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Review

Carbazoles: Role and Functions in Fighting Diabetes

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Abstract: Carbazole derivatives have gained a lot of attention in medicinal chemistry over the last few decades due to their wide range of biological and pharmacological properties, including antibacterial, antitumor, antioxidant, and anti-inflammatory activities. The therapeutic potential of natural, semi-synthetic or synthetic carbazole-containing molecules has expanded considerably owing to their role in the pathogenesis and development of diabetes. Several studies have demonstrated the ability of carbazole derivatives to reduce oxidative stress, block adrenergic hyperactivation, prevent damage to pancreatic cells and modulate carbohydrate metabolism. In this survey, we summarize the latest advances in the synthetic and natural carbazole-containing compounds involved in diabetes pathways.

Keywords: carbazoles; alkaloids; diabetes mellitus; antihyperglycemic agents

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1. Introduction

The term "diabetes mellitus" (DM) refers to a group of chronic metabolic disorders characterized by hyperglycemia due to insufficient insulin secretion (type 1 DM) or to an inadequate response of the body to the action of this hormone (type 2 DM) [1]. Since a constant increase in glucose concentration in the blood can lead to serious consequences for several organs, including the eyes, kidneys, cardiovascular system, and central nervous system (CNS) [2,3] monitoring glycemia is of primary importance [4,5]

An effective approach to reduce postprandial blood glucose concentration is to inhibit the enzyme α-glucosidase, which catalyzes the final stage of the digestion process of carbohydrates to monosaccharides. These latter sugars are then absorbed and enter the bloodstream, thus increasing blood glucose levels [6]. The damages caused by hyperglycemia are related to the alteration of several physiological pathways. Several studies have shown, for example, that high levels of glucose, fatty acids, and insulin in the blood promote the production of reactive oxygen species (ROS), which cause direct DNA damage and promote insulin resistance [7].

Furthermore, by overstimulating the IGF-1 factor or by activating different kinase proteins, hyperglycemia favors cellular hyperproliferation and consequently the onset of cancer [8–10]. As a result of scientific advances, a wide range of anti-diabetic drugs are now available, improving the quality and length of life in type 2 diabetic patients.

These drugs, which belong to different chemical classes, can lower blood glucose levels through a variety of mechanisms (see Table 1 and Figure 1).

Table 1. Classes of antidiabetic medications.

DRUG CLASS	MECHANISM OF ACTION	MORE COMMON SIDE EFFECTS AND DISADVANTAGES
BIGUANIDES: **Metformin**	AMP-Kinase activation; Decrease in hepatic glucose production.	Gastrointestinal side effects (diarrhea, abdominal cramping); Lactic acidosis risk; Vit B12 deficiency; Hypoxia; Dehydration.
SULPHONYLUREAS: **Glibenclamide** **Gliclazide** **Glipizide** **Glimepiride**	Closure of KATP channels on β cell plasma membranes; Increase in insulin secretion.	Hypoglycemia; Weight gain.
GLINIDES (MEGLITINIDES): **Repaglinide** **Nateglinide**	Closure of KATP channels on β cell plasma membranes; Increase in insulin secretion.	Hypoglycemia; Weight gain.
α-GLUCOSIDASE INHIBITORS: **Acarbose** **Miglitol**	Inhibition of intestinal α-glucosidase; Intestinal carbohydrate digestion and absorption reduction.	Generally modest HbA1c efficacy; Gastrointestinal side effects (flatulence, diarrhea).
THIAZOLIDINEDIONES (TZDs): **Pioglitazone** **Rosiglitazone** **Lobeglitazone**	Nuclear transcription factor PPAR-γ activation; Increase in insulin sensitivity.	Weight gain; Edema; Heart failure; Bone fractures.
DPP4 INHIBITORS (GLIPTINS): **Sitagliptin** **Vildagliptin** **Saxagliptin** **Alogliptin** **Alogliptin** **Linagliptin**	DPP-4 inhibition; Increase in postprandial active incretin (GLP-1, GIP) concentrations; Increase in glucose-dependent insulin secretion; Decrease in glucose-dependent glucagon secretion.	Generally modest HbA1c efficacy; Urticaria; Angioedema.
GLP-1 AGONISTS: **Exenatide** **Liraglutide** **Lixisenatide** **Dulaglutide**	GLP-1 receptors activation; Increase in glucose-dependent insulin secretion; Decrease in glucose-dependent glucagon secretion.; Slowing of gastric emptying; Satiety increase.	Gastrointestinal side effects (nausea/vomiting); Pancreatitis; C-cell hyperplasia.
SGLT2 INHIBITORS: **Dapagliflozin** **Empagliflozin** **Canagliflozin**	Block of sodium/glucose cotransporter 2 (SGLT2) in renal tubules Reduction of glucose reabsorption in the kidney; Decrease in serum blood glucose level.	Renal failure; Increased risk of genital and urinary trac fungal infection; Increased risk of euglycemic diabetic ketoacidosis.
AMYLIN ANALOGUES **Pramlintide**	Amylin receptors activation; Glucagon secretion reduction; Slowing of gastric emptying; Satiety increase.	Generally modest HbA1c efficacy; Gastrointestinal side effects Hypoglycemia.

