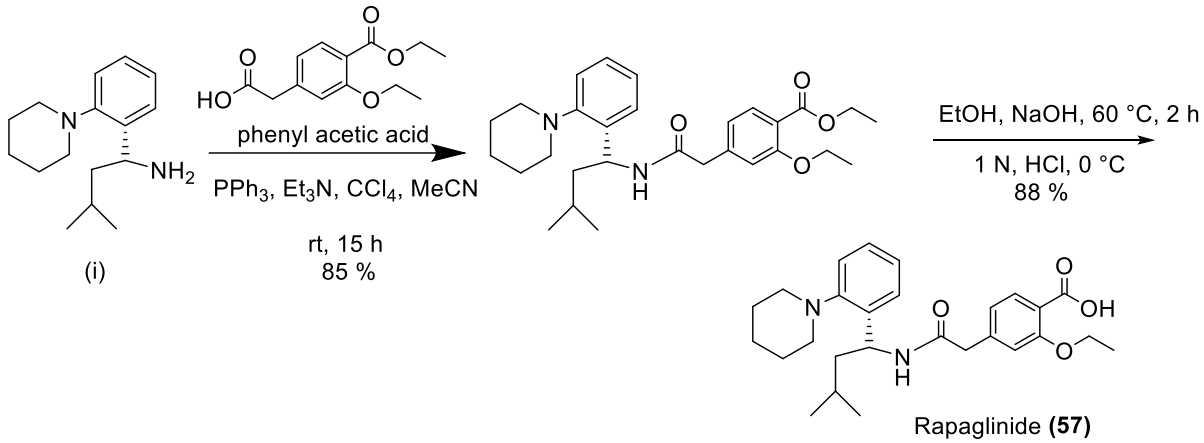


Scheme 22. Synthesis of Nateglinide from Phenylalanine and *trans*-isopropylcyclohexyl-Carbonyl acyl chloride derivative

By blocking potassium (K+ATP) channels that are dependent on adenosine triphosphate, Nateglinide lowers potassium outflow. The β cell becomes depolarized as a result, opening voltage-dependent calcium channels and resulting in calcium influx. Pancreatic islets release insulin in response to the subsequent rise in intracellular calcium[62-64]. A similar method of action is exploited by Repaglinide[65]. Nateglinide functions only in patients with functional β cells in the pancreatic islets, as is the case with all insulin secretagogues. Nateglinide's action is glucose-dependent; lower glucose concentrations cause it to work less actively[66]. Nateglinide is more selective for β cells, has a quicker onset of inhibitory impact on the K+ATP channels, and a quicker reversal of effect than Repaglinide, although being less effective. After Nateglinide was added, the 50% inhibition of K+ ATP channel activity was observed after 4.1 minutes (t1/2(on)), but Repaglinide required 12 minutes. After Nateglinide was removed, the time needed to restore to 50% blockage of K+ ATP channel activity (t1/2(off)) was 35 minutes, whereas Repaglinide required 175 minutes. With an estimated off-rate of 1-2 seconds, Nateglinide dissociates from the sulfonylurea receptor 1 (SUR1) quickly[67]. As a selective agent, Nateglinide exhibits a low affinity for K+ ATP channels in vascular and cardiac tissues and a high affinity for K+ ATP channels in the β cells of the pancreatic islet. When compared to K+ ATP channels in cells from the coronary artery and aorta, Nateglinide exhibits a 311- and 45-fold stronger selectivity for these channels in the β cells of the pancreatic islet, respectively Glyburide, on the other hand, was nonselective between β cells and vascular cells, while Repaglinide was almost 16 times more selective for β cells than vascular cells. At therapeutic doses, glyburide, Repaglinide, and Nateglinide all decreased the K+ ATP current in pancreatic β cells by 62%; however, in cardiac myocytes, Nateglinide decreased the K+ ATP current by 39%, glyburide by 55%, and Repaglinide by 66%.

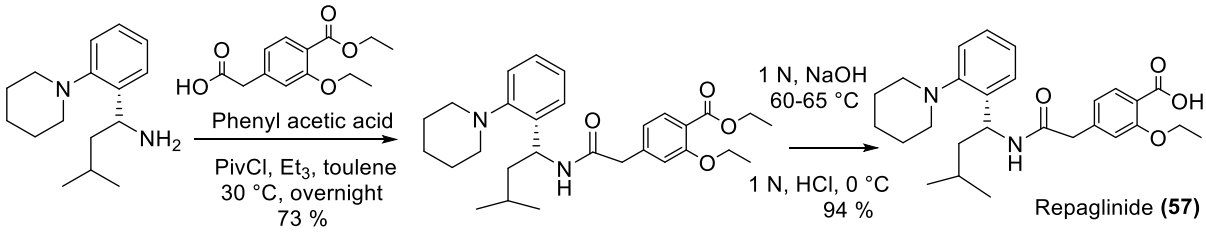
2.1.9. Repaglinide

Repaglinide **57** was made in two steps by Grell *et al.*[68] as clearly described in the following scheme 23 in a 75% total yield. The method's shortcomings include the use of a costly, hazardous, and extremely moisture-sensitive DCC and the time-consuming purification of the final product caused by the creation of DCU and Ph_3PO as by products. Moreover, CCl_4 is undesirable for large-scale manufacturing since it poses a risk to human health and ecosystems (Scheme 23).



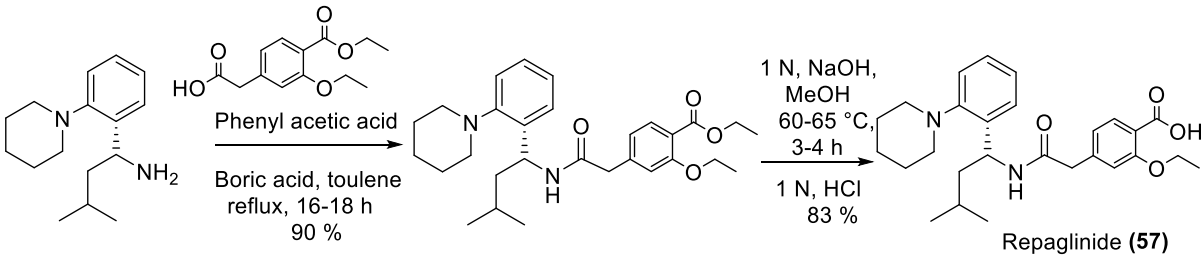
Scheme 23. Synthesis of Repaglinide from secondary amine derivative and 3-ethoxy-4 ethoxycarbonyl Phenyl acetic acid.

Similar to Grell *et al.* and Ray *et al.* published in 2003 a synthetic procedure for Repaglinide **57** that is both economical and practically applicable in industry. The only difference is that the authors utilized PivCl(Pivaloyl chloride) to activate the phenyl acetic acid during the amidation stage. Repaglinide was obtained with a 99.5% purity and 67% total yield. The use of DCC and PPh_3, which result in the by-products DCU and Ph_3PO, respectively, and demand laborious product purification, was eschewed by the authors. Nevertheless, compared to Grell *et al*'s. method, this process has a lower overall yield due to racemization, the usage of moisture, air-sensitive and corrosive PivCl, lengthy reaction durations, and other issues[69] (Scheme 24).



Scheme 24. Synthesis of Repaglinide in presence of PivCl

Byusing the less expensive boric acid for the amidation step, reported a two-step synthesis method to Repaglinide**57** that was comparable to Grell et al.'s and Ray *et al.*'s. The laborious purification that comes with using chemicals like DCC and PPh_3 was omitted by the authors. Repaglinide was obtained with 99.8% purity and 74% total yield. The process, which includes straightforward workup steps like filtration and precipitation, produced the required product in high yields and purity (Scheme 25).

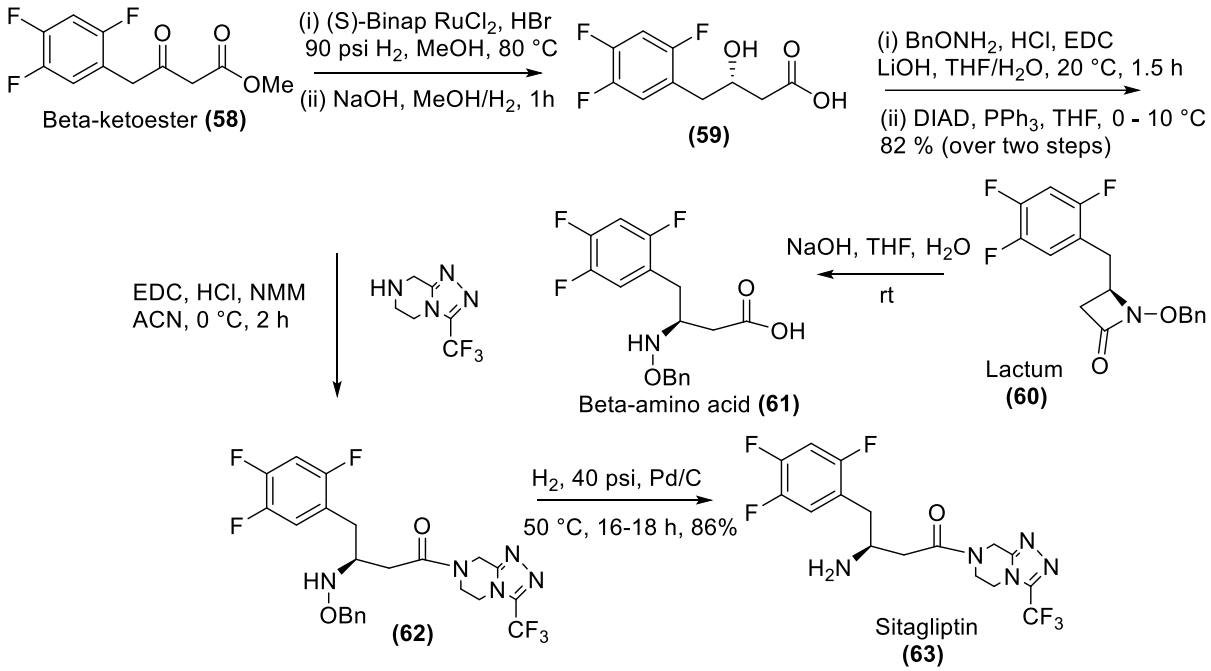


Scheme 25. Synthesis of Repaglinide using Boric acid in the first step.

