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Review on sulphonamide analogues for the perspective of antibacterial and antidiabetic activity

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Abstract

Several facets of sulphonamides are covered in this overview, including their chemistry, history, structure-activity relationship, classification systems, and contemporary synthesis techniques. The review also covers the range of sulphonamides pharmacological effects as antibacterial and antidiabetic agents. Sulphonamides work by competitively limiting microorganisms' ability to produce vitamin Bc, which stops bacteria from proliferating but does not actually kill them and need to be used against a range of fungi and gram-positive and gram-negative bacteria. According to the International Diabetes Federation's global cartographic image of diabetes (http://www.diabetesatlas.org/), type 2 diabetes mellitus (T2DM) is a pandemic that affects people worldwide. Hyperglycemia is the primary symptom of diabetes mellitus, a chronic, progressive, and poorly understood metabolic disease and discussed the mechanisms of metformin, glitazones, sulphonyl urea's and other agents. Worldwide, copious research has been conducted on molecular targets associated with type 2 diabetes, including PPAR-γ, incretin, GLP-1, DPP-4, and SGLT2, DPP-IV, GSK-3, Aldose-reductase, fructose-bisphosphatases, and β3 adrenoceptor are used to treat type 2 diabetes.

Keywords: Sulphonamide; Antibacterial; Antidiabetic; Biochemical Target; Synthetic scheme

1. Introduction

Using the knowledge that artificial azo dyes had been studied for their movement towards streptococci, Domagk tested the new compounds and discovered that mice with streptococcal and other infections could be blanketed with prontosil in 1932, during the patenting of Prontosil (Fig. 1) and numerous other azo dyes containing a sulphonamide organisation. The first medical case study was published in 1933 by Foerster, who treated a ten-month-old baby with staphylococcal septicaemia with prontosil and saw a remarkable recovery. Domagk received the 1938 Nobel Prize in Medicine for discovering the anticancer potential of prontosil [1].

Sulphonamide, with the general formula RSO_2NH_2, is also commonly used as a generic term for the para-amino benzene derivatives. Since the nitrogen atom in RSO_2NH_2 has several 1, the NH2 group has several 4 [2]. The N1 (sulphonamide N) substitution of each component varies, affecting the solubility, effectiveness, and pharmacokinetic properties. To have antibacterial activity, a loosened amino group at the p-position (N4) is required [3].

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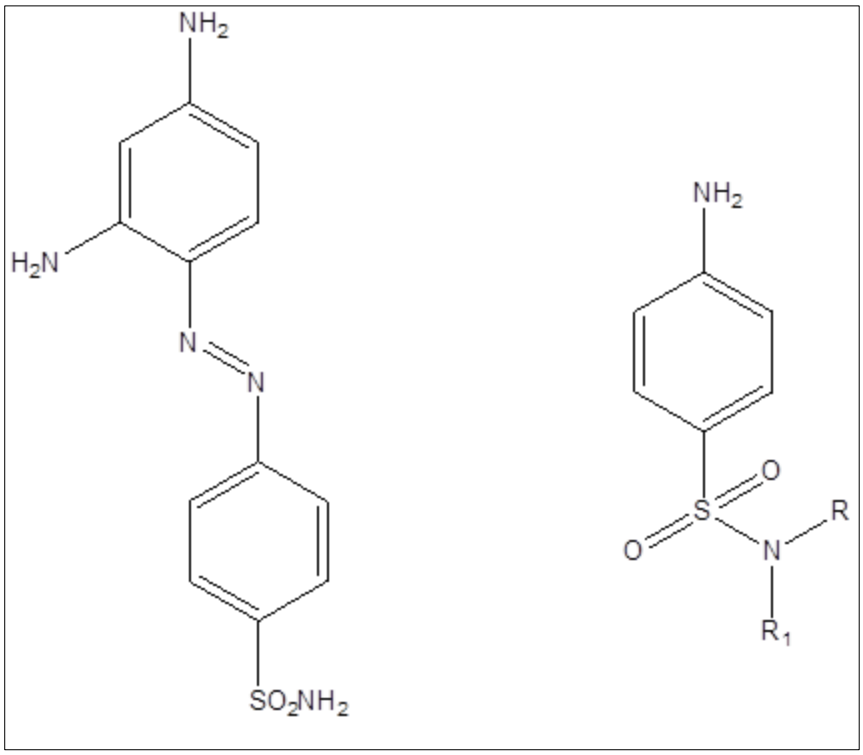

Figure 1 Prontosil and General structure of Sulphonamide

Sulphonamides are members of an important class of substances with a diverse array of biological functions. Numerous pharmacological actions of sulphonamide conjugates have been described during the past few decades. Furthermore, several lead compounds possessing sulphonamide activity are presently undergoing clinical trials to address a range of medical ailments.

It has long been known that several chemical compounds can lower blood sugar levels. Guanidine was shown to decrease blood sugar levels in 1918 [4]. The finding that galegine reduced blood sugar and had a modest trypanocidal effect came after the revelation that some trypanosomes require a high concentration of glucose and will perish in its absence. As a result, several highly effective trypanocidal drugs have been developed, including bisamidines, diisothioureas, and bisguanidines. Two excellent examples of exceedingly active trypanocidal drugs are pentamidine and synthalin, which are both trypanocidal at 1:250 million. In alloxanized, depancreatized, and normal animals, synthalin reduces blood sugar levels [5].