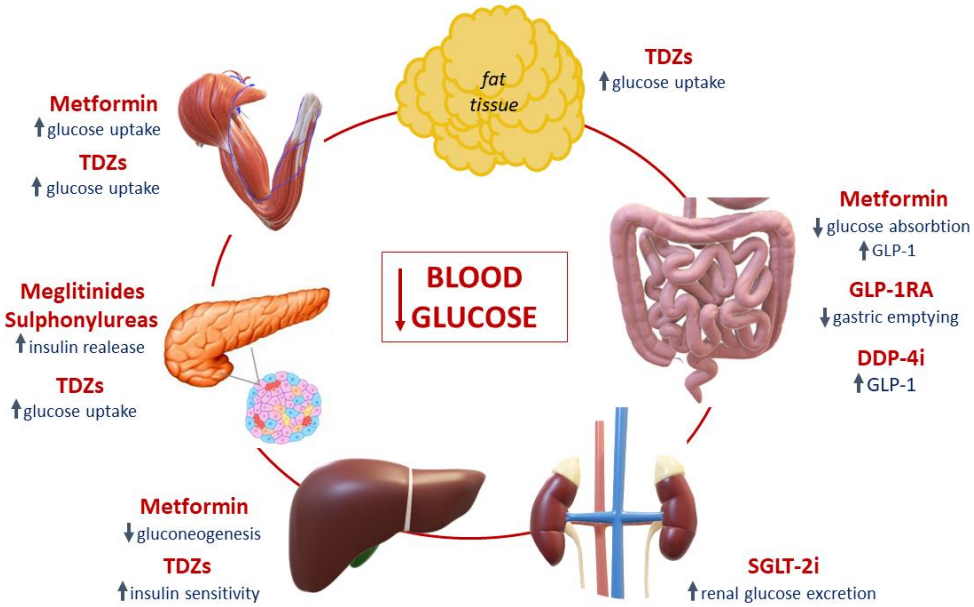
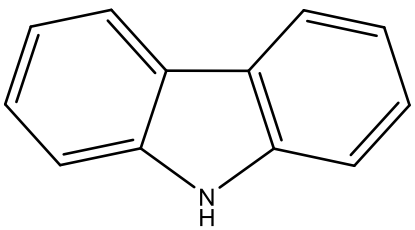


Figure 1. Mechanisms of action of antidiabetic drugs.

Metformin, one of the most commonly used oral hypoglycemic drugs, acts, for example, by increasing the utilization of glucose in peripheral tissues and by decreasing hepatic glucose production. Sulfonylureas, on the other hand, are able to modulate blood glucose levels by stimulating insulin secretion from pancreatic beta cells. Thiazolidinediones (TZDs) binds the peroxisome proliferator-activated receptor (PPAR) gamma, a transcription factor that regulates the expression of specific genes, and improves the sensitivity of fatty tissue, skeletal muscles and liver to insulin. More recently, new classes of drugs able to control hyperglycemia have been introduced. Among these, incretins, DPP-4 resistant GLP-1 analogs, and DPP-4 inhibitors play an important role; they are able to promote an increase in endogenous GLP-1 levels and stimulate pancreatic cells to release insulin. SGLT2 inhibitors increase glucose excretion in the urine by preventing glucose reabsorption in the renal tubules. Despite the therapeutic goals achieved by this diverse range of diabetes drugs, their clinical use is associated with undesirable side effects (summarized in Table 1), including dangerous hypoglycemic episodes [11]. Therefore, the identification of new molecules that preserve hypoglycemic activity while having reduced toxicity remains a goal of the scientific community. In this context, carbazole derivatives could represent valid therapeutic alternatives. Carbazole (I) (Figure 2) is a tricyclic heterocycle alkaloid consisting of two benzene rings fused on both sides of a pyrrole ring [12–15].



I

Figure 2. Structure of carbazole (I).

The first naturally occurring carbazole was isolated from Murraya *koenigii Spreng*. Murraya *euchrestifolia* has been found to be a rich source of carbazole alkaloids, providing a variety of novel structures. Some bioactive carbazole alkaloids have also been obtained from other sources such as actinomycetes, blue-green algae and mammalian systems [16,17].

A large number of studies reported in the literature were focused on the biological properties of carbazole and its derivatives, such as antimicrobial, anti-inflammatory, antitumor, antioxidant, antiepileptic, antihistamine, antidiarrheal, analgesic, neuroprotective, and inhibiting properties of pancreatic lipase [18–21].

In particular, some compounds belonging to this chemical class have shown promising activities in controlling glucose metabolism in hypertensive patients with type 2 DM and in improving insulin sensitivity [22]. In this review, we summarize the latest advances in the potential role of carbazole derivatives either in the prevention of or in the treatment of diabetes. Overall, the data herein reported could provide an important resource for the development of novel, efficient, and safe agents for innovative diabetes treatment.

2. Carbazole Derivatives in the Pathogenesis of Diabetes

Over the years, the academic community has delved into the chemical and pharmacological properties of small heterocyclic molecules, including those with a carbazole-based structure [23–26]. Growing interest in these derivatives has resulted in the development of various synthetic routes for their preparation as well as their extraction from various plants. Several carbazole-containing molecules have found application in the pharmaceutical field. In particular, the studies included in this review showed that certain derivatives are promising antidiabetic agents or may otherwise play an important role in the pathogenesis of diabetes. Data reported in the literature suggest that carbazoles are able to modulate glucose metabolism, block adrenergic hyperactivation, prevent damage to β cells of the pancreas, inhibit inflammatory and oxidative mediators, control the cryptochrome or inhibit α-glucosidase (Table 2). Therefore, carbazole represents a versatile scaffold for the preparation of biologically active derivatives, useful in the treatment of diabetes [6,7,27–46].

Table 2. Carbazole derivatives in the pathogenesis of diabetes.

Compound	Name	Biological Activity	References
1 (Synthetic compound)	Carvedilol (1-(9*H*-carbazol-4-yloxy)-3-[2-(2-methoxyphenoxy)ethylamino]propan-2-ol)	Reduction of insulin resistance by sensitizing insulin receptors and inhibiting the sympathetic nervous system Beneficial effects on left ventricular function, resting and exercise hemodynamics and clinical conditions Stimulation of endothelial NO production Beneficial effects on endothelial dysfunction caused by oxidative stress Long-term benefits on glucose metabolism Blockade of adrenergic hyperactivation Prevention of pancreatic *β*-cell damage Inhibition of inflammatory and oxidative mediators	[7,27–33]
2	Hydroxyphenyl-carvedilol (OHC) 4-[2-[[3-(9*H*-Carbaz-ol-4-yloxy)-2-hydroxypro-pyl]amino]ethoxy]-3-methoxyphenol	Metabolite of carvedilol	[30]
3	*O*-Desmethylcarvedilol (DMC) 2-[2-[[3-(9*H*-Carbaz-ol-4-yloxy)-2-hydroxypro-pyl]amino]ethoxy]phenol	Metabolite of carvedilol	[30]
4 (Synthetic compound)	1-((5,6-Di(furan-2-yl)-1,2,4-triazin-3-yl)thio)-3-(3,6-dibromo-9*H*-carbazol-9-yl)propan-2-ol	*α*-Glucosidase inhibition (IC_{50} = 4.27 ± 0.07 μM)	[6,34]
5 (Synthetic compound)	2-(3-(9*H*-Carbazol-9-yl)-2-hydroxypropyl)isothiazoline-1,1-dioxide	Cryptochrome modulator	[35]