Repaglinide stimulates release of insulin from pancreatic β-cells by inhibiting potassium efflux *via* closure of ATP-regulated K+ channels. This results in depolarisation of the cell and opening of voltage-dependent Ca++ channels, which increases influx of calcium into the β-cell and causes release of insulin. Repaglinide should be taken at least twice daily, with a maximum dosage of 16 mg before each meal. Repaglinide is quickly absorbed and has around 63% bioavailability after oral dosing. It is a good alternative for patients with renal failure since it is metabolized in the liver into inactive metabolites and is primarily eliminated into the faeces*via* the bile. However, as this drug's pharmacokinetics may be dramatically altered in patients with liver illness, vigilance should be exercised. According to another study of Repaglinide, the basal insulin release is not significantly affected by (10 uM). Still, when glucose levels are higher than 5 mmol/L, Repaglinide has been shown to induce the release of insulin in a concentration-dependent way. In contrast to Nateglinide, which mostly increases insulin in the first phase Repaglinide does not evidently cause biphasic insulin secretion in islets that have been perfused. Repaglinide did not prevent glucose-stimulated proinsulin production in isolated rat cells, in contrast to sulfonylureas. Repaglinide's insulinotropic effects were notably unrelated to a discernible rise in either endogenous or exogenous food metabolism. In experiments employing isolated perfused rat pancreas, neither Repaglinide nor Nateglinide significantly affected glucagon release[69].

2.1.10. Sitagliptin

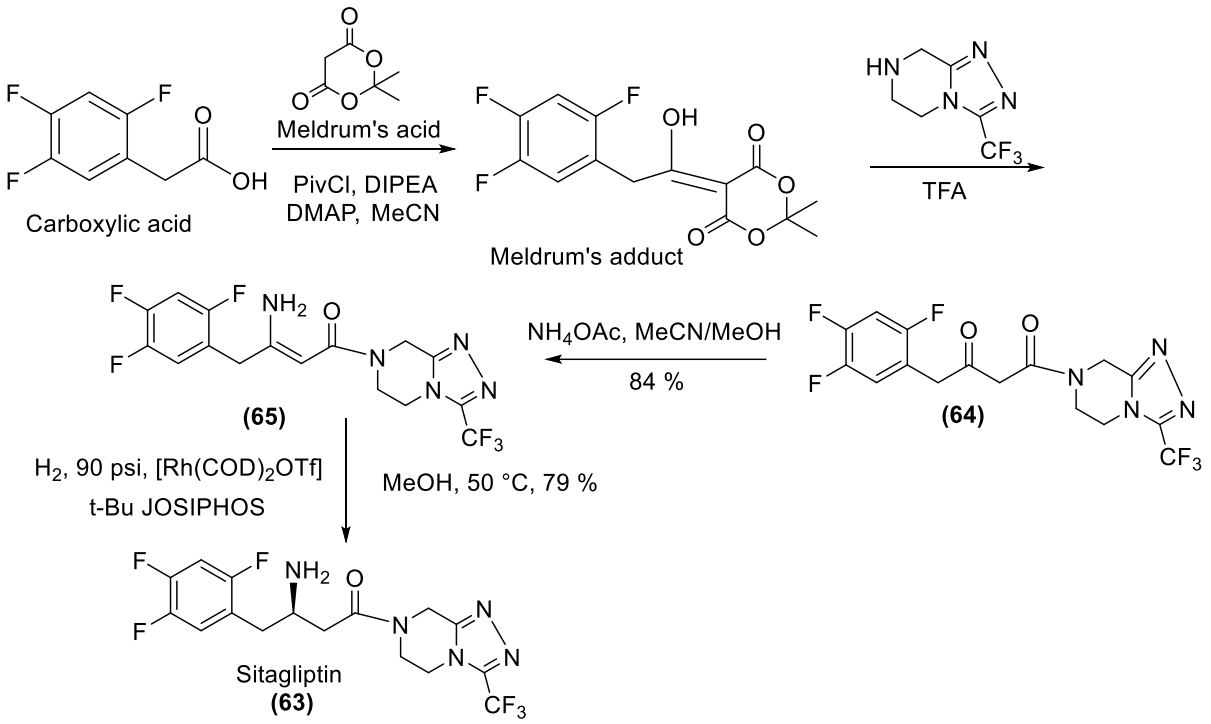
First-generation synthesis pathway for Sitagliptin was reported by Hansen *et al.*[70]. This method begins with asymmetric carbonyl group reduction and proceeds to ester hydrolysis of the beta-ketoester **58** to yield the chiral hydroxy acid **59**. After compound **59** was aminated, stereo-inversion and cyclization to lactam **60** occurred under Mitsunobu conditions. The beta-amino acid **61** was produced *via* ring opening of the lactam ring, and compound **62** was then formed by combining it with triazolopiperazine(3-trifluoromethyl-6,8-dihydro-5*H*-[1,2,4]triazolo[4,3-a]pyrazine). Sitagliptin **63** was obtained through hydrogenation of (ii, to remove protecting groups) in a 52% total yield. For a 7-step technique, the overall yield was high, but waste generation increased due to laborious isolations and purifications (Scheme 26).



Scheme **26**. Synthesis of Sitagliptin from β-ketoester

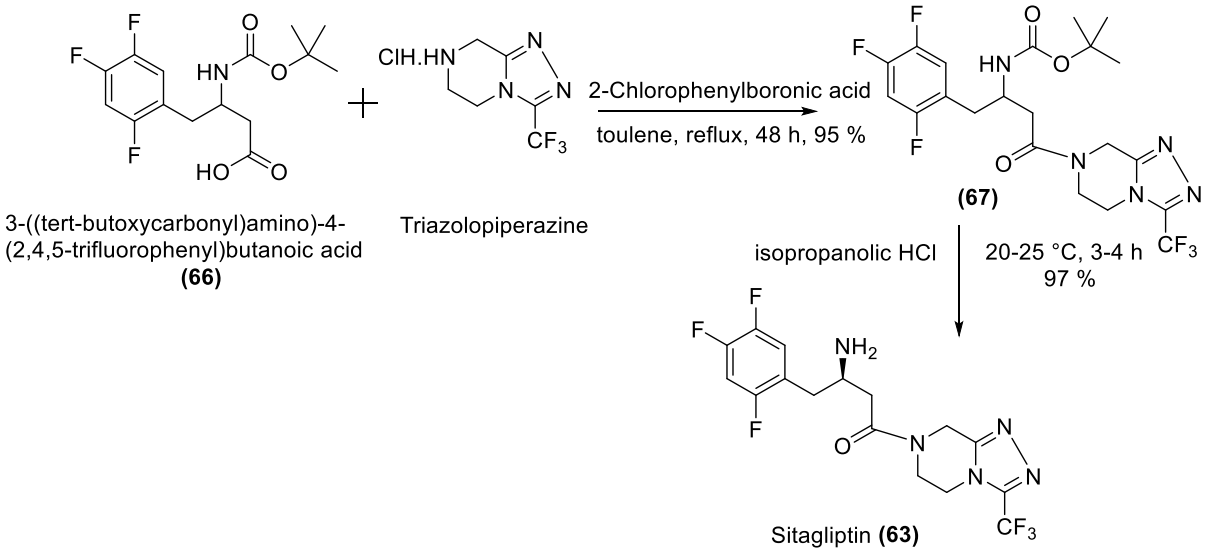
An extremely creative, effective, and reliable synthetic pathway to Sitagliptin was shown by Balsells and associates[71]. PivCl was used to activate carboxylic acid. Meldrum's acid was then added to the reaction to produce the Meldrum's adduct *in situ*. This was then combined with triazolopiperazine

to produce β-ketoamide **64** in situ. Enamine **65**was produced by aminating β-ketoamide with NH_4OAc. This was the crucial intermediate. Finally, Sitagliptin**63** was produced by enantioselective hydrogenation of enamine. An impressive 66% total yield was attained, a 14% rise over the β-lactam approach. Except for DIPEA, which was utilized in the first step, all of the stoichiometric reagents used in this approach were integrated into the final molecule, in contrast to the first-generation route (Scheme 27).



Scheme 27. Synthesis of sitagliptin from fluoro substituted aromatic carboxylic acid.

A synthetic approach for Sitagliptin**63** that is industrially practicable, less hazardous, and environmentally benign was reported by Gori *et al.*[72]. This route resulted in enhanced yield, chemical purity, and optical purity. The triazolopiperazine was condensed with amino protected chemical **66** to get intermediate **67**. Sitagliptin was produced by boc-deprotection in two steps with an overall yield of 92%, negating the need for chromatographic purification. Because of its simplicity, the approach can therefore be readily implemented for large-scale synthesis. Furthermore, this approach is made more appealing by the use of 2-chlorophenylboronic acid, a cheap, commercially accessible "green" catalyst (Scheme 28).



Scheme 28. Synthesis of Sitagliptin from 3-((tert-butoxycarbonyl)amino)-4-(2,4,5-trifluoro phenyl)butanoic acid in presence of 2-chlorophenylboronic acid

