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Outlook on Some Heterocyclic Scaffolds and Their Anti-Diabetic Activity

Dr. Gautam sadawarte[1], Dr. jamatsing Rajput [2], Dr. Anilkumar Jadhav [3] and Dr. Nilesh Halikar [4]
[1]Dept. of Chemistry, BP Arts SMA Science and KKC Commerce College Chalisgaon, Maharashtra, India.
[2]Dept. of Chemistry, Mahatma Gandhi Mahavidyalaya Ahmedpur, Dist.Latur, Maharashtra, India
[3 & 4] Dept. of Chemistry, DSDD Arts, Commerce and Science College Wada Dist. Palghar, Maharashtra, India
Emai:halikarnk76@gmail.com

Abstract

In the next decade, a significantly greater percentage of new drugs based on nitrogen and sulfur will be developed. Novel N-heterocyclic moieties have a wide range of intriguing applications in medicinal chemistry, as well as significant physiological properties. In this review, we've compiled the most recent findings on novel five- and six-membered heterocycles with nitrogen and sulfur atoms, as well as their distinct antidiabetic activities that have been reported over the past few years. This review focuses on trends in drug design related to five- and six-membered heterocycles, having anti-diabetic activity.

Keywords: *Diabetes mellitus, Hyperglycemia, AMPK, NIDDM, Thiazolidinediones, Flavonoids*

Introduction

Diabetes mellitus (DM) is a chronic, complicated disease that necessitates ongoing medical attention along with multifactorial risk-reduction techniques to minimize complications. Globally, the disease's prevalence among adults is rising quickly. The International Diabetes Federation (IDF) estimates that 415 million people worldwide between the ages of 20 and 79 had diabetes in 2015, that the disease was responsible for 5.0 million deaths, and that the total cost of diabetes-related medical expenses was 673 billion US dollars. By 2040, 642 million people between the ages of 20 and 79 are expected to have diabetes, with type 2 diabetes accounting for the majority of these cases [1].

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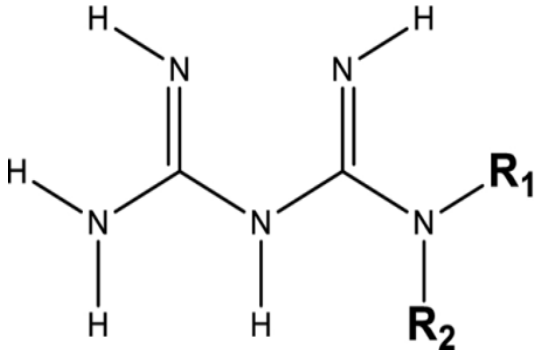
Hyperglycemia brought on by a relative lack of insulin or insulin resistance is a hallmark of diabetes mellitus.As a rare condition that arises when the kidney is unable to properly concentrate urine, diabetes insipidus—which is also characterized by polyuria distinct from diabetes mellitus.[2] This is because it is not associated with insulin secretion or insulin resistance. There are two types of polygenic diabetes mellitus: type 1 and type 2. Previously known as insulin-dependent diabetes, type 1 diabetes mellitus is characterized by an absolute lack of insulin as a result of islet cell destruction. It typically manifests acutely in younger individuals. Insulin resistance and beta cell dysfunction in the presence of insulin resistance and hyperglycemia are hallmarks of type 2 diabetes mellitus, formerly known as non-insulin-dependent diabetes mellitus.[3] Additionally, there is secondary diabetes, which can result from a variety of illnesses or drugs. Diabetes mellitus is a collection of metabolic diseases marked by persistently elevated blood sugar levels and abnormalities in the metabolism of fat, protein, and carbohydrates brought on by deficiencies in either insulin action or secretion, or both[4]

2. Some Synthetic Antidiabetic Compounds



2.1. Biguanides

Metformin and phenformin, the two main biguanides, were first made available orally in 1957 as glucose-lowering medications for the treatment of non-insulin-dependent diabetes mellitus (NIDDM). Due to its link to lactic acidosis, phenformin was withdrawn in numerous countries; however, when taken as directed, metformin does not carry the same risk.[5]