Table 2. *Cont.*

Compound	Name	Biological Activity	References
6 (Synthetic compound)	1-(3-(3,6-Difluoro-9*H*-carbazol-9-yl)-2-hydroxypropyl)imidazolidin-2-one	Cryptochrome modulator	[22]
7 (Synthetic compound)	2-(4-((9*H*-Carbazol-9-yl)methyl)-1*H*-1,2,3-triazol-1-yl)-1-(3-bromo-4-hydroxyphenyl) ethanone	α-Glucosidase inhibition (IC_{50} = 1.0 ± 0.057 μM)	[36]
8 (Synthetic compound)	9-((1-(Pyridin-3-yl-methyl)-1*H*-1,2,3-triazol-4-yl) methyl)-9*H*-carbazole	α-Glucosidase inhibition (IC_{50} = 0.8 ± 0.01 μM)	[36]
9 (Synthetic compound)	6-(Benzyloxy)-9-(4-chlorobenzoyl)-2,3,4,9-tetrahydro-1*H*-carbazole-3-carboxylic acid	Hypoglycemic effect via the AMPK pathway	[37]
10 (Synthetic compound)	Ethyl 8-(benzyloxy)-5-(4-chlorobenzoyl)-7-fluoro-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate	Hypoglycemic effect via the AMPK pathway	[38]
11 (Naturalcompound)	Mahanine 3,5-Dimethyl-3-(4-methylpent-3-enyl)-11*H*-pyrano[3,2-*a*]carbazol-9-ol	Prevention of insulin resistance due to lipid induced signaling defects α-Glucosidase inhibition (IC_{50} = 21.4 ± 0.4 μM) Antioxidant properties Increase in the translocation of GLUT4 protein from intracellular vesicles into the plasma fraction and glucose uptake through the activation of phosphorylation of Akt	[39–41]
12 (Naturalcompound)	Bisgerayafoline D 3,3′-Bis((*E*)-3,7-dimethylocta-2,6-dien-1-yl)-9′-methoxy-3,3′,5,5′-tetramethyl-3,3′,11,11′-tetrahydro-[9,10′-bipyrano[3,2-*a*]carbazol]-10-ol	Antioxidant and α-glucosidase properties	[40]
13 (Naturalcompound)	Bismahanimbinol 3,3′,5,5′-Tetramethyl-3,3′-bis(4-methylpent-3-en-1-yl)-3,3′,11,11′-tetrahydro-[9,10′-bipyrano[3,2-*a*]carbazol]-8-ol	Antioxidant and α-glucosidase properties	[40]
14 (Naturalcompound)	Bispyrayafoline 3,3′,5,5′-Tetramethyl-3,3′-bis(4-methylpent-3-en-1-yl)-3,3′,11,11′-tetrahydro-[10,10′-bipyrano [3,2-*a*]carbazole]-9,9′-diol	Antioxidant and α-glucosidase properties	[40]
15 (Naturalcompound)	*O*-Methyl mahanine 9-Methoxy-3,5-dimethyl-3-(4-methylpent-3-en-1-yl)-3,11-dihydropyrano[3,2-*a*]carbazole	Antioxidant and α-glucosidase properties	[40]
16 (Naturalcompound)	*O*-Methyl mukonal Koenimbine 8-Methoxy-3,3,5-trimethyl-11*H*-pyrano[3,2-*a*]carbazole	Antioxidant and α-glucosidase properties Antidiabetic activity in L6-GLUT4 myc myotubes	[40,42]
17 (Naturalcompound)	*O*-Methylmurrayamine A 9-Methoxy-3,3,5-trimethyl-11*H*-pyrano[3,2-*a*]carbazole	Antidiabetic activity in L6-GLUT4 myc myotubes Decrease in blood glucose profile	[42]

Table 2. *Cont.*

Compound	Name	Biological Activity	References
18 (Naturalcompound)	Koenidine 8,9-Dimethoxy-3,3,5-trimethyl-11*H*-pyrano [3,2-*a*]carbazole	Antidiabetic activity in L6-GLUT4myc myotubes Increase in insulin sensitivity and progressive reduction of blood glucose level	[42]
19 (Naturalcompound)	Mahanimbine 3,5-Dimethyl-3-(4-methylpent-3-enyl)-11*H*-pyrano[3,2-*a*]carbazole	Antidiabetic activity in L6-GLUT4myc myotubes	[42]
20 (Naturalcompound)	Murrayazoline (14*R*,17*S*,19*S*)-3,13,13,17-Tetramethyl-21-oxa-12-azahexacyclo[10.7.1.1^{2,17}.0^{5,20}.0^{6,11}.0^{14,19}]henicosa-1,3,5(20),6,8,10-hexaene	Antidiabetic activity in L6-GLUT4myc myotubes	[42]
21 (Synthetic compound)	(*S*)-3-(4-(2-(9*H*-Carbazol-9-yl)ethoxy)phenyl)-2-ethoxypropanoic acid	Improve of the insulin sensitivity Activity on PPARR and PPARγ	[43]
22 (Synthetic compound)	Chiglitazar (2*S*)-3-[4-(2-Carbazol-9-ylethoxy)phenyl]-2-[2-(4-fluorobenzoyl)anilino]propanoic acid	Reduction of glycosylated hemoglobin A1c (HbA1c) Hypoglycemic effect Increase in insulin sensitivity Reduction of triglycerides	[44–46]