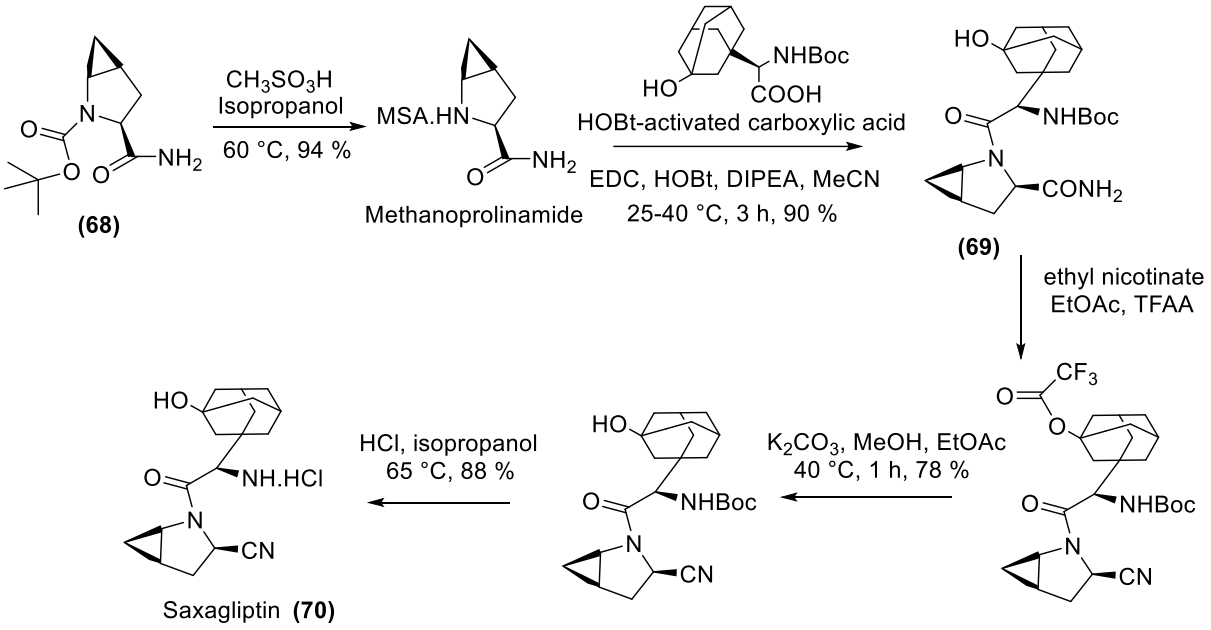
Sitagliptin enhances the effects of the incretin hormones glucose-dependent insulinotropic peptide (also known as gastric inhibitory polypeptide [GIP]) and GLP-1. Secreted in the intestine in response to food, GIP and GLP-1 have a role in the regulation of glucose homeostasis. Activation of GIP and GLP-1 receptors on pancreatic β-cells leads to increased levels of cyclic adenosine monophosphate and intracellular calcium, with subsequent glucose-dependent insulin secretion. In addition, sustained receptor activation is associated with insulin biosynthesis and stimulation of β-cell proliferation. Animal and *in vitro* data fur their suggest that activation of GIP and GLP-1 receptors promotes β-cell resistance to apoptosis, proliferation, and neogenesis, resulting in enhanced β-cell function. Additional functions of GLP-1 include inhibition of glucagon secretion from pancreatic α-cells, resulting in decreased hepatic glucose production; slowing of gastric emptying; suppression of food intake; and enhancement of glucose disposal *via* neural mechanisms[73,74].

2.1.11. Saxagliptin

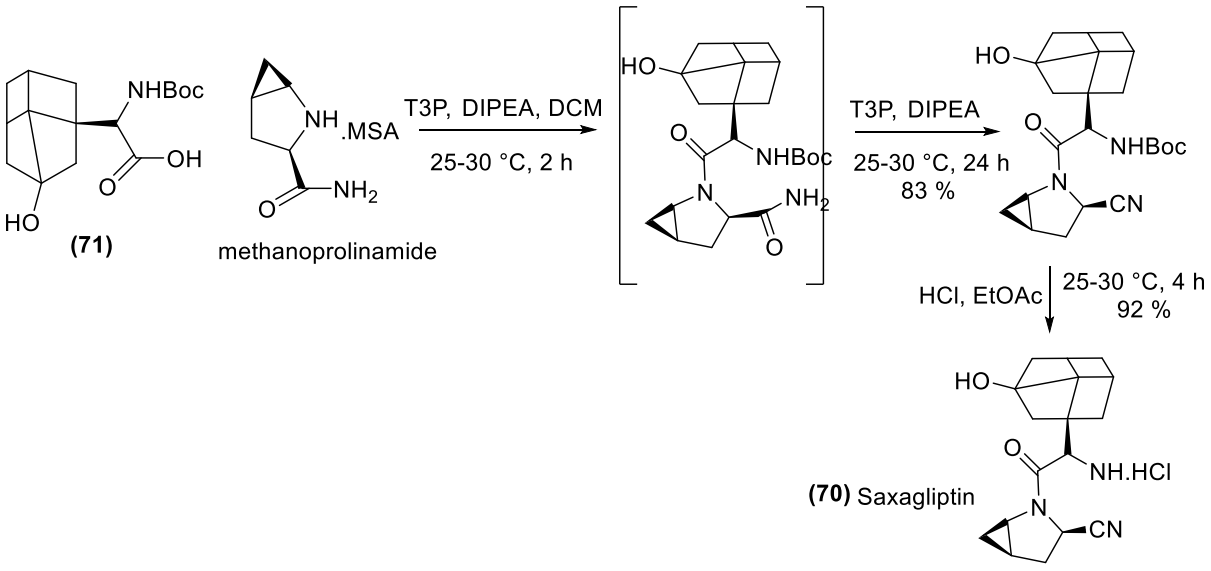
The Boc protected methanoprolinamide **69** was obtained by Savage and colleagues' preparation[75] of Saxagliptin, which began with **68** and continued as shown in Scheme 29to provide. Saxagliptin **70** with an overall yield of 58%. The process necessitates significant purification despite the high overall yield because it involves the use of extremely dangerous compounds including TFAA, EDC, and HOBt, and using protective group chemistry which was not a desirable option.

A straightforward, economical, reliable, high-yielding, safer synthesis method for Saxagliptin was shown by Macharla *et al*.[76]. The authors began by amidatingthe MSA salt of 2,3-methanoprolinamide using the N-Boc derivative **71** and proceeded as shown in Scheme 30 to provide 76% total yield of Saxagliptin **70**. Although the usage of protective group chemistry could not be avoided, column chromatographic purification was avoided.

The impact of DPP-4 inhibitors, particularly Saxagliptin, on the cardiovascular system is a topic of discussion. Saxagliptin (10 mg/kg/day) treatment for human atherosclerosis was investigated *in vivo* using transgenic mice model CETP-ApoB100. The results showed that Saxagliptin therapy addressed endothelial dysfunction and a smaller region of atherosclerotic plaques. Nevertheless, research including 16,492 T2DM patients found that hospitalization rates for heart failure were rising even while DPP-4 Saxagliptin-induced suppression did not alter the risk of ischemic episodes[77]. Thus, Saxagliptin enhances glycaemic control; however, further techniques are needed to reduce cardiovascular risk in individuals with type 2 diabetes.



Scheme 29. Synthesis of Saxagliptin from 1-N-Bocmethanoprolinamide.

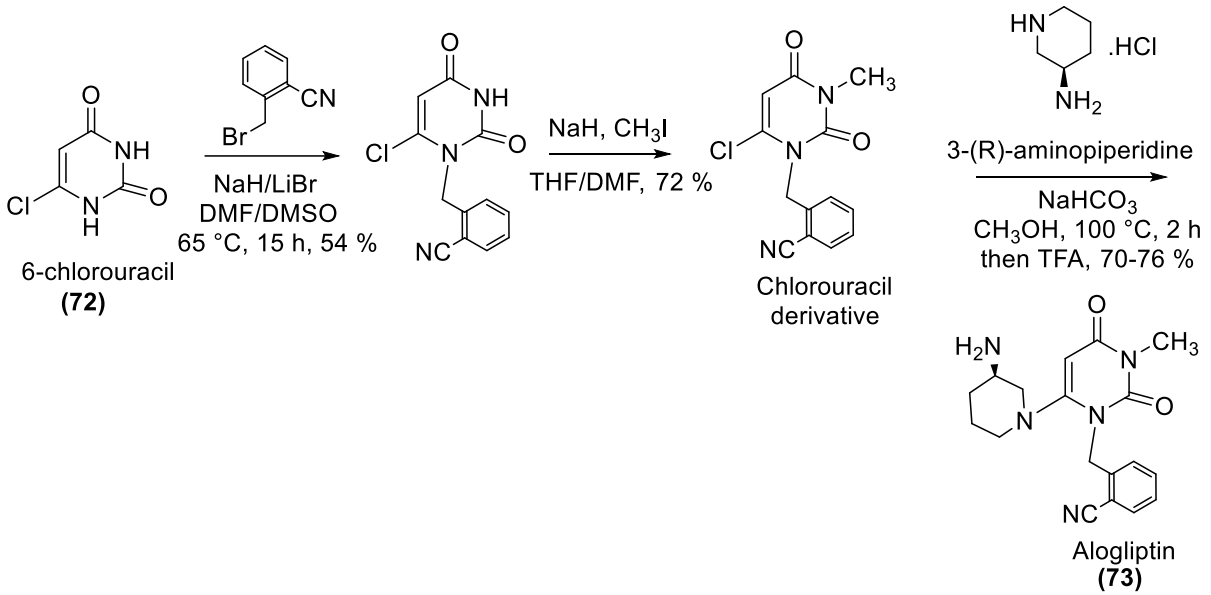


Scheme 30. Synthesis of Saxagliptin from 2,3-methanoprolinamide in presence of DIPEA.

However, it was found that Saxagliptin works well as an antidiabetic drug for T2DM patients who are having renal failure. These individuals were given 2.5 mg of Saxagliptin once day, and the frequency of adverse events and hypoglycemia episodes was similar in the treatment and placebo groups[78]. Further research is needed to validate these findings and understand how DPP-4 inhibitors work in cells and organs. Saxagliptin is a DPP-4 inhibitor that improves glycemic control by blocking the inactivation of the incretin hormones GLP-1 and glucose-dependent insulinotropic polypeptide. Its active metabolite, M2, is two times less effective than the parent medication. This lowers postprandial glucose and glucagon levels, boosts insulin production, and raises GLP-1 levels. When it comes to inhibiting DPP-4, Saxagliptin and M2 exhibit greater selectivity than DPP-8 (400- and 950-fold), DPP-9 (75- and 160-fold), or a broad range of other proteases (>4000-fold)[79].