The antimicrobial sulfonamide p-aminobenzene sulfonamid oisopropylthiadiazole was discovered to cause hypoglycemia in 1942. This outcome sparked research into the creation of artificial hypoglycemic agents, some of which are still in use today. Sulfonylureas are still the drug of choice for treating mild diabetes that is not ketosis-prone, having been made widely accessible in 1955 [6]. Since 1957, phenformin—a member of the biguanide class of compounds—has been the sole medication used in this class. However, phenformin was taken off the market in the United States due to the possibility of lactic acidosis, which has been linked to fatalities [7].

For these reasons, the development of a more effective method for sulphonamide synthesis has consistently been acknowledged in organic synthesis investigations. Over time, a great deal of research was done to show how successful sulfonylation and n-alkylation strategies are for synthesising sulphonamide. Primary or secondary amines react with sulfonyl chloride in the presence of organic or inorganic bases in the most common synthesis method [8]. Numerous sulphonamide compounds have been demonstrated to exhibit potent protease inhibitory actions over time [9]. Artificial antibacterial drugs known as sulphonamides can effectively inhibit the dihydropteroate synthetase (DHPS) enzyme [10].

The basic sulphonamide institution, SO_2NH, is found in a variety of biologically active substances that are widely utilised as carbonic anhydrase inhibitors, anticancer, antibacterial capsules, and antithyroid agents [11,12]. Sulphonamides are used clinically to treat gastrointestinal infections and a few urinary tract illnesses [13]. Carbonic anhydrase is inhibited by aromatic or heteroaromatic sulphonamides, which are employed as anticancer agents.

Due to their structural similarities, sulphonamides, and p-amino benzoic acid (PABA) may compete for inclusion since PABA may be a cofactor required by bacteria for the synthesis of folic acid. Veterinary medications called sulphonamide antibiotics are used to treat infections in herds of cattle [14, 15]. Sulphonamides also show a wide spectrum of biological actions, such as antiviral, anticancer, and anti-inflammatory properties, making them very valuable medicinal chemicals [16–19]. Due to its great efficiency and simplicity of the reaction, the sulphonylation of amines with sulphonyl chlorides in the presence of a base continues to be the technique of choice [20]. Under mild circumstances, sulphonamides are employed as protective groups of OH or NH functionality for easy removal [21, 22].

2. Synthesis of sulphonamides

2.1. Synthesis of sulphonamide using primary amines and aryl sulfonyl chloride

Youn et al. reported [23] on the synthesis of sulphonamide at a temperature range of 0 to 25 °C by employing pyridine as a base and aryl primary amine and aryl sulfonyl chloride is employed as the main amine and benzene sulfonyl chloride or 4-nitrobenzyl sulfonyl chloride is used as the sulfonylation agent, they have found a 100% yield. For the reaction between p-toluidine and tosylchloride, a quantitative yield is additionally provided. The study's objective shifted to the regioselective synthesis of 3-arylindoles from styrenes and N-Ts-Anilines.

2.1.1. Sulfonylureas

By boosting insulin release in the pancreas and inhibiting KATP channels, sulfonylureas lower blood glucose levels. In the liver, they also restrict gluconeogenesis. Sulfonylureas inhibit the liver's ability to eliminate insulin and the breakdown of fats into fatty acids (24). Currently, sulfonylureas are recommended as supplemental or second-line treatments for the management of type 2 diabetes.