Metformin, the most commonly used biguanide, lowers blood glucose levels primarily by inhibiting hepatic gluconeogenesis and enhancing insulin sensitivity in peripheral tissues. It activates AMP-activated protein kinase (AMPK), a key regulator of energy metabolism. Metformin is a commonly used medication that has definite advantages when it comes to glucose metabolism and complications associated with diabetes. These advantages are underpinned by intricate mechanisms that are still poorly understood. Metformin has been demonstrated physiologically to decrease hepatic glucose production;

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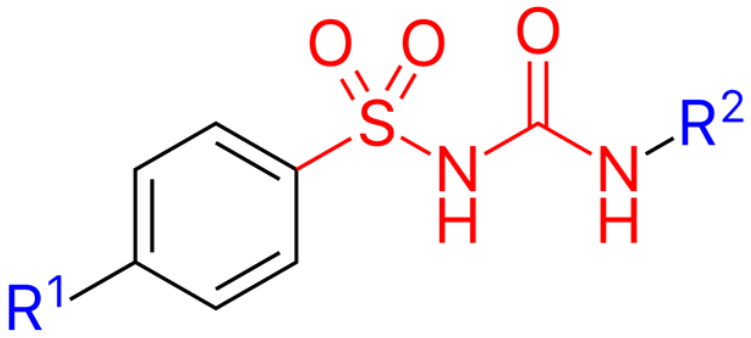
however, this mechanism cannot account for all of its effects, and there is mounting evidence that the gut plays a crucial role[6].

The lack of structural data has hindered molecular insights into the mode or modes of action of metformin, the most often prescribed medication for type II diabetes and related conditions. A growing body of research showing its effects on one-carbon metabolism and structural considerations point to the potential for anti-folate and folate mimicry[7].

2.2. Sulfonylureas



The hypoglycemic action of sulfonamides was described by Janbon in 1942, but World War II caused the implications for diabetes treatment to be overlooked until Franke and Fuchs' research on carbutamide proved its hypoglycemic action. the first of several sulfonylureas used to treat diabetes mellitus that is not insulin-dependent (NIDDM)[8].

Precision medicine is expected to further refine the selection of T2D patients who may benefit more from sulfonylureas based on specific phenotypes and genotypes. Sulfonylureas are the preferred treatment for certain types of monogenic diabetes. The most common second-line treatment for type 2 diabetes in many parts of the world is still sulfonylureas, which are widely accessible and reasonably priced[9].

By attaching to the sulfonylurea receptor (SUR1), a part of the adenosine triphosphate (ATP)sensitive potassium channel (KATP) expressed in the pancreatic β cells, sulfonylureas promote the release of insulin secretion[10-11]. Sulfonylureas, such as glibenclamide and glipizide, function by stimulating pancreatic beta cells to release insulin. They bind to ATP-sensitive potassium channels (KATP) on beta cells, leading to cell depolarization and subsequent insulin secretion [12]