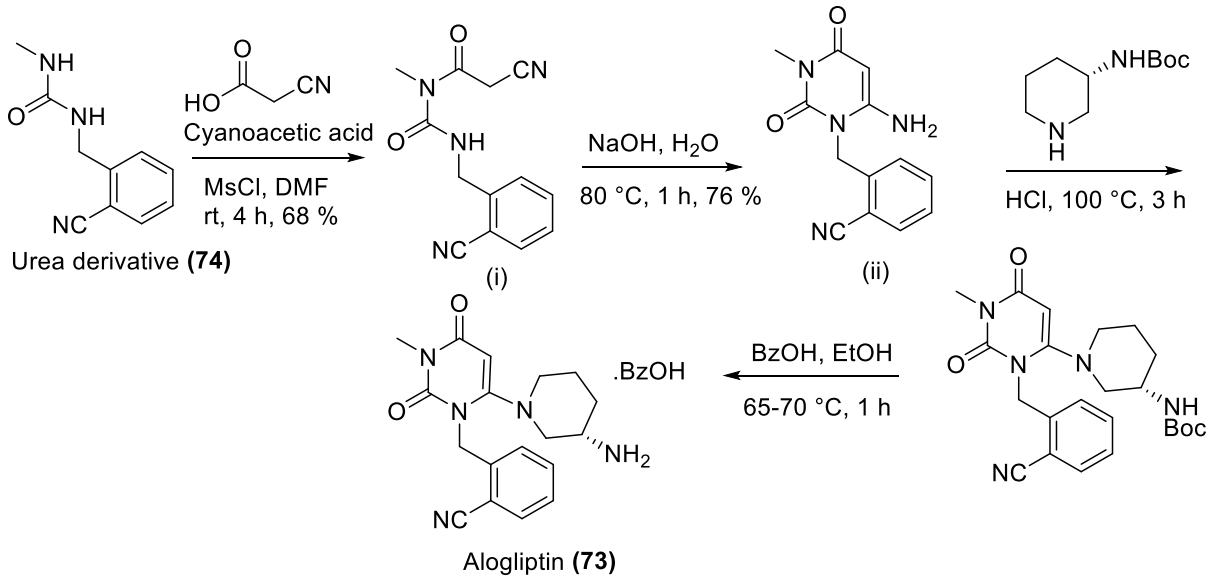
2.1.12. Alogliptin

Following its initial discovery in Japan by Feng *et al.*[80] the US FDA first approved Alogliptin, which is marketed under the trade names Nesina® and Vipidia®. Starting from 6-chlorouracil and involving 3-(*R*)-aminopiperidine hydrochloride according to Scheme 31, Algoliptin can be prepared in an overall yield of 27–30%. However, the difficulty of separating and purifying solvent mixtures with high boiling points (like DMF/DMSO) for recycling, the use of strictly anhydrous conditions and NaH are a significant drawback of this approach.



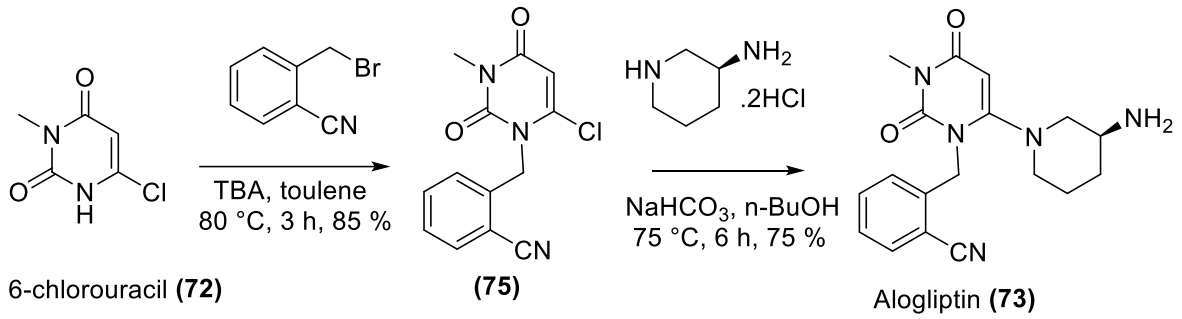
Scheme 31. Synthesis of alogliptin from 6-chlorouracil.

The authors began the second approach[80]from 1N-*o*-cyanobenzyl-3N-methylurea **74** and continued as described in Scheme 32 to providea 49% increase in overall yield without the need for chromatographic purification.



Scheme 32. Synthesis of alogliptin from 1N-*o*-cyanobenzyl-3N-methyl urea

A two-step synthesis of Alogliptin was revealed in 2014 by Jiatong and colleagues[81]. The intermediate 6-chloro-1(*o*-cyanobenzyl-3- methyluracil**75** was converted to Alogliptin**73**rapidly in overall yield of 64% without theuse of chromatographic techniques (Scheme 33).

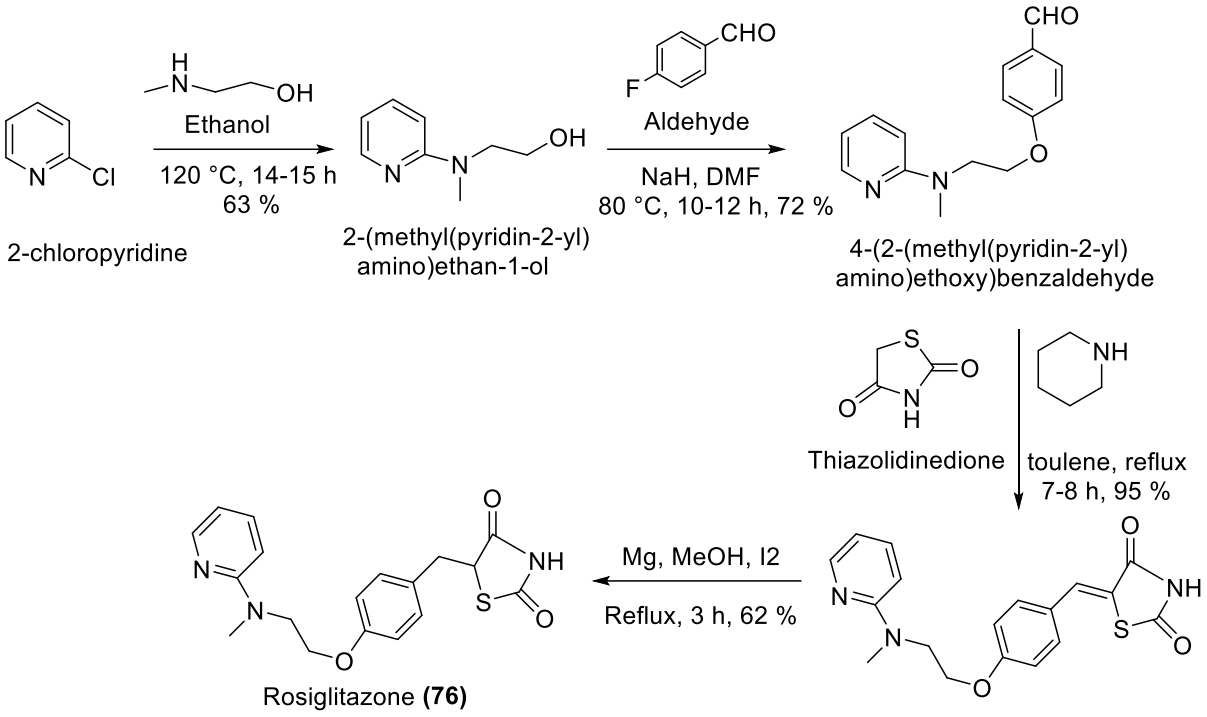


Scheme 33.A two steps synthesis of Alogliptin from 6-chlorouracil

Alogliptin inhibits the DPP-4 enzyme system in a highly selective and effective competitive manner[82]. GLP-1, glucose-dependent insulinotropic polypeptide (GIP), and endogenous incretin hormones are all rapidly cleaved by DPP-4. Following a meal, the gastrointestinal system releases GLP-1 and GIP, which block the release of glucagon and boost postprandial insulin secretion. GLP-1 slows down the rate of stomach emptying, which also contributes to satiety. Although GLP-1 levels and GIP sensitivity are lower in T2DM patients, the insulinotropic response to GLP-1 is not affected[83]. Thus, by inhibiting DPP-4, Alogliptin increases the circulation of endogenous GLP-1 that is active and prevents its inactivation, which has an antihyperglycemic effect. It has been demonstrated that Alogliptin inhibits DPP-4 activity by more than 80%[84].

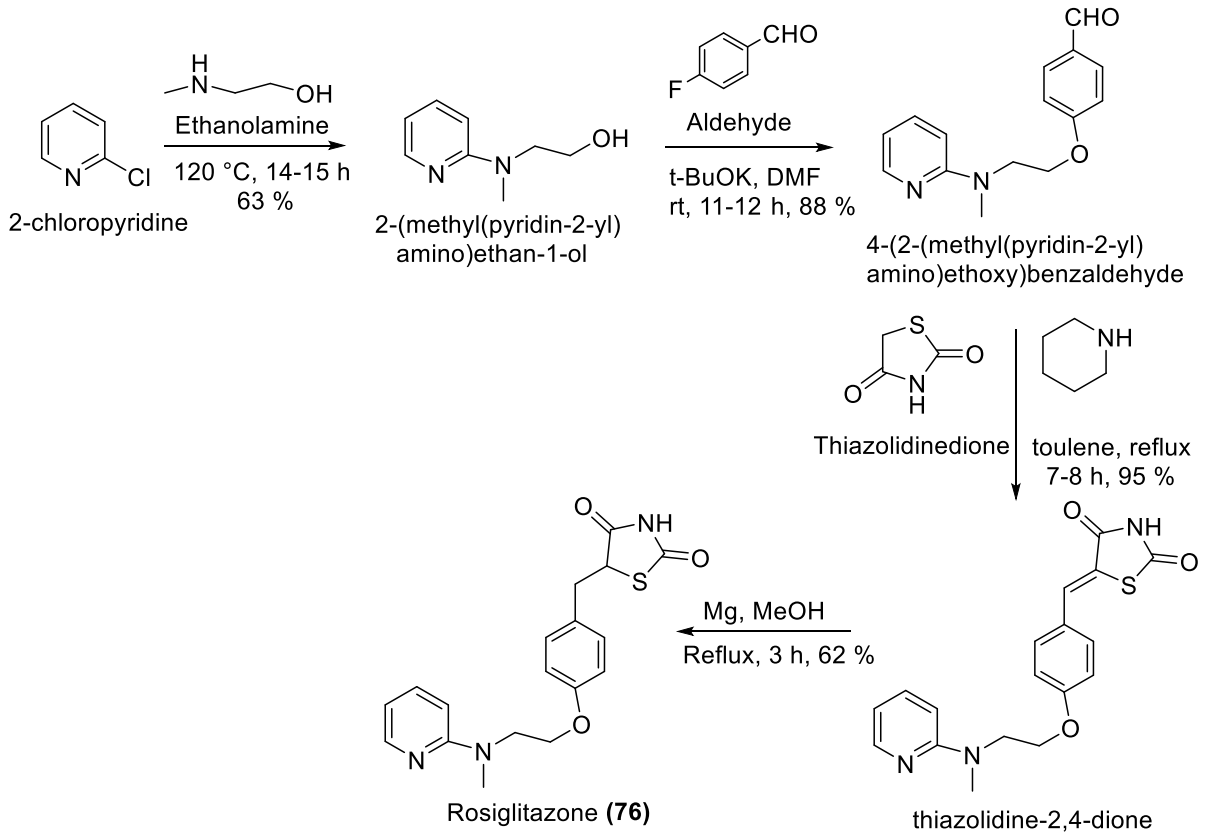
2.1.13. Rosiglitazone

Cantello and colleagues[85]started from 2-chloropyridine and synthesized Rosiglitazone **76** in four steps following the reactions depicted in Scheme 34in overall yield of 26%. Although it is a four-step process, it involves the use of toxic reagents including piperidine and NaH, a lengthy reaction time (36 hours), several lengthy steps for chromatographic purification and a low overall yield.