2.1. Carvedilol

The carbazole derivative **1** (carvedilol, 1-(9*H*-carbazol-4-yloxy)-3-[2-(2-methoxyphenoxy) ethylamino]propan-2-ol) (Figure 3), synthesized by the reaction of 4-(oxirane 2-ylmethoxy)-9*H*-carbazole with 2-(2-methoxyphenoxy)ethylamine [47], was discovered in a study devoted to discovering agents useful in the treatment of congestive heart failure. The interaction of carvedilol (**1**) with beta-adrenergic receptors is stereospecific, in a similar way that was demonstrated for carazolol, a veterinary medicine drug used to reduce stress in animals during transport [48]. This optically active compound exhibits activity as a selective beta-adrenergic receptor blocker such as the *S* (−) enantiomer, whereas the *R* (+) enantiomer is capable of antagonizing both alpha-1 and beta-adrenergic receptors. These characteristics make this molecule more effective than other traditional beta-blockers in the treatment of heart failure and in the regulation of myocardial functions. Furthermore, unlike other beta-blockers, it does not cause alterations in the metabolism of carbohydrates and lipids [49].

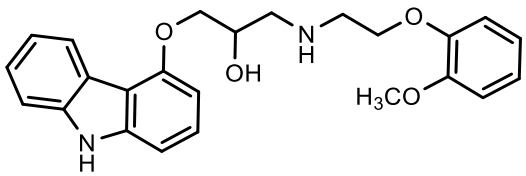


Figure 3. Structure of carvedilol (**1**).

Carvedilol (**1**) was found to reduce insulin resistance by increasing the sensitivity of insulin receptors (IRs) and by reducing the activity of the sympathetic nervous system [50]. The adrenergic system, in part through beta-2 adrenergic receptors, regulates glucose and lipid metabolism in the liver, adipose tissue, and skeletal muscle.

Taking into consideration all these properties, several studies were focused on the evaluation of the efficacy of carvedilol (**1**) in preventing heart complications in patients with diabetes [7,51–53]. In an earlier study on the efficacy and tolerability of long-term

administration of carvedilol (**1**), Nodari et al. [27] evaluated the drug's effects in patients with chronic heart failure, a number of whom were also diabetic. Treatment with increasing doses of carvedilol was well tolerated by all treated patients, showing positive effects on left ventricular function and on resting and exercise hemodynamics. Furthermore, unlike traditional beta-blockers, it did not affect insulin sensitivity and glycemic values in diabetic patients treated with oral hypoglycemic agents or insulin [27,54,55].

In a separate study, carvedilol (**1**) was found to be more effective than metoprolol, one of the most prescribed selective beta-1 adrenergic antagonists, in controlling glucose metabolism in diabetic hypertensive patients without affecting insulin resistance [51,54]. This was most likely due to carvedilol's ability to also block beta-2 and alpha-1 receptors [56]. Unlike patients treated with metoprolol, who gained weight after 2 months of treatment, no significant change in body weight was observed in those treated with carvedilol (**1**). Long-term carvedilol treatment may have beneficial effects on endothelial dysfunction caused by oxidative stress in patients with type 2 DM. This could be due to the antioxidant properties of the compound, which acts as a radical scavenger, and to its capability to modulate endothelial NO production [28,57].

Vardeny et al., in 2012 [29], found that in hypertensive patients treated with metoprolol succinate, after six months, insulin levels increased by approximately 36%, whereas a decrease of about 10% was observed in those treated with carvedilol (**1**) ($p = 0.015$).

Many studies have discovered a relation between β2-AR polymorphisms and metabolic disorders, including hypertriglyceridemia, insulin resistance, and obesity [58–60]. In particular, two common β2-AR single-nucleotide polymorphisms, Arg16Gly and Gln27Glu, have been shown to be responsible for altered receptor function and, consequently, for an inadequate response to β-blocker treatment.

Farhat et al., in 2019, demonstrated that low-dose carvedilol (**1**) can efficiently prevent hypoglycemic crises in rats treated with β-blockers. This study showed that rats with recurrent episodes of hypoglycemia treated with carvedilol required less exogenous glucose during the hypoglycemic clamp, thus supporting use of the drug to preserve hormonal responses to hypoglycemia. Furthermore, carvedilol treatment had no effect on plasma lactate levels, indicating that the drug can prevent some of the central adaptations that occur during recurrent hypoglycemic episodes [61].

In 2017, Nardotto et al. [30] conducted a study aimed at evaluating the pharmacokinetic profile of the enantiomers of carvedilol and the corresponding metabolites, hydroxyphenylcarvedilol (OHC) (**2**) and O-desmethylcarvedilol (DMC) (**3**) (Figure 4), in healthy volunteers and in patients with type 2 DM but with good glycemic control.

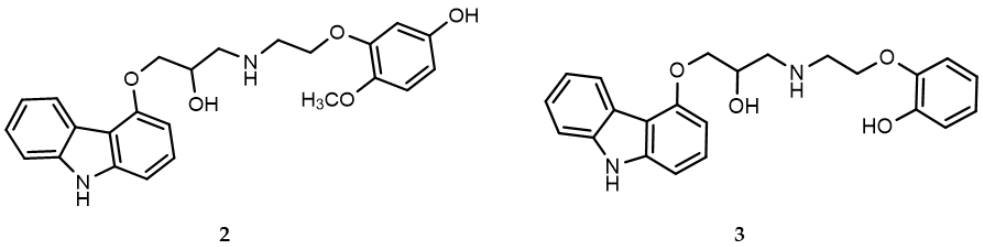


Figure 4. Structures of: hydroxyphenylcarvedilol (OHC) (**2**) and O-desmethylcarvedilol (DMC) (**3**).

For this purpose, thirteen healthy subjects were recruited and divided into two groups: the first group underwent treatment with carvedilol as a single agent, while the second one received a treatment of carvedilol (**1**) in combination with glibenclamide and metformin. In addition, patients with type 2 DM were enrolled and were treated with carvedilol as a single agent. The results of this study demonstrated that the pharmacokinetic profile of the carvedilol enantiomers did not differ between each other, even in the patients treated with glibenclamide and metformin.