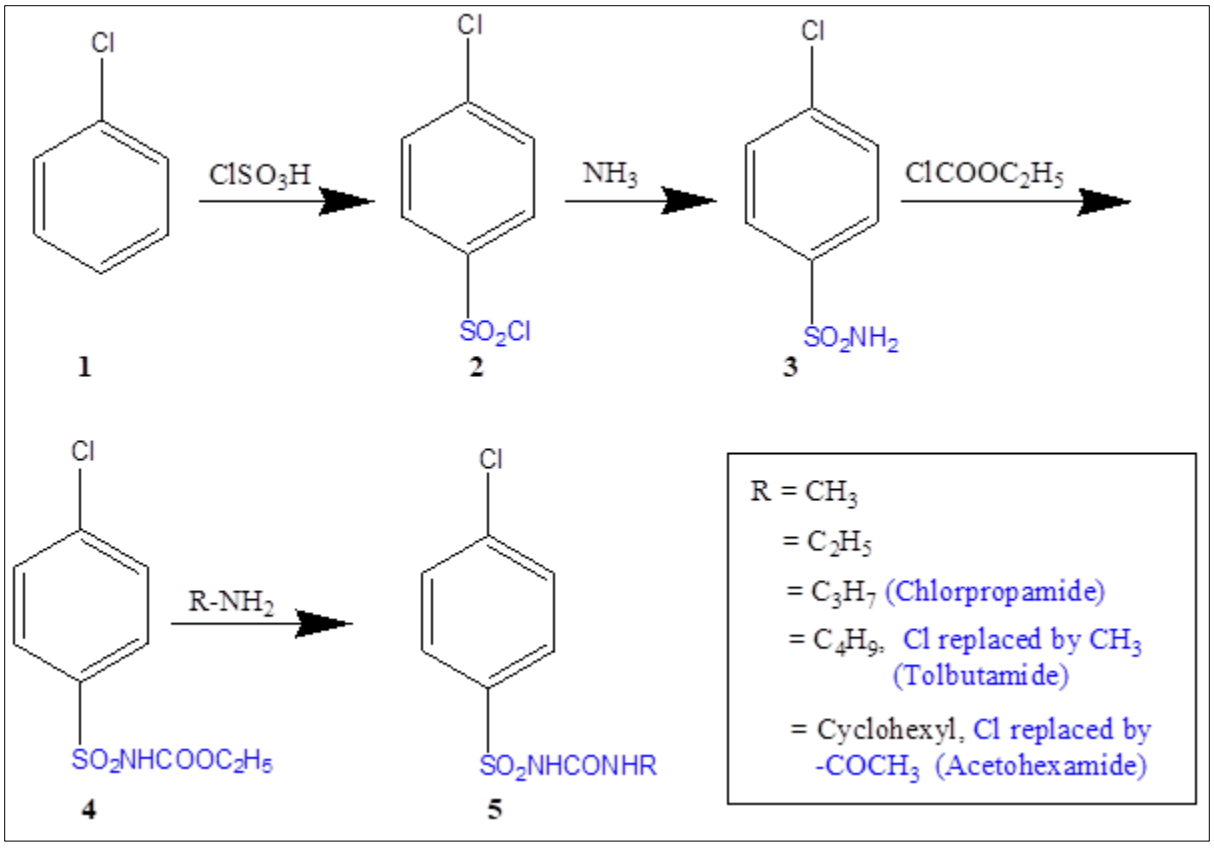

Figure 2 Synthesis of Sulphonyl Urea Analogues

First-generation agents, When Chloro benzene undergoes chloro sulphonylation followed by amination gives 4-chloro benzene sulphonamide and which reacts with ethyl chloro formate gives corresponding ester and which upon amination with various alkyl amines gives respective sulphonyl urea analogues such as chlorpropamide, tolazamide, and tolbutamide (Fig.2). Second-generation agents, such as glipizide, glibenclamide, glimepiride, and glyburide, are

synthetic strategies were given in Fig.3 and Fig.4. In comparison to second-generation sulfonylureas, first-generation sulfonylureas are known to have longer half-lives, a higher risk of hypoglycaemia, and a later beginning of action. Second-generation sulfonylureas are currently recommended and preferred over first-generation drugs in clinical practice because to their shown potency (given to patients at lower doses with less frequency), with glimepiride having the safest profile [25].