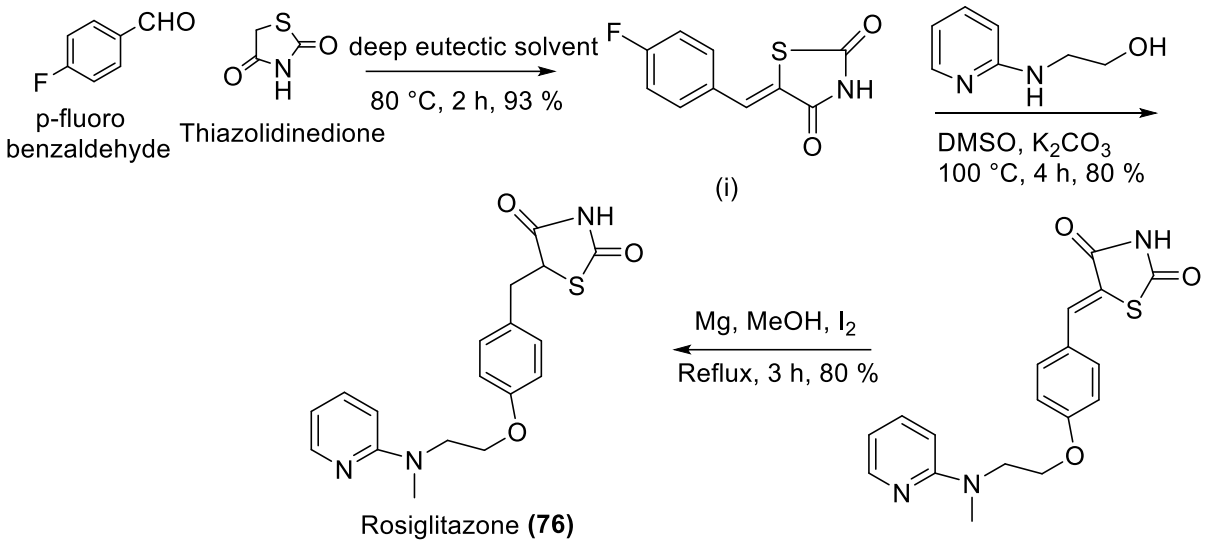
Scheme 34. Synthesis of rosiglitazone from 2-chloropyridine involving NaH.

For the preparation of Rosiglitazone, Vyas[86]marginally improved (from 26% to 32%) the above synthesis of Cantello *et al*. by substituting t-BuOK for NaH and negating the requirement for chromatographic purification (Scheme 35).



Scheme 35. Synthesis of rosiglitazone from 2-chloropyridine involving t-BuOK.

Jawale *et al.*[87] created an alternative improved four-step synthetic pathway to Rosiglitazone **76** in 54% total yield as displayed in Scheme 36. They used the thiazolidine-2,4-dione in the first step in recyclable non-volatile deep eutectic solvent and used the gentler base K_2CO_3 instead of NaH in the second step.

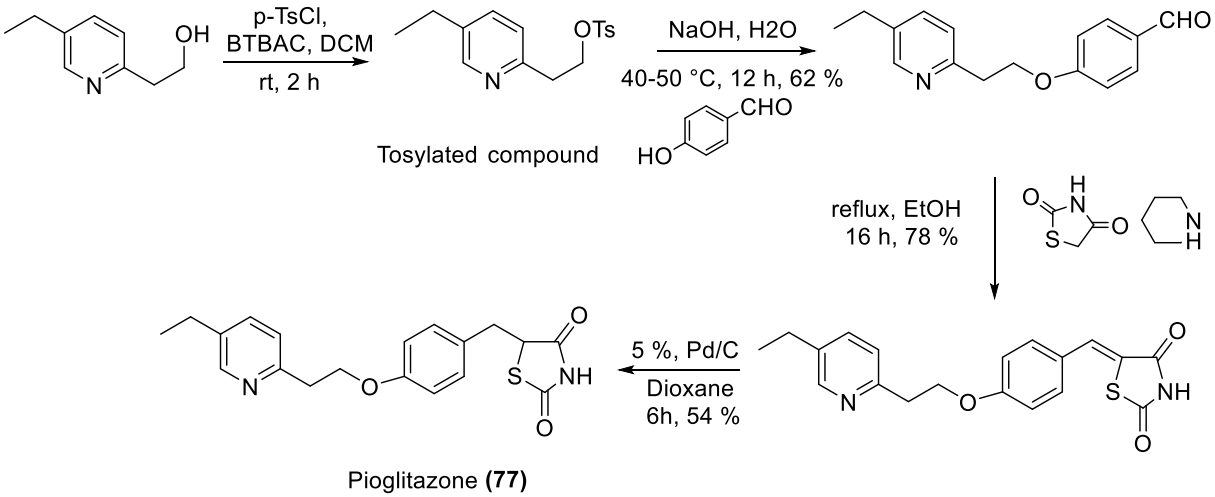


Scheme 36. Synthesis of Rosiglitazone from p-fluorobenzaldehyde and 2,4-thiazolidinedione.

Improvement in insulin sensitivity in muscle and adipose tissue as well as suppression of hepatic gluconeogenesis is the principal pharmacologic activities of thiazolidinediones. Since thiazolidinediones have a range of cellular actions that contribute to their pharmacologic effects, the precise mechanism of action of the medicine is likely complex. Target tissues see a reduction in insulin resistance when PPAR-g is activated because it modifies the expression of genes related to adipogenesis, insulin signaling, and glucose transport, among other metabolic processes. In particular, Rosiglitazone enhances the glucose transporter GLUT4's expression and translocation to the cell surface in adipose tissue[88,89]. Additionally, it raises the expression of genes that are involved in the metabolism of fatty acids in adipocytes, such as adipocyte lipid-binding protein and lipoprotein lipase[90]. The medication reduces leptin expression both *in vivo* and *in vitro*. Leptin is a peptide hormone released by adipocytes that regulates hunger and energy expenditure, and it may also play a role in controlling the amount of fat cells[91]. Rosiglitazone's direct and indirect actions may be combined to produce improved muscle glucose uptake. Tumor necrosis factor-a (TNF-α) may be involved in this signaling process since increases in TNF-α cause insulin resistance in target tissues. Activation of PPAR-g in muscle can also cause adipocytes to send an endocrine signal to muscle that enhances insulin action[92]. The inhibitory effects of TNF-α on insulin activity are blocked by Rosiglitazone[93]. Since TNF-α also promotes the release of free fatty acids from adipocytes, decreased TNF-α activity would be expected to lead to lower rates of lipolysis and lower levels of free fatty acids in circulation. One possible mechanism *via* which Rosiglitazone promotes insulin sensitivity is a reduction in adipocyte lipolysis.

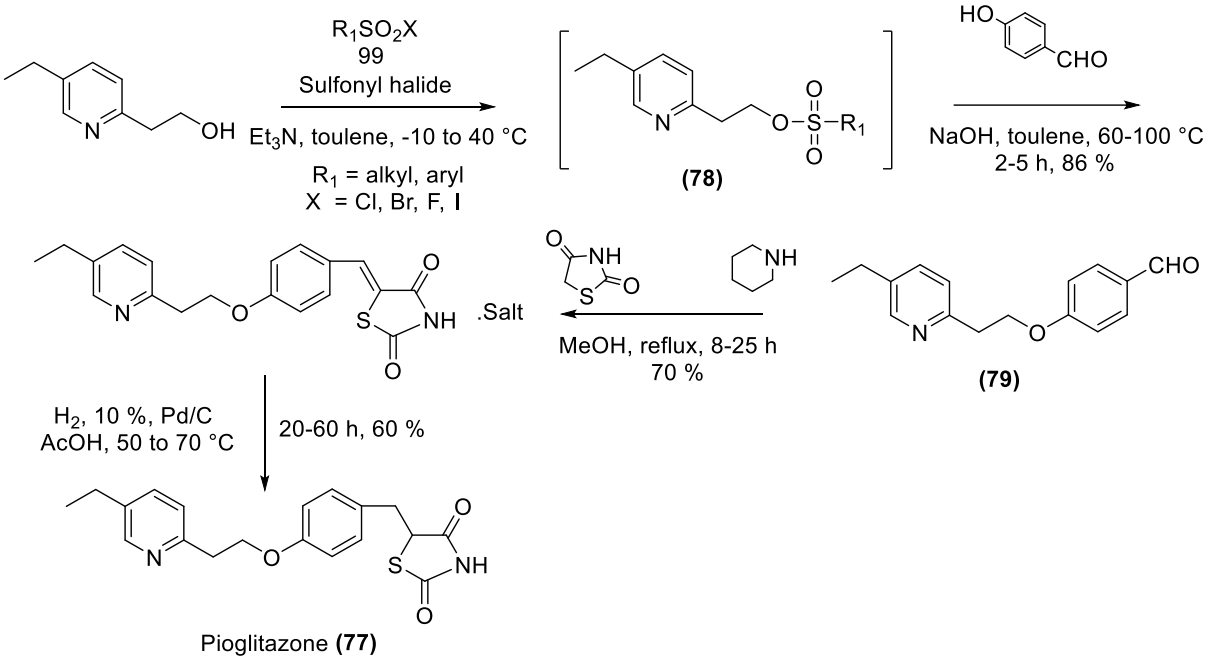
2.1.14. Pioglitazone

Later, Meguro and colleagues[94] developed the synthetic approach to Pioglitazone 77 shown in Scheme 37. Starting from 3- ethyl-4-hydroxyethylpyridine, Pioglitazone was prepared in 26% overall yield in 36 hours *via* tosylation, reaction with *p*-hydroxybenzldehyde, condensation with thiazolidine-2,4-dione and finally catalytic reduction and evading chromatographic processes for intermediate purification.



Scheme 37. Synthesis of Pioglitazone from tosylated3-ethyl-4-hydroxyethylpyridine derivative and Thiazolidinedione.

Pioglitazone was also produced by treating the tosylated compound **78** with *p*-hydroxybenzldehyde, to produce the 4-hydroxybenzaldehyde-ether **79**, which was condensed with thiazolidine-2,4-dione and finally hydrogenated to produce Pioglitazone[95] **77** with a 37% yield overall (Scheme 38).