In a separate study, the same authors, using an integrated population pharmacokinetic modeling approach, confirmed that carvedilol does not induce insulin resistance or

worsen glycemic control in diabetic hypertensive patients [31]. More recently, Nguyen et al. conducted a study to evaluate the effects of carvedilol (**1**) treatment in subjects with obesity induced by a high-fat diet (HFD). The findings not only confirmed the improvement in glucose tolerance and insulin sensitivity, but also indicated that these effects are related to the suppression of hepatic glucose overproduction and to the enhancement of the muscle insulin signaling pathway. Hence, as a result of the drug's ability to block adrenergic hyperactivation, long-term treatment with carvedilol (**1**) may provide significant benefits in obese subjects [32,60,61].

The efficacy of carvedilol (**1**) is, however, limited due to its poor bioavailability. Therefore, various studies have been conducted in order to formulate the drug in transport systems capable of guaranteeing the desired therapeutic effect without increasing the dose to be administered. Since a high insulin concentration significantly increases DNA fragmentation, Farahani-Zangaraki et al., in 2021 [7], used the Comet test to assess the genoprotective effects of carvediol included into niosomes against supraphysiological insulin levels in human umbilical vein endothelial cells (HUVEC) [62]. As a result, incorporating carvedilol (**1**) into the nanoparticles increased efficiency by about fivefold. In particular, treatment of HUVEC cells with niosome-carvedilol (**1**) nanoparticles 24 h before insulin administration resulted in a significant decrease in DNA fragmentation related to the insulin-treated group, confirming the better genoprotective effect of the drug loaded in the niosomes compared to the free drug. Treatment of HUVEC cells with niosome carvedilol (**1**) nanoparticles 24 h before insulin administration decreases DNA fragmentation compared to the insulin-treated group, confirming the greater genoprotective effect of the drug loaded in the niosomes compared to the free drug [7].

Recently, carvedilol (**1**) had also been investigated as an alternative therapeutic strategy for the treatment of type 1 DM. In an in vivo experimental model of type 1 DM, Amirshahrokhi and Zohouri [33] demonstrated carvedilol's protective effect against pancreatic β-cell damage, confirming the drug's ability to significantly reduce blood glucose levels, weight loss, and insulitis in pancreatic tissue, as well as the onset of diabetes. Significant increases in the antioxidants glutathione (GSH), superoxide dismutase (SOD), and catalase were observed in pancreatic tissue from carvedilol-treated mice. On the other hand, a reduction in malondialdehyde (MDA), nitric oxide (NO), and myeloperoxidase (MPO) levels was also observed. In addition, the treatment promoted an appreciable reduction in the β-cell damage in pancreatic tissue as well as in the expression of inflammatory modulators including the nuclear factor kappa B (NF-κB), cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iN-OS). Similarly, a reduction of proinflammatory cytokines tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6 IL-12, IL-17, interferon (IFN)-γ, and chemokine had been also observed, while the expression of anti-inflammatory cytokine IL-10 increased [33].

Despite that the experimental evidence points to carvedilol as having a decidedly positive effect in the treatment of diabetes, more research into the drug's mechanism of action is required.

2.2. 1,2,4-Triazine-Carbazoles

As already mentioned, α-glucosidase represents a valuable target for the treatment of type 2 DM. As a result, numerous efforts are being made by the scientific community to identify new compounds capable of inhibiting this enzyme in order to delay carbohydrate digestion and glucose absorption, thus leading to a reduction in postprandial glycemia values [63]. Accordingly, in 2016, Wang et al. [6] developed a small series of triazines, used as different starting substitute carbazoles, in order to identify novel α-glucosidase inhibitors.

A number of the newly synthesized compounds showed noteworthy activity against the enzyme. In particular, compound **4** (1-((5,6-di(furan-2-yl) -1,2,4-triazin-3-yl)thio)-3-(3,6-dibromo-9H-carbazol-9-yl)propan-2-ol)) (Figure 5) was found to be the most promising,

with IC_{50} values of 4.27 ± 0.07 μM, significantly higher than the control drug acarbose (IC_{50} = 995.55 ± 2.71 μM).

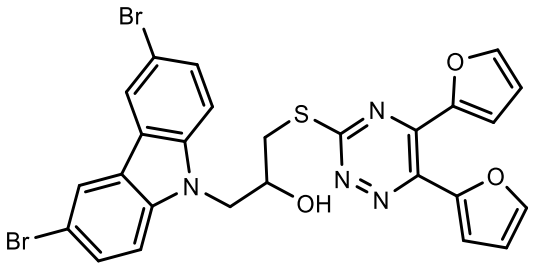


Figure 5. Structure of 1-((5,6-di(furan-2-yl)-1,2,4-triazin-3-yl)thio)-3-(3,6-dibromo-9H-carbazol-9-yl)propan-2-ol (**4**).

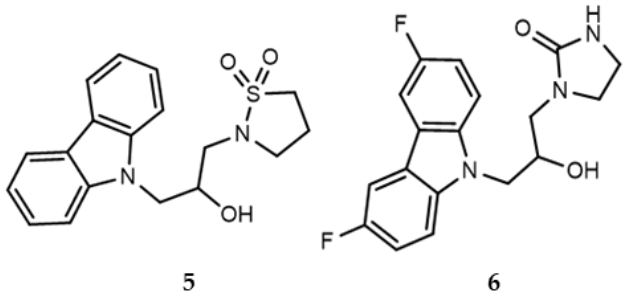
Molecular docking experiments confirmed its capability to interact with the active site of the enzyme, and furthermore, the kinetic analysis revealed that **4** acts as a non-competitive inhibitor. In particular, the carbazole ring of **4** forms arene-cation interactions with residues Arg-439 and Arg-312, respectively, and the furan ring interacts with residues Leu-176, Phe-157, Phe-177 and Pro-240. Overall, the findings of this study could represent a starting point for the future development of efficient α-glucosidase inhibitors.

2.3. Sulfonamide Carbazole and Carbazole-Containing Cyclic Urea

Variants of the cryptochrome (Cry) gene have been demonstrated to be correlated to the onset of type 2 DM and insulin resistance, as it is involved in glucose homeostasis, control of *β*-cell function liver lipid content, and the circadian system of mammals [22,64,65].