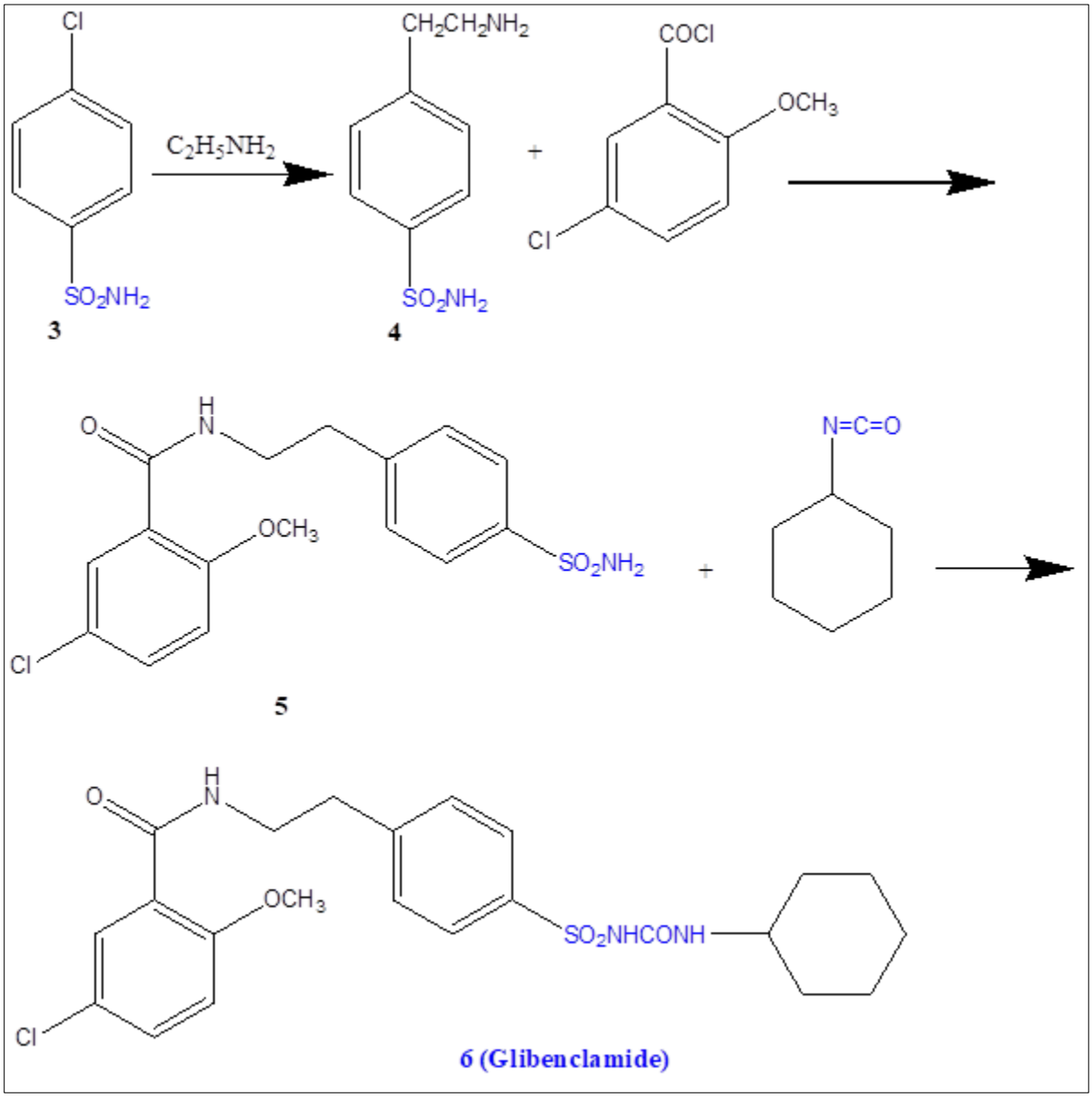

Figure 3 Synthesis of Glibenclamide

Structure—Activity Relationships: One substituent should be present in the benzene ring, ideally in the para position. The following substitutions appear to increase hypoglycaemic activity: amino, trifluoromethyl, methyl, acetyl, chloro, bromo, and methylthio groups. The second-generation agents, compounds with p-(-β-arylcarboxamidoethyl) substituents, exhibit superior activity compared to the first-generation drugs. This is thought to be caused by a certain spacing between the substituent's nitrogen atom and the sulphonamide nitrogen atom. The group that is joined to the terminal nitrogen of the molecule must have a specific size and provide it lipophilic characteristics. N-propyl to N-hexyl is the most active, while N-methyl and N-ethyl are inactive. If the N-substituent has 12 or more carbons, activity is lost [26].