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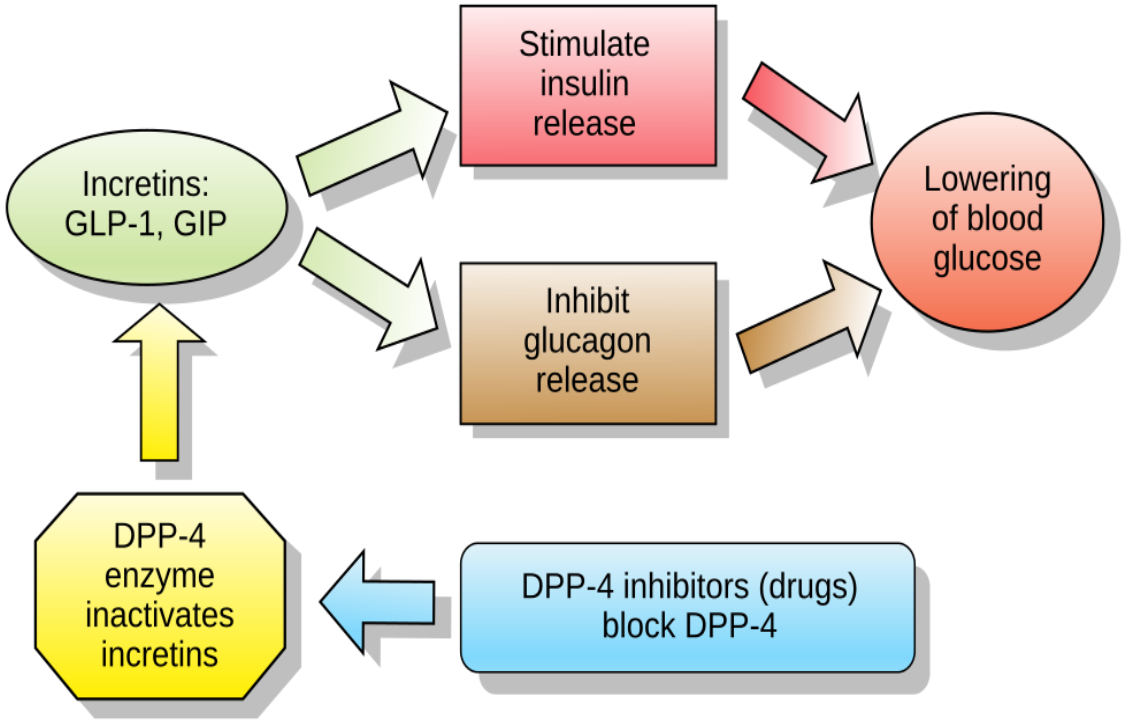
2. 3. Dipeptidyl Peptidase-4 (DPP-4) Inhibitors



Dipeptidyl peptidase-4 (DPP-4) inhibitors, also known as gliptins, are a class of oral hypoglycemics that inhibit the enzyme. Type 2 diabetes can be treated with them. The FDA approved sitagliptin, the class's first agent, in 2006[13-14]. Dipeptidyl peptidase-4 (DPP-4) inhibitors, also known as "gliptins," are a class of oral anti-hyperglycemic drugs that block the enzyme DPP-4. This increases the biological activity of the "incretin" hormones, such as glucose-dependent insulinotropic polypeptide [GIP] and glucagon-like peptide-1 [GLP-1], and resolves many of the pathophysiological issues associated with diabetes. They have already been used to treat the illness for more than ten years[15]. DPP-4 inhibitors, including sitagliptin and vildagliptin, enhance the levels of incretin hormones such as glucagon-like peptide-1 (GLP-1), which promotes insulin secretion and inhibits glucagon release. These drugs are beneficial due to their minimal risk of hypoglycaemia[16].