In order to identify compounds capable of modulating the cryptochrome activity, Humphries et al. in 2016 [35] carried out a systematic SAR study that led to a series of sulfonamide and sulfamide carbazole-based derivatives. Among these compounds, cyclic sulfonamide, 2-(3-(9*H*-carbazol-9-yl)-2-hydroxypropyl)isothiazoline-1,1-dioxide (**5**) (Figure 5) was identified as the first small molecule, orally bioavailable, active as a cryptochrome modulator in an in vivo model of type 2 diabetes. The efficacy of this compound was evaluated in mice with diet-induced obesity (DIO), using rosiglitazone as a positive control.

The results obtained by an oral glucose tolerance test confirmed a significantly improved glucose clearance [35]. In 2018, the same research team discovered a new class of carbazole-containing amides and ureas as cryptochrome modulators [22]. In particular, compound 1-(3-(3,6-difluoro-9*H*-carbazol-9-yl)-2-hydroxypropyl)imidazolidin-2-one (**6**) (Figure 6) resulted as the most promising derivative, implying its potential use in the treatment of metabolic disorders including type 2 DM [22,66–69].



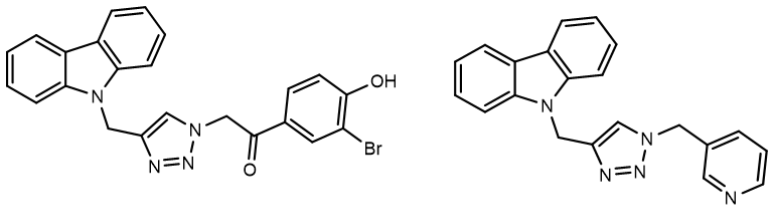
5 **6**

Figure 6. Structures of: 2-(3-(9*H*-carbazol-9-yl)-2-hydroxypropyl)isothiazoline-1,1-dioxide (**5**) and 1-(3-(3,6-difluoro-9*H*-carbazol-9-yl)-2-hydroxypropyl)imidazolidin-2-one (**6**).

2.4. Carbazole Triazoles

Recently, a series of derivatives of carbazole linked to a variously substituted triazole have been developed and tested as *α*-glucosidase inhibitors [36]. The synthesis of these compounds was carried out by a click reaction using *N*-propargyl-9*H*-carbazole, acetophenone azide, and a suitable heterocycle as starting reagents. Almost all of the synthesized compounds inhibited the target enzyme more efficiently than acarbose, used as a positive control.

Compounds 2-(4-((9*H*-carbazol-9-yl)methyl)-1*H*-1,2,3-triazol-1-yl)-1-(3-bromo-4-hydroxyphenyl) ethanone (**7**) and 9-((1-(pyridin-3-yl-methyl)-1*H*-1,2,3-triazol-4-yl) methyl)-9*H*-carbazole (**8**) (Figure 7), with IC_{50} values of 1.0 and 0.8 μM, respectively, resulted as the most promising and thus represent suitable lead compounds for the development of innovative non-sugar derivative antidiabetic agents.

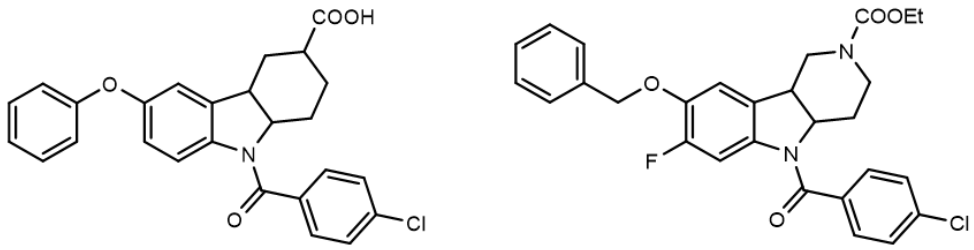


7 8

Figure 7. Structures of: 2-(4-((9*H*-carbazol-9-yl)methyl)-1*H*-1,2,3-triazol-1-yl)-1-(3-bromo-4-hydroxyphenyl) ethanone (**7**) and 9-((1-(pyridin-3-yl-methyl)-1*H*-1,2,3-triazol-4-yl) methyl)-9*H*-carbazole (**8**).

2.5. Tetrahydrocarbazole Derivatives

Zhang et al., in 2018 [37], developed a new series of tetrahydrocarbazoles and tested them in an in vitro assay on human hepatoma cell lines (HepG2) to assess their hypoglycemic activity. Several of the compounds tested exhibited significant activity, with carboxyl (**9**), 6-(benzyloxy)-9-(chlorobenzoyl)-2,3,4,9-tetrahydro-1*H*-carbazole-3-carboxylic acid (Figure 8) being the most promising. This compound was thus selected for further in vivo experiments. The results obtained confirmed that compound **9** has comparable hypoglycemic properties to that of pioglitazone and causes less weight gain compared to the drug in clinical use.



9 10

Figure 8. Structures of: 6-(benzyloxy)-9-(chlorobenzoyl)-2,3,4,9-tetrahydro-1*H*-carbazole-3-carboxylic acid (**9**) and ethyl 8-(benzyloxy)-5-(4-chlorobenzoyl)-7-fluoro-3,4-dihydro-1*H*-pyrido[4,3-*b*]indole-2(5*H*)-carboxylate (**10**).

A recent study [42], reported by the same above research group, led to the identification of an azatetrahydrocarbazole derivative, namely ethyl 8-(benzyloxy)-5-(4-chlorobenzoyl)-7-fluoro-3,4-dihydro-1*H*-pyrido[4,3-b]indole-2(5*H*)-carboxylate (**10**) (Figure 8). This derivative showed hypoglycemic activity, in cell assays, approximately 1.2 times higher than that of metformin, used as a positive control. Studies aimed at elucidating the mechanism of action responsible for the hypoglycemic activity of these compounds have suggested

involvement of the AMP-activated protein kinase (AMPK). The AMPK-mediated pathway plays a key role in controlling the energy and metabolic homeostasis of cells, acting as a sensor for the cellular energy status [70,71].