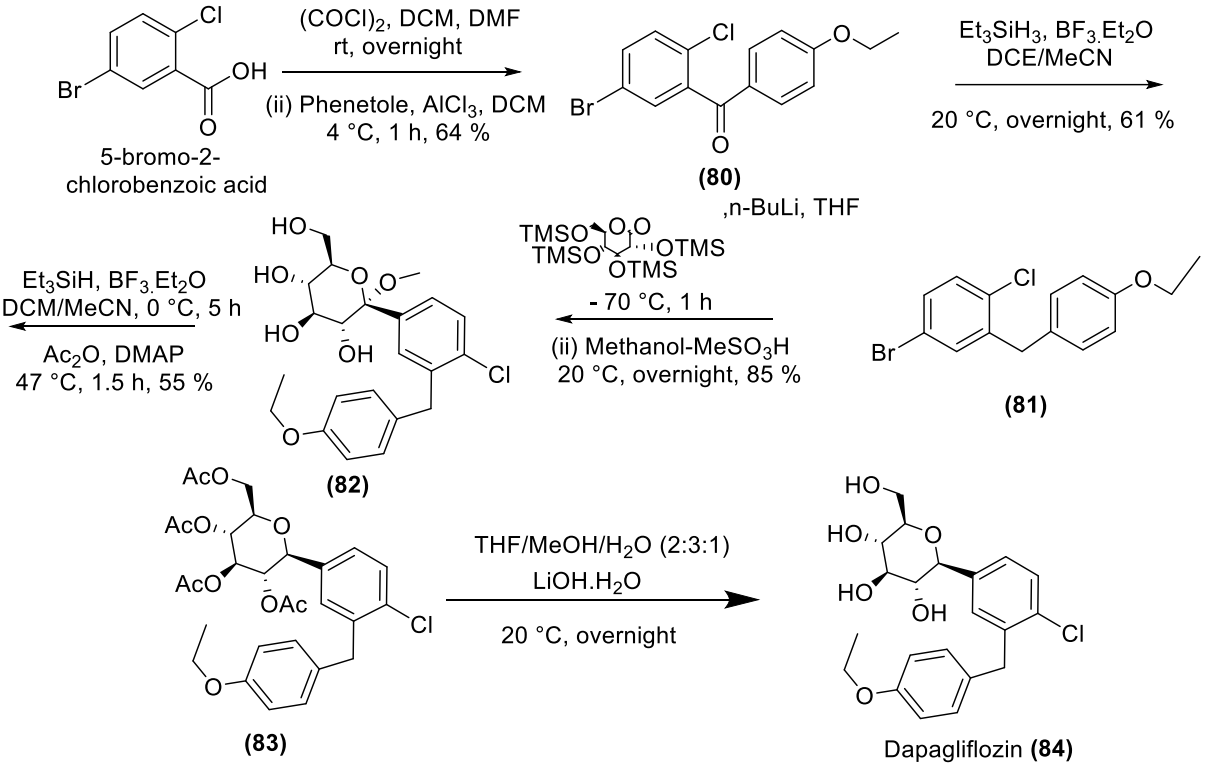
Scheme 38. Synthesis of pioglitazone from 3-ethyl-4-hydroxyethyl pyridine and sulphonyl halides.

Pioglitazone activates PPARY, which increases insulin sensitivity in the liver, adipocytes, and peripheral tissues[96]. The precise mechanism underlying this effect is still unknown. Thiazolidinediones facilitate the uptake and storage of free fatty acids (FFA) as well as the differentiation and proliferation of adipocytes. This may shield pancreatic β-cells and other insulin-sensitive organs from the deleterious metabolic effects of elevated FFA levels[97]. Different adipocyte signaling factors, particularly adiponectin, may be released in a different way to modify non-adipose tissue's insulin sensitivity. Pioglitazone is not an insulin secretagogue; rather, it is dependent on insulin for its positive effects to

occur. It may also help to maintain the activity of β-cells in the islets of Langerhans. By reducing insulin resistance in the liver and peripheral tissues, pioglitazone and its active metabolites—the hydroxy derivatives MII and MIV and the keto derivative MIII—improve dysfunctional glucose homeostasis. This increases insulin-dependent glucose disposal and lowers hepatic glucose output. The antihyperglycemic effects of MII, MIII, and MIV in animal models are 40–60% greater than those of Pioglitazone[98]. Furthermore, MII has a two-fold higher potency than the parent molecule in lowering triglycerides (TG), although MIII and MIV had a somewhat poorer TG-lowering effect than Pioglitazone. In individuals with type 2 diabetes, Pioglitazone lowers hyperglycemia and hyperinsulinemia. In randomised, placebo-controlled trials spanning 12 to 26 weeks, Pioglitazone improved peripheral insulin sensitivity in patients with type 2 diabetes, thereby improving both splanchnic and peripheral glucose uptake[99].

2.1.15. Dapagliflozin

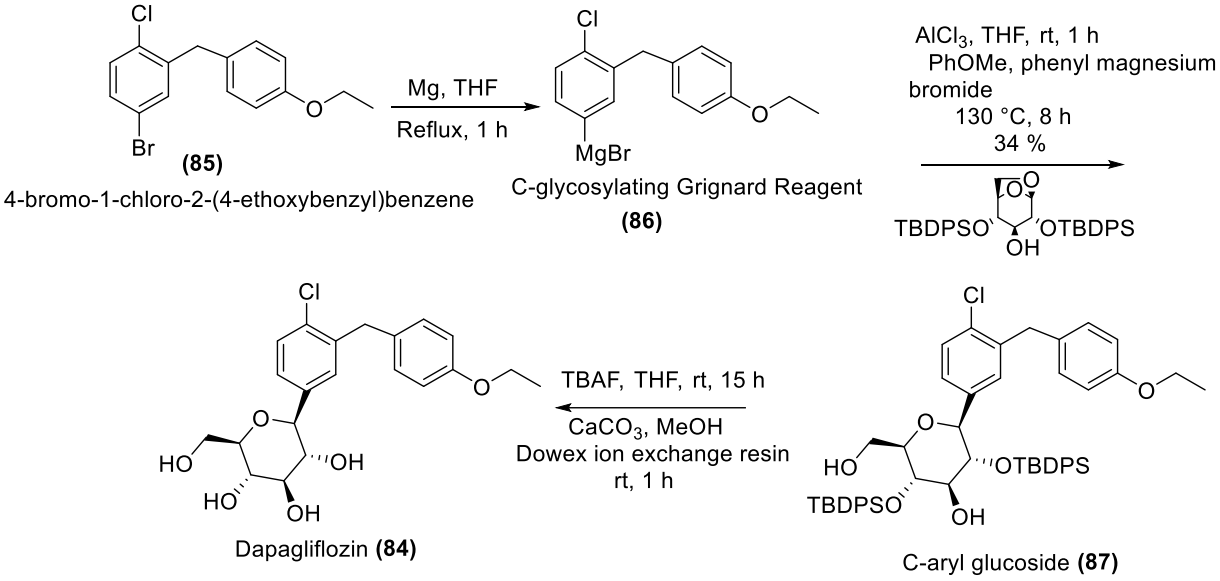
Dapagliflozin was synthesized from commercially available 5-bromo-2-chlorobenzoic acid by Ellsworth and colleagues[100]. They synthesised it starting with aFriedel- Crafts acylation of freshly prepared 5-bromo-2-chlorobenzoyl chloride and phenetole to form the substituted benzophenone **80** which was reduced to the corresponding substituted diphenylmethane **81**, and its bromine atom was substituted by trimethylsilylatedgluconolactone at the carbonyl carbon with concurrent desilylation and mesylation to the methoxy-tetrahydroxy derivative **82** followed by reduction (by $Et_3SiH/BF_3/Et_2O$, 0°C) and acetoxylation (Ac_2O/DMAP) to the respective tetra-acetoxydiphenylmethane**83** which was hydrolysed (with LiOH, THF/MeOH/H_2O) to Dapagliflozin **84** in 94% purity; however, the authors did not specify the isolated yields for this process(Scheme 39).



Scheme 39. Synthesis of dapagliflozin from 5-bromo-2-chlorobenzoic acid.

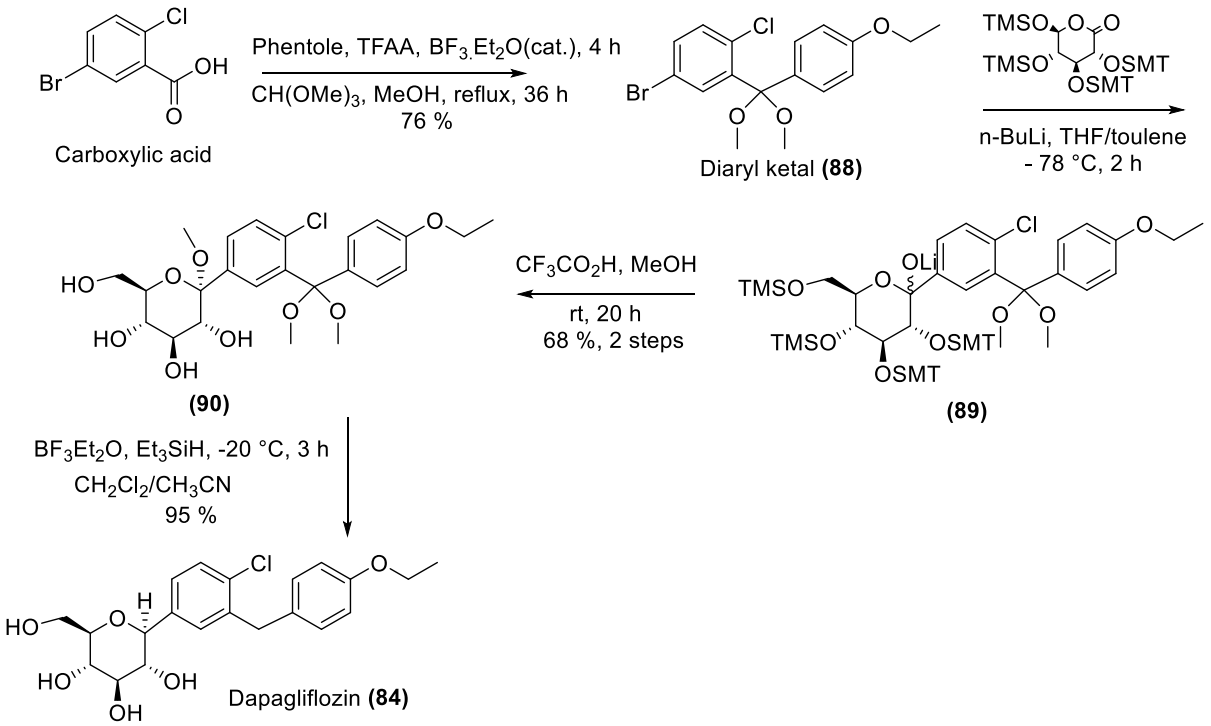
A new and redox-economic method for the synthesis of C-aryl glucosides, a crucial intermediary in the production of Dapagliflozin, was devised by Henschke *et al.*[101]. First, the authors made a Grignard reagent **86** from 4-bromo-1-chloro-2-(4-ethoxybenzyl)benzene **85**, and proceeded as clearly displayed in Scheme 40. C-arylated glycoside **87** was produced by C-glycosylating Grignard reagent with protected levoglucosan. Ultimately, Dapagliflozin was made possible by deprotecting C-aryl glucosides

with TBAF. Dapagliflozin **84** was obtained in fewer steps when compared to the standard gluconolactone process. Furthermore, the target β-anomer of C-aryl glucoside was acquired in a stereoselective fashion, thereby reducing the number of side products.