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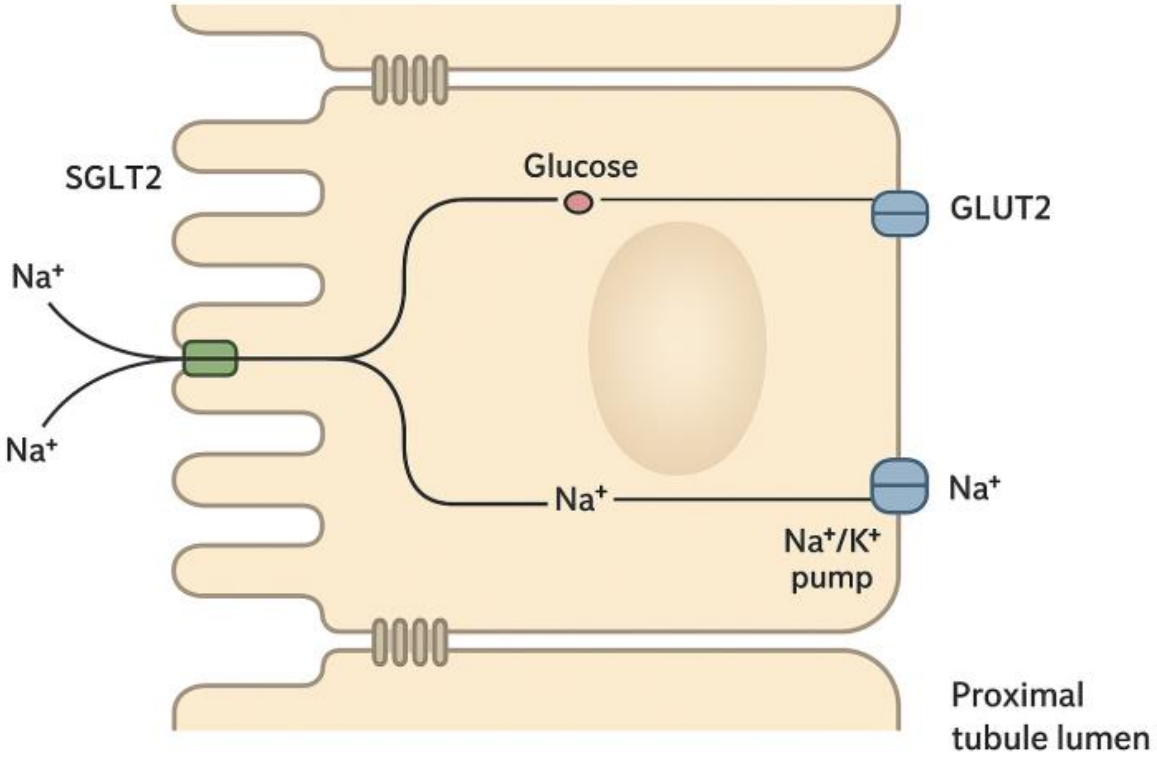
2. 4. Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitors



Mechanism of Glucose Reabsorption in the Proximal Convoluted Tubule (PCT)

The FDA has approved a class of prescription drugs called SGLT2 inhibitors to help adults with type 2 diabetes lower their blood sugar levels in conjunction with diet and exercise[17-18]. The SGLT2 inhibitor class of medications includes empagliflozin, dapagliflozin, and canagliflozin. Both single-ingredient products and combinations with other diabetes medications, like metformin, are available[19]. By encouraging the kidneys to eliminate sugar from the body through urine, SGLT2 inhibitors reduce blood sugar. The FDA has not authorized the use of SGLT2 inhibitors in patients with type 1 diabetes because their safety and effectiveness have not been proven[20]. SGLT2 inhibitors, such as empagliflozin and canagliflozin, lower blood glucose by inhibiting glucose reabsorption in the kidneys, leading to glucosuria. They also offer cardiovascular benefits, making them an attractive option for T2DM treatment [21]

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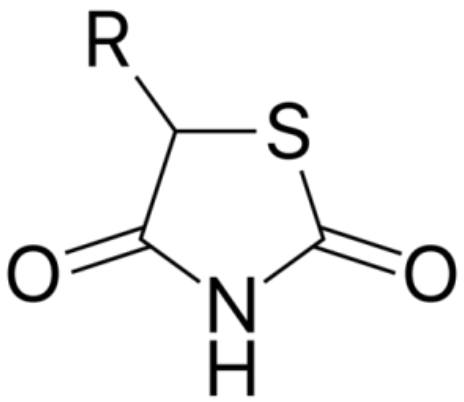
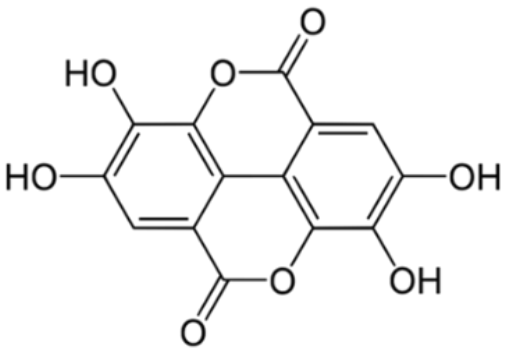
2. 5. Thiazolidinediones (TZDs)