Compound **10** also showed appreciable chemical stability in gastrointestinal fluids and plasma in in vivo studies, which also confirmed a good tolerance of the compound after oral administration [38]. The promising hypoglycemic, pharmacokinetic, and pharmacodynamic properties of compound **10** validate the potential of carbazole as a versatile scaffold for the preparation of derivatives with improved bioactivities that can be useful in a variety of therapeutic applications.

2.6. Carbazole Alkaloids

Murraya koenigii (L.) *Spreng* is an endemic plant of India belonging to the *Rutaceae* family, also known as "meethi neem" or "curry patta" [42]. The extracts of this plant have been extensively investigated for their antidiabetic activity. Recent studies have demonstrated that the main phytocompounds of this plant are alkaloids whose structures contain a carbazole nucleus [42,72,73]. In 2010, Biswas et al. [39] investigated the hypoglycemic effects of mahanine (**11**) (Figure 9), a carbazole-containing alkaloid, isolated from the leaves of the plant. The results of the experiments on mice with diet-induced diabetes showed a significant reduction in hyperglycemia and insulin resistance, most likely due to the ability of this phytocompound to modulate the expression of the IR gene and the activation of the NF-jB pathway [74].

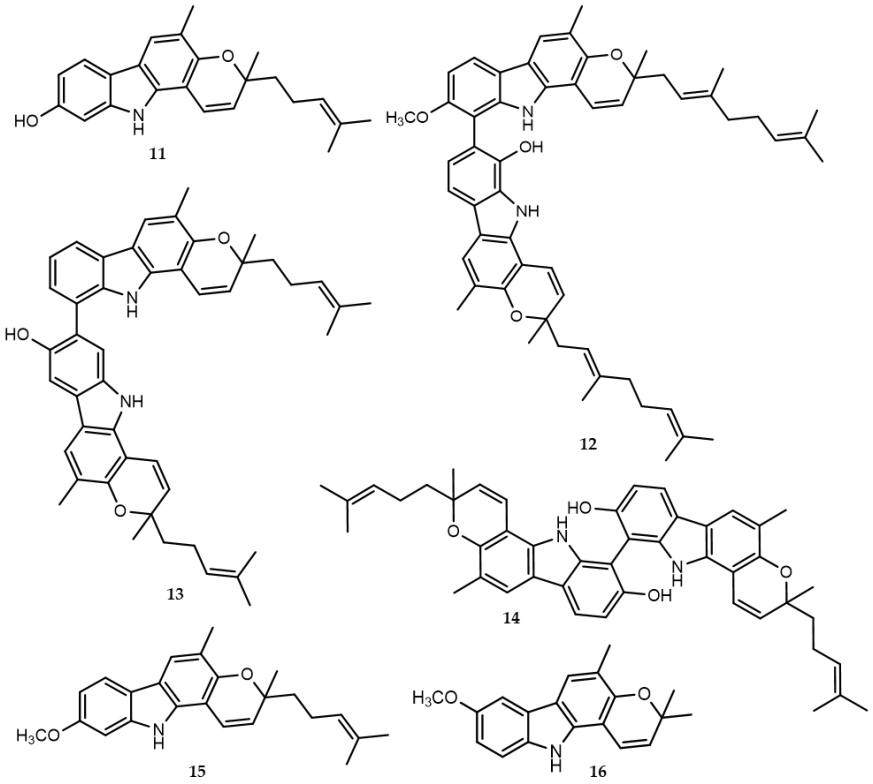


Figure 9. Structures of: mahanine (**11**), bisgerayafoline D (**12**), bismahanimbinol (**13**), bispyrayafoline (**14**), *O*-methyl mahanine (**15**) and *O*-methyl mukonal (**16**).

In a separate study, in addition to mahanine (**11**), Uvarani et al. isolated from the fruit pulp extract another six carbazole-containing alkaloids: bisgerayafoline D (**12**), bismahanimbinol (**13**), bispyrayafoline (**14**), *O*-methyl mahanine (**15**), *O*-methyl mukonal (**16**) (Figure 9). All these compounds (**11**–**16**) were tested for antioxidant, anti-α-glucosidase, DNA binding, protein interactions, and cytotoxic activities. Out of all the phytochemicals tested, mahanine (**11**) resulted to be the most promising as a radical scavenger and as

an α-glucosidase inhibitor (IC_{50} of 21.4 $\pm$ 0.4 μM). Furthermore, this compound showed cytotoxic activity due to its ability to act as a DNA-intercalating agent [40].

The antidiabetic action of mahanine (**11**) was also confirmed in a study by Nooron et al. [41] in which the effects of the phytocompound on glucose uptake and translocation of glucose transporter 4 (GLUT4) in skeletal muscle and adipocyte cells were evaluated. In particular, the mahanine (**11**) treatment promoted a dose-dependent increase in glucose uptake in L6 myotubes and adipocyte cells through the stimulation of the Akt signaling pathway. These findings suggested that mahanine (**11**) acted similarly to insulin, promoting an enhancement of the Akt-mediated signaling pathway and leading to an increased translocation of GLUT4 on the cell membrane and, consequently, to a higher glucose uptake.

Carbazole-containing alkaloids (**16** (Figure 9) and **17–20** (Figure 10)) found in *M. koenigii* leaf extract promoted a substantial increase in glucose uptake, which was correlated to a higher translocation of GLUT4 into L6-GLUT4myc myotubes. The activity of compounds **16–19** was also investigated in rats with streptozotocin-induced diabetes. Compound **18**, koenidine, was found to be the most effective in lowering blood glucose and was therefore selected for further in vivo assays in leptin-receptor-deficient db/db mice. As expected, a significant increase in insulin sensitivity and a progressive lowering of blood glucose level were recorded.