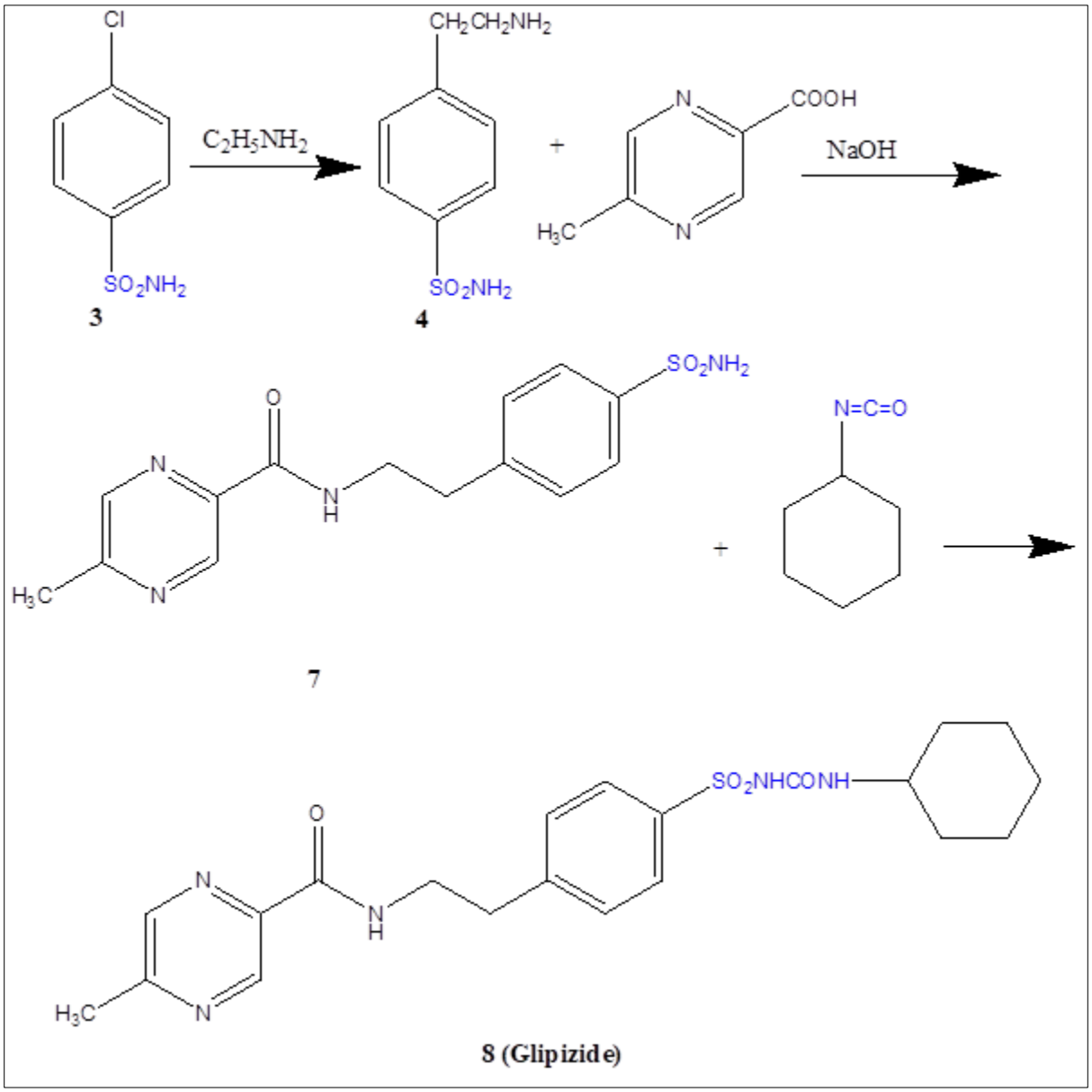

Figure 4 Synthesis of Glipizide

2.1.2. Biguanides

In the Middle Ages, biguanide and its derivatives were discovered to be useful in the treatment of diabetes. It was discovered that the herbaceous plant Galega officinalis contained biguanide, galegine, and guanidine, all of which lowered blood glucose levels. The primary first-line oral medication of choice for the treatment of type 2 diabetes in all age categories is Metformin and Phenformin, a biguanide, synthetic protocol was given in Fig.5. Metformin inhibits gluconeogenesis by activating adenosine monophosphate-activated protein kinase in the liver, which results in the hepatic absorption of glucose through intricate interactions with mitochondrial enzymes. Moreover, it raises tyrosine kinase activity and activates insulin receptor expression to increase insulin sensitivity. According to recent data, metformin also inhibits the peroxisome proliferator-activated receptor (PPAR)-α pathway, hence preventing cardiovascular diseases (27). Reduced food intake may be the result of incretin-like effects mediated by glucagon-like peptide-1 (GLP-1). Therefore, in overweight and obese people at risk for diabetes, metformin may provide a little amount of weight loss [28].

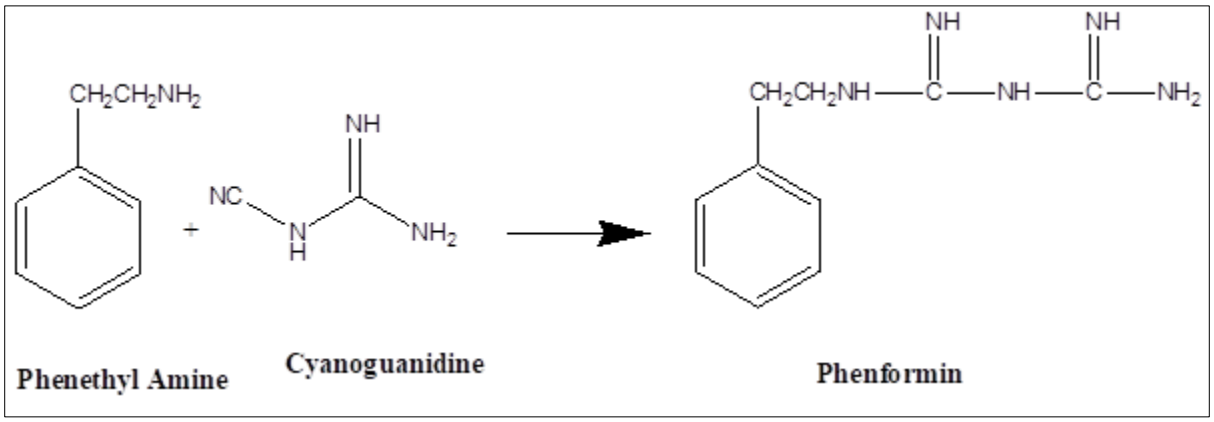

Figure 5 Synthesis of Phenformin

2.1.3. Meglitinide

Meglitinides, which include nateglinide and repaglinide, are non-sulfonylurea secretagogues that were authorised in 1997 for the treatment of type 2 diabetes. Meglitinide interacts to the sulfonylurea receptor in pancreatic β-cells via the same mechanism as sulfonylureas. Nonetheless, meglitinide is regarded as a short-acting insulin secretagogues due to its lesser affinity to the receptor than sulfonylurea, which allows for more administration flexibility. Also, it is less effective than sulfonylurea since it requires a higher blood sugar level before it can promote the release of insulin by β-cells. Patients who experience erratic meal schedules or develop late postprandial hypoglycemia while on sulfonylureas may benefit from switching to rapid-acting secretagogues, such as meglitinides, instead of sulfonylureas, structures presented in Fig.6 [29,30].