Thiazolidine-2,4-dione nucleus-containing compounds have demonstrated promising activity in a variety of categories, including anti-hyperglycemics, aldose reductase inhibitors, anti-cancer, anti-inflammatory, anti-arthritics, anti-microbials, etc., making them an essential anchor for the development of novel therapeutic agents[22]. Thiazolidinedione (TZD) is a significant class of heterocycles due to its special advantages in the management of type II diabetes and insulin resistance. TZDs, which include the medications troglitazone, pioglitazone, and rosiglitazone, target the nuclear receptor peroxisome proliferator activated receptor gamma[23].Thiazolidin-4-ones and thiazinan-4-ones that are comparable to the powerful antidiabetic medication rosiglitazone[24]. TZDs, including pioglitazone and rosiglitazone, act as peroxisome proliferator-activated receptor gamma (PPAR-γ) agonists, improving insulin sensitivity in adipose tissue, muscle, and liver. However, their use is limited due to adverse effects such as weight gain and fluid retention[25]

3. Some Natural Antidiabetic Compounds

3.1. Polyphenols



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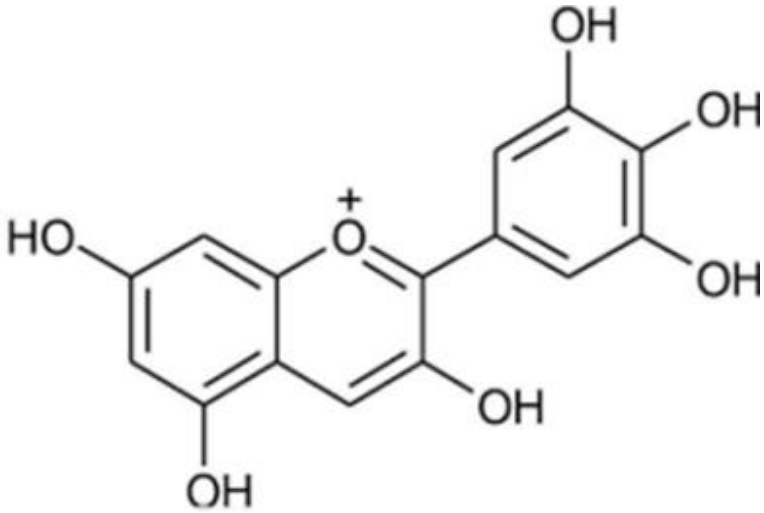
Polyphenols, found in tea, coffee, and various fruits, have been reported to exhibit antidiabetic effects by improving insulin sensitivity and reducing oxidative stress. Phenolic bioactives found in plant-based foods have protective effects on human health that are important for preventing chronic diseases like type 2 diabetes (T2D) that are influenced by diet and lifestyle[26]. Dietary phenolic bioactives' molecular structural characteristics enable antioxidant activities pertinent to preventing the metabolic breakdown brought on by chronic oxidative stress, which is frequently linked to type 2 diabetes[27]. Resveratrol, a well-known polyphenol, activates AMPK and enhances glucose uptake in muscle cells[28].

3.2. Flavonoids



A class of plant-based substances called flavonoids can be found in a variety of foods, including fruits and vegetables. Their antioxidant qualities are well-known, and they may offer several health advantages[29]. They can be found in tea, wine, cocoa, and the bark, roots, stems, flowers, and leaves of plants[30]. Flavonoids are what give many fruits and vegetables their color, flavor, and scent. Inhibiting alpha-glucosidase activity and altering insulin signaling pathways, flavonoids like quercetin and catechins cause hypoglycemic effects by postponing the digestion and absorption of carbohydrates [31].