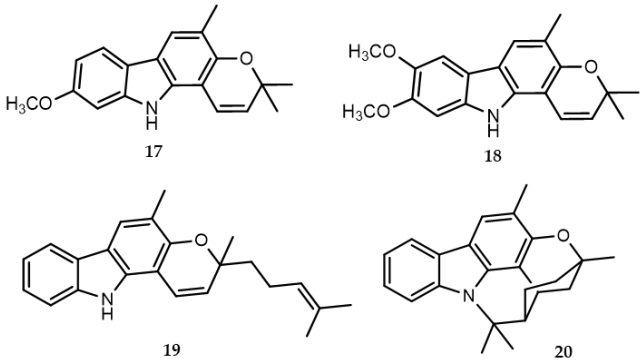


Figure 10. Structures of: O-methylmurrayamine A (**17**), koenidine (**18**), mahanimbine (**19**) and murrayazoline (**20**).

Furthermore, Western blot studies confirmed that the stimulation of GLUT4 translocation observed in L6-GLUT4myc myotubes is mediated by activation of the AKT-modulated signaling pathway. In vitro and in vivo pharmacokinetic studies revealed that compound **18** outperformed the other alkaloids due to its higher metabolic stability and systemic availability. The combination of properties of compound **18** makes it an ideal drug candidate for the treatment of diabetes and the treatment of insulin resistance [42].

2.7. Carbazole-Ethoxy-Phenyl Propionic Acid Derivative

The discovery of the nuclear receptor peroxisome proliferator-activated receptor (PPAR) -α and γ, as primary targets for fibrates and the thiazolidinediones (TZDs), respectively, has opened up new possibilities for the development of alternative tools for the treatment of type 2 DM [75,76].

The ability of TZD and fibrates to lower blood sugar and lipids, respectively, demonstrated in experimental models of insulin resistance and hyperlipidemia, has been known for decades. The improvement in insulin sensitivity promoted by TZDs (pioglitazone or rosiglitazone), although modest, is nevertheless significant and has justified the investments in the search for alternative diabetes treatments, using these compounds as starting compounds [77,78]. Thus far, several computational and in vitro studies on the PPAR receptor have been conducted for this purpose.

One of these research works has led to the identification of compound (*S*)-3-(4-(2-(9*H*-carbazol-9-yl)-ethoxy)phenyl)-2-ethoxypropanoic acid (**21**) (Figure 11), which showed dual activity on both PPAR isoforms α and γ [43]. The results of an oral glucose tolerance test (OGTT) showed that treatment with compound **21** promoted an improvement in insulin sensitivity, greater than that seen with both pioglitazone and rosiglitazone. Compound **21** was also able to lower plasma concentrations of triglycerides and cholesterol in rats fed high cholesterol, whereas treatment with other PPARγ agonists did not have the same results [43].

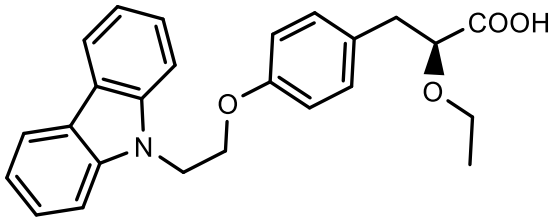


Figure 11. Structure of (*S*)-3-(4-(2-(9*H*-carbazol-9-yl)ethoxy)phenyl)-2-ethoxypropanoic acid (**21**).

2.8. Chiglitazar

Chiglitazar (Bilessglu®) (**22**) (Figure 12) is a small molecule with agonist activity against PPARα, δ and γ, recently developed by Chipscreen Bioscience.

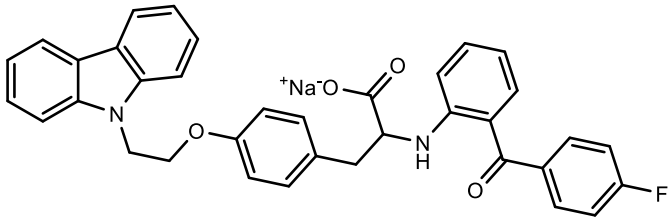


Figure 12. Structure of Chiglitazar (**22**).

In China, this drug was approved in October 2021 for the treatment of diabetes and is currently in phase II clinical trials for the treatment of non-alcoholic steatohepatitis [44]. In a very recent phase III study [45], the efficacy and safety of chiglitazar (**22**) were investigated in patients with type 2 DM who were unable to control their blood sugar with diet and exercise alone. Treatment with the drug resulted in significantly better blood glucose control than the placebo, with no significant toxic effects. Multiple administrations of different doses of chiglitazar (**22**) were generally well tolerated by patients of different ages.

An enhancement in insulin sensitivity and triglyceride level reduction were also recorded. Overall, clinical studies confirmed the drug's properties observed in preclinical experiments, bolstering the value of PPAR pan-agonists as efficient and safe tools for the treatment of diabetes [46].

3. Conclusions

In conclusion, we covered several studies on carbazoles (Table 2), both of synthetic and natural origin, having a role in the pathogenesis and development of diabetes. Some of these compounds, such as carvedilol (**1**) and mahanine (**11**), have been extensively investigated by different research groups, demonstrating a critical role in diabetes control due to their ability to modulate various pathways involved in the onset or evolution of the pathology.

Chiglitazar (**22**), one of the most promising carbazole derivatives, passed the preclinical experimentation and very recently entered clinical trials.

Important considerations also emerge from the structure–activity relationships of the described carbazole compounds. In particular, it seems that *N*-substitution with triazinic

(see compound **4**) or triazolic portions (see compounds **7** and **8**) favors α-glucosidase inhibitory activity; the presence of cyclic sulfonamidic (see compound **5**) or cyclic urea groups (see compound **6**) modulates the cryptochrome activity, whereas the presence of ethylphenoxy groups improves insulin sensitivity (see compounds **21** and **22**). Moreover, hydrogenation of a ring of the carbazole core favors the hypoglycemic effect via the AMPK pathway (see compounds **9** and **10**), and the tetracyclic system of the mahanine derivatives seems to be important in glucose uptake and translocation of glucose transporter GLUT4 in skeletal muscle and adipocyte cells (see compounds **11**, **16**–**20**). Finally compounds with a high conjugation effect show predominant antioxidant activity (see compounds **12**–**15**). Overall, the data herein reported could provide an important reference guide for the development of alternative and effective antidiabetic agents.

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