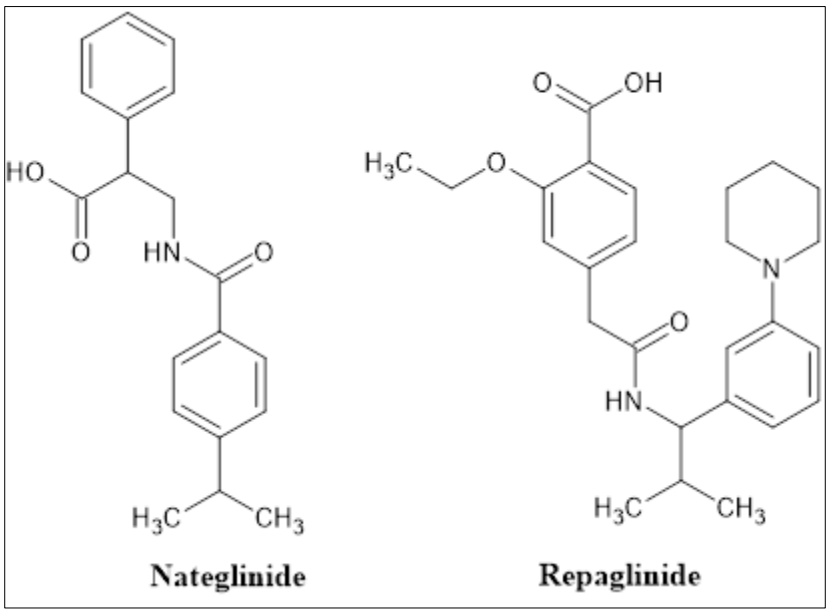

Figure 6 Meglitinides

2.1.4. Thiazolidinediones

TZDs enhance the effect of insulin, just like biguanides do. Representative agents are pioglitazone and rosiglitazone, structures presented in Fig.7. TZDs are PPAR agonists that promote greater absorption of glucose in a variety of organs, such as the liver, muscle, and adipose tissue. Reduced accumulation of free fatty acids decreased levels of inflammatory cytokines, increased levels of adiponectin, and maintenance of β-cell integrity and function are among the mechanisms of action that reduce insulin resistance and β-cell exhaustion. High worries exist, nonetheless, that the hazards will outweigh the advantages. Heart failure is caused by insulin-TZD therapy combination. TZDs are therefore not recommended as first-line or even as a step-up treatment [31-35].

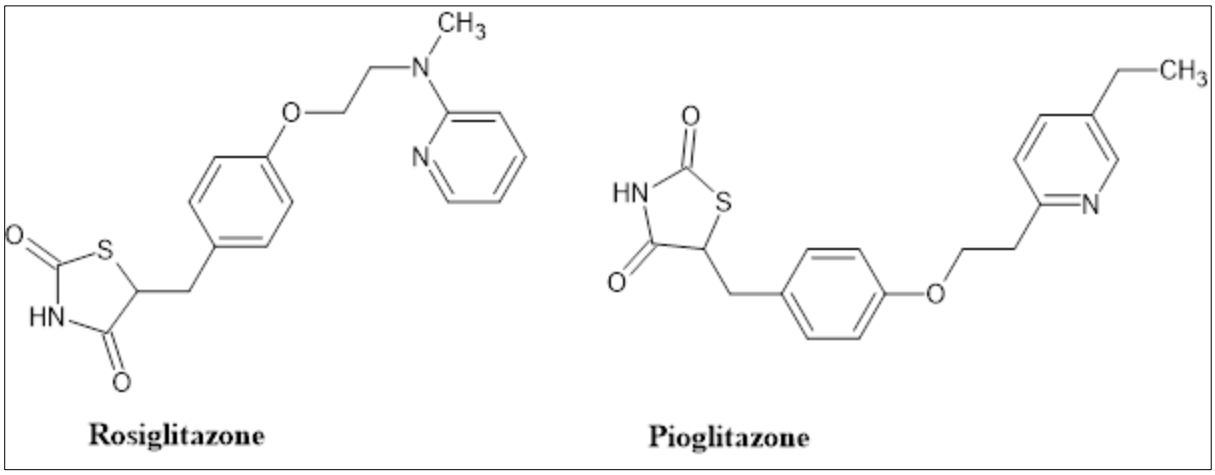

Figure 7 Thiazolidinediones

2.1.5. Incretins Mimetics

The difference between the insulin secretory response to an oral glucose load and an intravenous glucose administration is known as the incretin effect, can see in Fig.8. After oral glucose ingestion, 50–70% of total insulin production is attributed to the incretin effect (35). Glucagon-like peptide (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP, or incretin), are two naturally occurring incretin hormones that are important for maintaining glycaemic control. These peptides have a short half-life because DPP-4 inhibitors hydrolyse them quickly in less than 1½ minutes. Incretin pathway targeting has emerged as a key therapeutic strategy for T2DM. DPP-4 inhibitors and GLP-1 receptor agonists are examples of these two medication types [36-41].