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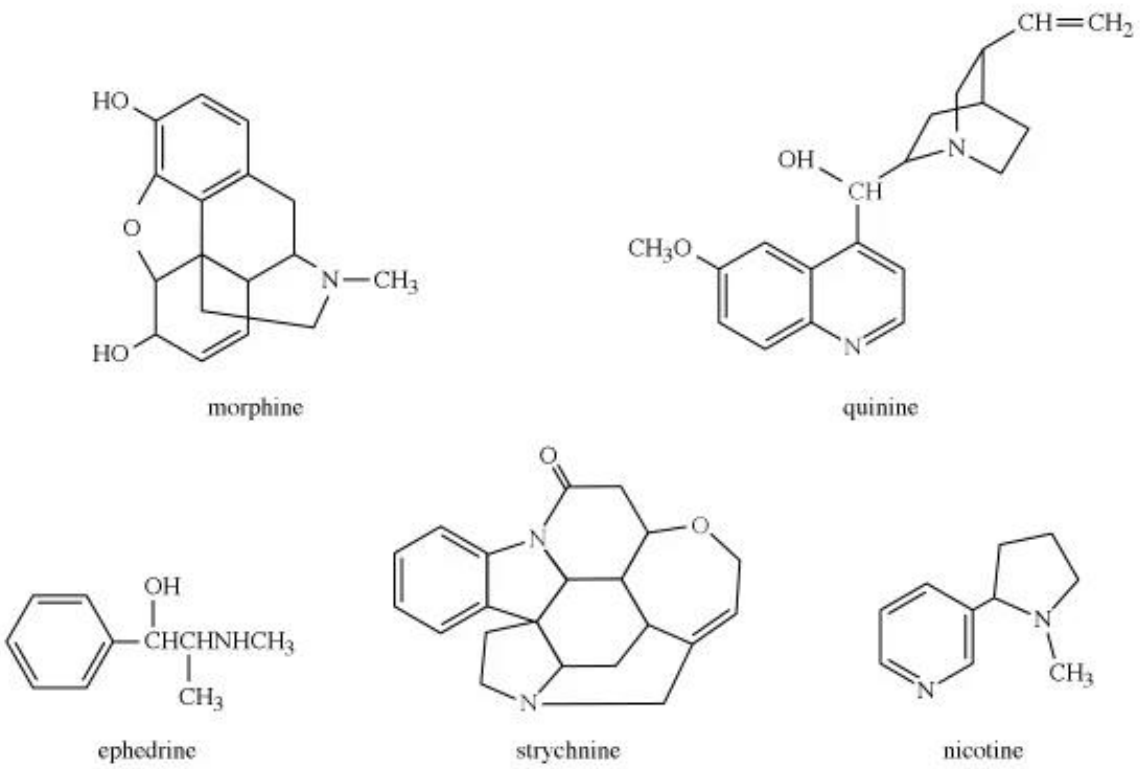
3.3. Alkaloids



Alkaloids are a class of organic compounds that occur naturally and contain nitrogen. Animals, fungi, bacteria, and plants all contain them. Alkaloids are used in medicine and exhibit a variety of biological activities[32].

The antidiabetic effects of berberine, an alkaloid derived from plants, have been thoroughly investigated. By AMPK activation and gut microbiota composition modulation, it controls glucose metabolism[33].

2.4. Saponins

Plants and marine invertebrates contain bioactive substances called saponins, which are well-known for their soap-like qualities and capacity to create froth in water. Composed of sugar-chained aglycones or sapogenins, they are utilized in the food, pharmaceutical, and vaccine industries and have a variety of biological activities[34].

By increasing insulin secretion and enhancing lipid metabolism, saponins from plants such as the ginseng Panax ginseng and Trigonellafoenum-graecum (fenugreek) have shown promise in lowering blood glucose levels[35].

2.5. Terpenoids

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Terpenoids that affect insulin secretion and glucose uptake, like ginsenosides from ginseng, have hypoglycemiceffects. Additionally, it has been demonstrated that they alter important metabolic enzymes that maintain glucose homeostasis[36].

Conclusion

Research on the creation of new antidiabetic substances with improved safety and efficacy profiles is still crucial. Even though synthetic medications effectively control blood sugar levels, the negative effects they cause make it necessary to investigate natural substances as complementary or alternative treatments. To confirm these bioactive molecules' therapeutic potential and clarify their mechanisms of action, more research including clinical trials is needed

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