Scheme 40. Synthesis of dapagliflozin by using the C-glycosylating Grignard reagent

Hu *et al.* devised an environmentally friendly, 4-step synthetic process[102]to manufacture Dapagliflozin using commercially available chemicals. Following a Friedel-Crafts acylation of phenetole by 5-bromo-2-chlorobenzoic acid to form the desired benzophenone which was converted into the dimethyl ketal with trimethyl orthoformate. The dimethyl ketal**88** was then converted into lithium salt **89** which was desilylated to the methoxy derivative**90** which upon reduction by Et_3SiH resulted in Dapagliflozin **84**in 49% yield and >98% purity (Scheme 41).

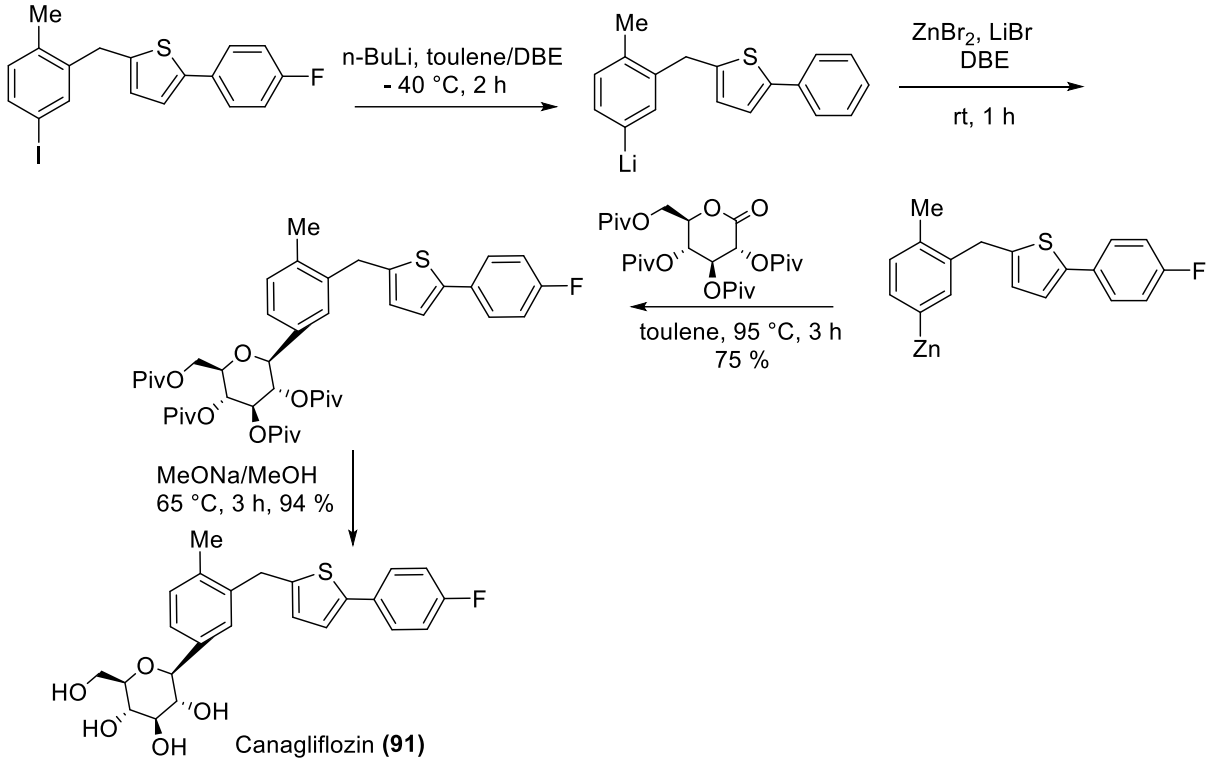


Scheme 41. Synthesis of dapagliflozin by using diaryl dimethyl ketal.

Nearly all the glucose in the glomerular filtrate is re-absorbed by the human nephron, which begins to happen as early as 34 weeks of gestation[103]. This is equivalent to 180 g of glucose daily[104]. Ninety percent of the filtered glucose is reabsorbed by SGLT2, which is expressed by the epithelial cells lining the first segment of the proximal convoluted tubule. Only 1% of the filtered glucose is excreted in the urine. Lower in the nephron, SGLT1 reabsorbs the remaining 10% of glucose[105] . At the luminal surface of the proximal tubular epithelium, where SGLT2 actively transports glucose from the glomerular filtrate into the epithelial cells, the process of glucose reabsorption[106] begins.The Na+ /K+ - adenosine triphosphatase pump actively transports sodium out of the basolateral cells, which in turn drives the cotransporters to move glucose along with sodium. Passive glucose transporters, or GLUTs, are responsible for transferring glucose over the basolateral membrane and out of the cell. This takes place along with the concentration gradient. Glucose is transferred from the proximal tubule back into the circulationbecause of the entire process.

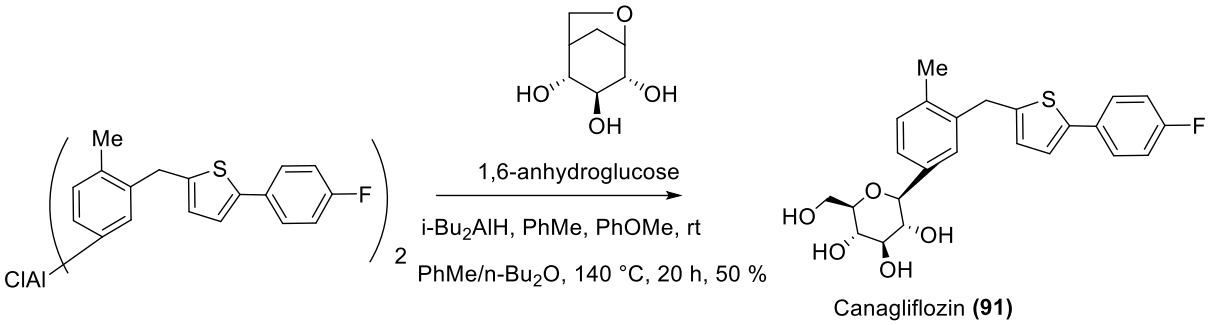
2.1. 16. Canagliflozin

Through the use ofdiaryl zinc reagents and transition metal-free C-glycosylation of O-pivaloyl protected glucosyl bromide, Lemaire *et al.*[107] successfully and highly stereoselectively synthesized Canagliflozin **91** in high yield. This is clearly displayed in Scheme42below.



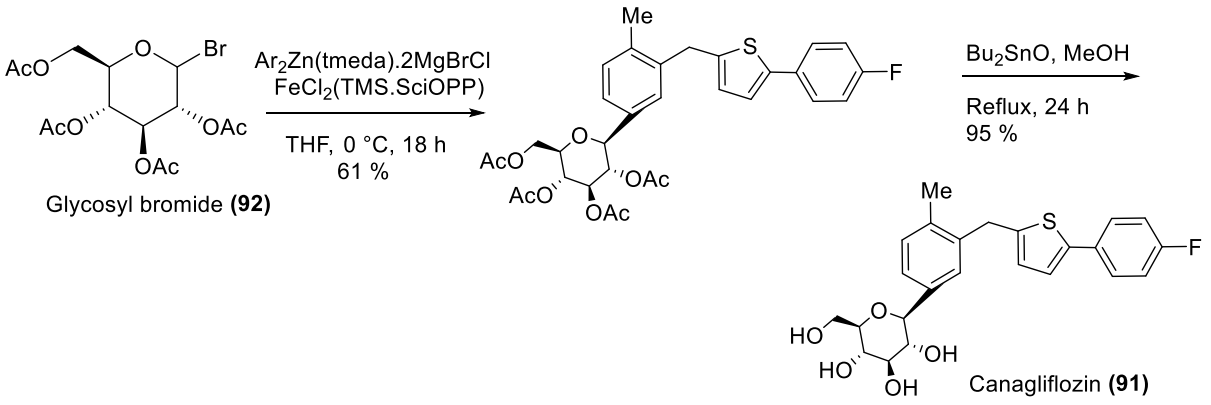
Scheme 42. Synthesis of Canagliflozin by using aryl lithium and zinc intermediates.

Alternatively, using commercially available 1,6-anhydroglucose as a starting point, the same research group [108] reported a protection group chemistry free synthesis of canagliflozin **91**. It was produced by treating the arylating reagent, which was synthesized in accordance with literature with 1,6-anhydroglucose that had been pre-treated with Bu_2AlH as shown in Scheme 43below.