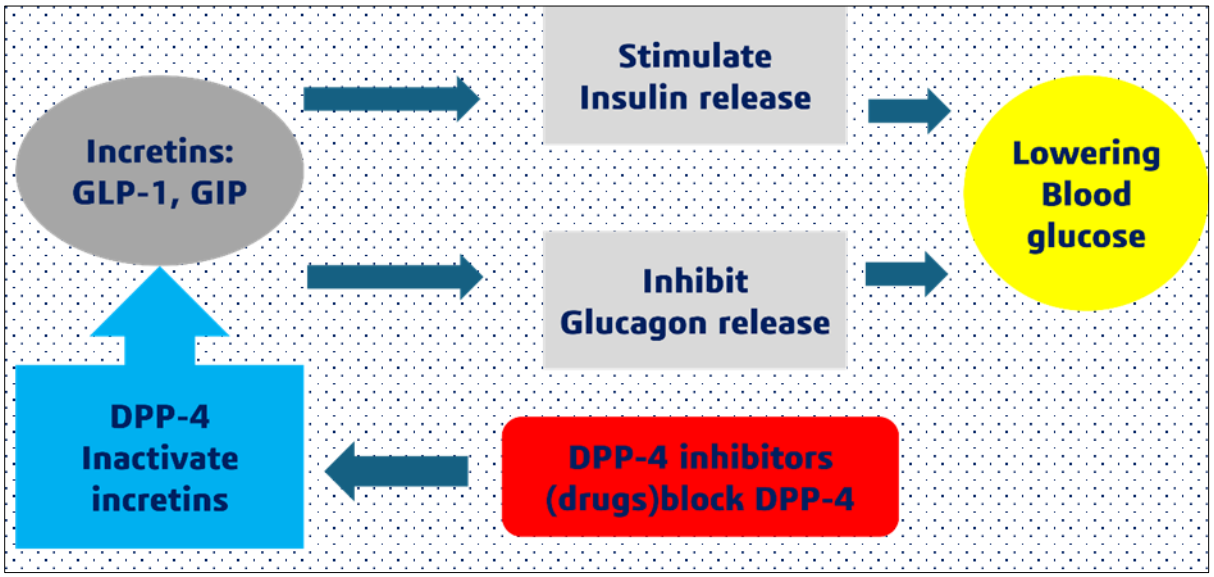

Figure 8 Incretins Mimetics

2.1.6. GLP-1 Receptor Agonists

Exenatide and liraglutide are the GLP-1 receptor agonists that are currently on the market. These medications are more resistant to being broken down by DPP4 enzymes. Treatment with GLP-1 analogues, which would help with weight loss and ameliorate metabolic dysfunction, should be considered for young patients with central obesity, recent diagnosis of T2DM, and aberrant metabolic profile. When renal failure occurs, GLP-1 analogues should not be used [42-48].

2.1.7. DPP-4 Inhibitors

Alogliptin, vidagliptin, saxagliptin, sitagliptin, and linagliptin are examples of dipeptidyl peptidase 4 inhibitors, represented in Fig.9. These drugs can be taken either on their own or in conjunction with TZD, sulfonylurea, or

metformin. An oral active antihyperglycemic drug called vildagliptin (LAF237) specifically inhibits the dipeptidyl peptidase-4 (DPP-4) enzyme. In type II diabetes mellitus, where GLP-1 secretion and insulinotropic effects are compromised, it is employed as a management tool. The incretin hormones that stimulate insulin secretion and control blood glucose levels, glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are not broken down by vildagliptin because it inhibits DPP-4. Vildagliptin has a comparatively low risk of hypoglycaemia in clinical trials. The European Medicines Agency authorised oral vildagliptin in 2008 for the treatment of people with type II diabetes mellitus. Patients with insufficient glycaemic control may benefit from monotherapy or combination with metformin, a sulfonylurea, or a thiazolidinedione. The other oral antidiabetic medications and this treatment are comparable. There is no evidence that the gliptins increase the risk of hypoglycaemia episodes when compared to controls [49-54].

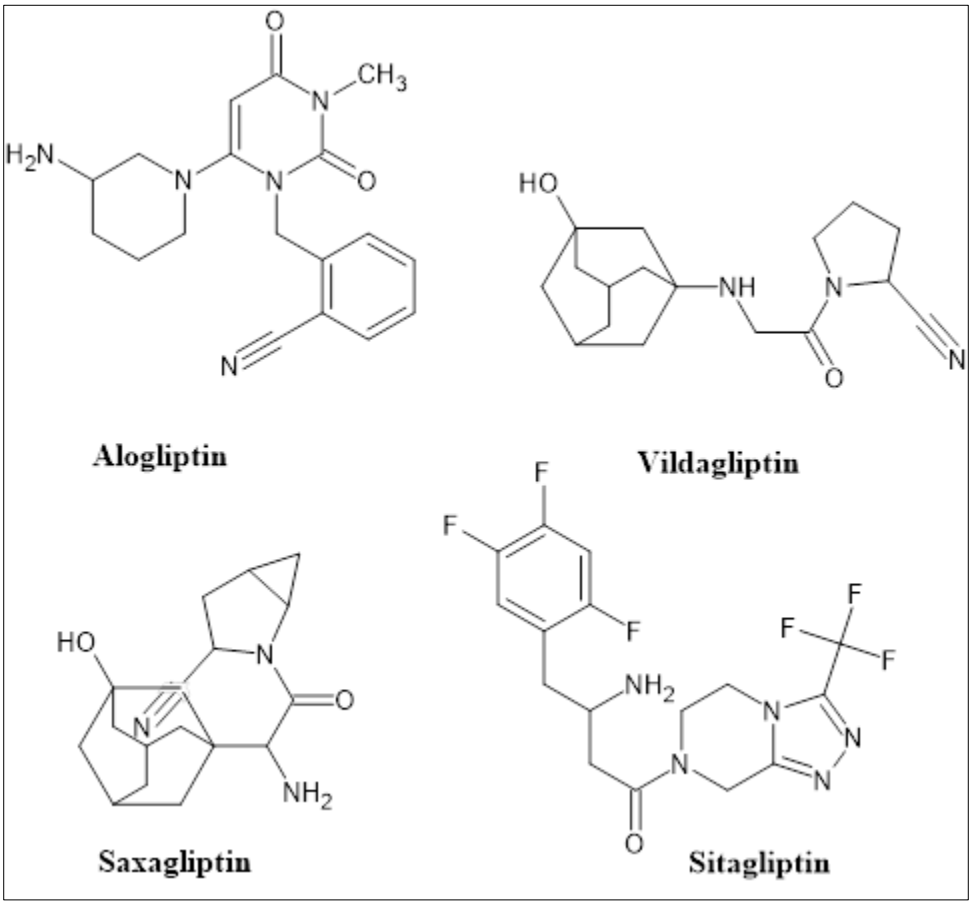

Figure 9 DPP-4 Inhibitors

2.1.8. Inhibitors of SGLT2

Canagliflozin, dapagliflozin, and empagliflozin are three novel kinds of glucosuric medicines that are sodium-glucose cotransporter inhibitors. By inhibiting SGLT2, SGLT2 drugs prevent glucose reabsorption in the proximal renal tubule, so enabling insulin-independent glucose reduction (38). A C-glycosyl drug called canagliflozin (in hemihydrate form) inhibits sodium-glucose transport protein subtype 2 to treat type II diabetes. It functions as an inhibitor of sodium-glucose transport protein subtype 2 and a hypoglycaemic agent. It is an organofluoride chemical, a member of the thiophene family, and a C-glycosyl compound. Dapagliflozin is a C-glycosyl comprising beta-D-glucose in which the anomeric hydroxy group is replaced by a 4-chloro-3-(4-ethoxybenzyl) phenyl group. These medications' glucose-independent mode of action makes them potentially useful in later stages of type 2 diabetes when pancreatic β-cell reserves have been irreversibly depleted. These medications lower blood pressure and cause a slight reduction in weight [55-60].

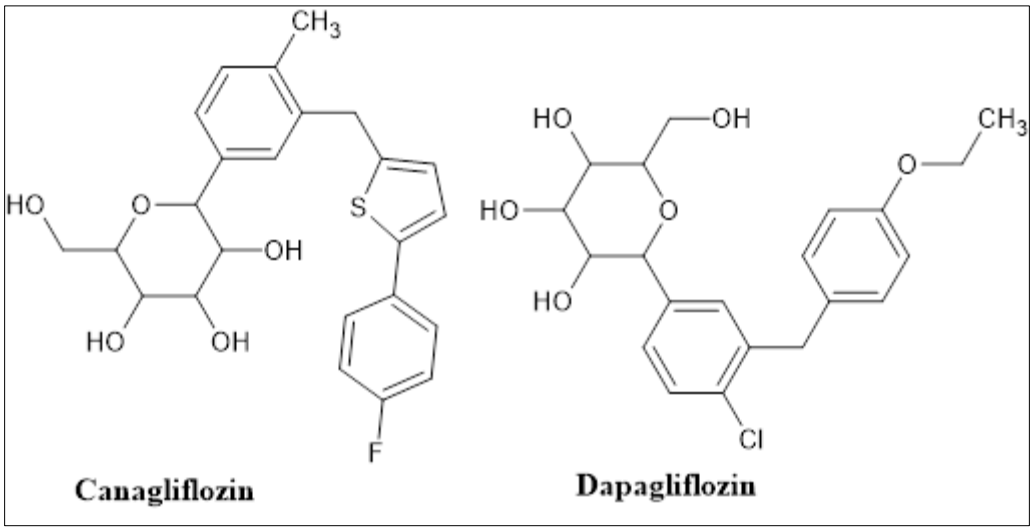

Figure 10 SGLT-2 Inhibitors

3. Conclusion

This review articles covers all the drugs as antibacterial and antidiabetic agents specifically with focus on sulphonamide analogues, their features, mode of actions and synthetic strategies were discussed. Based on the review declared that Sulphomoyl amides are potential compounds against many biochemical targets widely used in T2DM. Chemical components of many sulphonamides can treat fifteen proteins linked to type 2 diabetes, out of which few were discussed. The research work will be continuing regarding design the potential compounds for T2DM using *in-silico* approach and docking method and when the compounds with strong docking scores bound to the proteins like prediction of significant bioactivities against GLP-1, GSK 3β, and aldose reductase in future.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

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