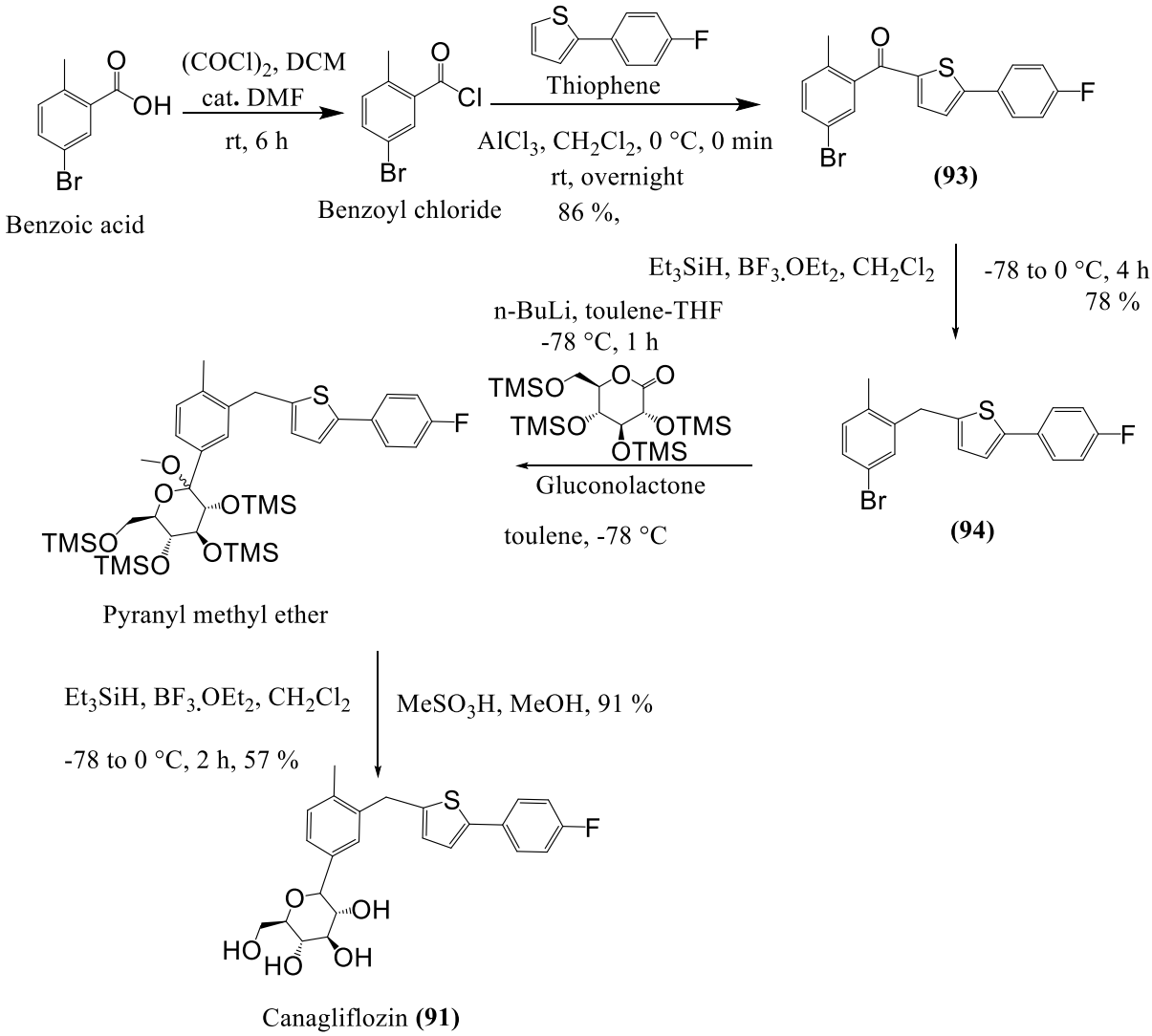


Scheme 43. Synthesis of Canagliflozin by using Arylating reagent.

By using an aryl metal reagent and an iron catalyst to cross-couple glycosyl halide **92**, Adak *et al.* created a unique synthetic pathway[109] towards Canagliflozin **91**in 58% yield. Scheme 44below clearly reveals the steps involved. The process yielded good results with high selectivity. Furthermore, the method is feasible on a wide scale due to the iron catalyst's low cost and non-toxic nature.



Scheme 44. Synthesis of canagliflozin by using glycosyl bromide.



Scheme 45. Synthesis of canagliflozin by using *m*-bromotoluic acid.

The first synthetic method of Canagliflozin was disclosed by Nomura *et al.* and summarised in Scheme 45[110]. It involved acylating *m*-bromo-*o*-toluicacid to the acid chloride, which was then subjected to Friedel-Crafts acylation of thiophene in order to obtain 2(*m*-bromo-*o*-toluoyl)-5(*p*fluorophenyl) thiophene **93**.The latter ketone was then reduced with $Et_3SiH/BF_3.Et_2O$ to the respective bromo-methylbenzylthiophene**94**, which was reacted with fully silylated gluconolactone after displacing the bromine atom by lithium to form the required 2[4- fluorophenyl]-5[5(tetrasilylated-2ron catalyst's loc technique eliminated the reduction p desilylated and lastly reduced stereoselectively using Et_3SiH/BF_3 by removal of the -OMe group to provide. Canagliflozin in a 34% total yield. Without using column chromatography for the purification of intermediates, the authors showed how to synthesize Canagliflozin**91** efficiently and in moderate yields. However, this method requires cryogenic temperatures.

SGLT-1 and SGLT-2 are the two subtypes of SGLT receptors that Canagliflozin affects. Roughly 90% of the glucose filtered by the kidneys is reabsorption due to SGLT-2, which is expressed in the proximal renal tubules[111-112]. Canagliflozin lowers blood glucose levels and increases glucose excretion in the urine by blocking SGLT-2. Additionally, data indicates that patients with T2DM have higher glucose reabsorption *via* SGLT-2 than patients without T2DM, which makes it a more appealing target for prospective medication[113]. Hypoglycemia is rare when SGLT-2 inhibition is used because urine glucose excretion falls as blood glucose levels do. While most SGLT-1 expression is found at the

distal brush-border membrane surface of the villi in the small intestine lumen, where it permits the reabsorption of glucose and galactose, the protein is also expressed in the proximal renal tubules[114].Heart myocytes also express SGLT-1, which could be involved in the underlying mechanism for the cardiovascular benefits associated with certain SGLT-2 inhibitors[115].Comparing Canagliflozin to other medications in the same family, such as Dapagliflozin, empagliflozin, and tofogliflozin, reveals that it is less selective for the SGLT-2 receptor than the SGLT-1 receptor[116].

3. Conclusion

The development and synthesis of antidiabetic medications have significantly advanced over the years, with various classes of drugs being introduced to target the underlying mechanisms of diabetes. These medications include insulin and its analogs, sulfonylureas, biguanides, thiazolidinediones, DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT-2 inhibitors, each with unique synthetic pathways and mechanisms of action. The synthetic pathways of these drugs involve complex chemical processes designed to enhance efficacy, reduce side effects, and improve patient compliance. The variety of antidiabetic medications on the market fosters an exciting area of study that is always growing, particularly considering the concerning rise in the prevalence of DM across all age groups. With an increasing demand for knowledge in this field, the scientific community is confronted with novel obstacles. While there is a need for novel compounds, the marketed compounds' pleiotropic properties make them appropriate for usage in certain patient populations, such as those with cardiovascular disorders, which are the world's leading cause of mortality. Insulin resistance has a constantly changing natural history, causing hyperinsulinemia at first but eventually leading to β-cell failure. As a result, various treatments are needed at various phases of the illness process. To bring blood glucose and related vascular risk factors back to as close to normal as is practically possible, intensive use of currently available medications targeted against various pathogenic elements of the condition is strongly advised.

The alarmingly high prevalence of type-2 diabetes worldwide necessitates appropriate management of this condition. As a result, numerous oral drugs for the treatment of type-2 diabetes have been created and put on the market. Still, finding more powerful medications and refining the current synthetic approaches continue to be top priorities. In this work, we analysed synthetic pathways leading to different anti-diabetic medications based on their classification, emphasizing the advantages, disadvantages, and accomplishments associated with each pathway. Most of the known disadvantages, including low selectivities, contaminants, poor yields, and safety issues in the majority of synthetic pathways, are specific to the application of batch production technology. It's interesting to note that continuous flow manufacturing technology, a new enabling technology, is quickly taking the pharmaceutical industry by storm as it solves most of the problems that occur with using traditional batch manufacturing technology. The adoption of enabling technologies, such as continuous flow chemistry, photocatalysis, and artificial intelligence, can be used in conjunction with this review to provide a thorough foundation and reference source. This will help academia and industry develop more effective, affordable, and environmentally friendly synthetic strategies for anti-diabetic drugs, ultimately improving the health and welfare of society.

The activity of these drugs is crucial in tailoring treatment regimens to individual patient needs, taking into consideration factors like disease progression, side effect profiles, and the patient’s overall health. Ongoing research into the synthesis and activity of antidiabetic drugs promises to further refine existing therapies and introduce novel agents, providing better control and improved quality of life for individuals living with diabetes. As the field continues to evolve, understanding the interplay between classification, synthesis, and activity will remain fundamental to advancing diabetes treatment and management strategies.

List of Abbreviations

SGLT2	Sulfonylureas, thiazolidinediones, meglitinides
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
GDM	Gestational diabetes mellitus

API	Active Pharmaceutical Ingredients
GLP-1	Glucagon-LikePeptide-1
GIP	Gastric inhibitory polypeptides
EEV-4	2-Epi-5-epi-valiolone
DHQS	dehydroquinate synthase
EEV7P-5	2-epi-5-epi-valiolone 7-phosphate
ATP	adenosine triphosphate
AcbL	Acyl-CoA binding protein
NDP	Nucleoside Diphosphate
dTDP	deoxythymidine diphosphate
AUC	area under the glucose concentration time curve
FPG	fasting plasma glucose concentration
NIDDM	non-insulin dependent diabetes mellitus
NHEG	N-2-Hydroxyethyl-glucamine
DHES	6-deoxy-6-hydroxylethyl-amino-L-sorbose
HbA1c	glycated hemoglobin
HepG2	Human Hepatocellular Carcinoma cell line.
PPHG-	Post prandial hyperglycaemia
OHA-	oralhypoglycaemic agents
mRNA	messenger ribonucleic acid
GGT	γ-glutamyl transferase
AMPK	AMP-activated protein kinase
SUR1	sulfonyl urea receptor
HMDS	Hexamethyldisilazane
DCU	Dicarboxylate Carrier proteins
PivCl	Pivaloyl chloride
DIPEA	N,N-Diisopropylethylamine
GIP	glucose-dependent insulinotropic polypeptide

ORCID
Bhushan Popatkar:0000-0002-4402-291X
Shweta Tiwari **:** 0009-0003-5791-6052
Satish Manjare: 0000-0003-3550-8237
Ramchandra Thorat:0000-0003-1231-8342
Vikas V. Borge:0009-0001-1923-9770

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