International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 3 May-June 2024, pp: 1541-1552 www.ijprajournal.com ISSN: 2456-4494

Oxadiazole and its derivatives: A review on recent progress in an anti-diabetic activity.

Ms. Ujwala B. Belge[1], Dr. Vijaya S. Vichare[2]*
Department Of Pharmaceutical Chemistry Of Dr.V.V.P.F'S,College Of Pharmacy , Ahmednagar,414111, Maharshtra,India
Department of Pharmaceutical Chemistry of PES Modern College *of* Pharmacy *(For Ladies),* Moshi, *Pune, 412105 Maharashtra, India*

Date of Submission: 28-05-2024 Date of Acceptance: 05-06-2024

ABSTRACT
The United States ranks third in the world in terms of the number of deaths related to diabetes. In the treatment of diabetes mellitus, antidiabetic drugs control blood glucose levels. Except for insulin, exenatide, and pramlintide, most drugs are taken orally. During this review, we will discuss six main types of oxadiazole-containing anti-diabetic drugs: Peroxisome proliferator-activated receptor (PPAR) agonist, PAR alpha and gammareceptoragonistG protein-coupled receptors 119 (GPR119) agonist and G protein-coupled receptors 40 (GPR40) agonist, inhibiting DPP-4**,** inhibiting α-amylase, inhibiting α-glucosidase, inhibiting advanced glycation end-product (AGEPs) formation. Among the recently reported anti-diabetic agents is oxadiazole, which has several pharmacological targets. Reviews of recent approaches and developments in oxadiazole derivatives for anti-diabetes treatment are presented in this review, including characteristics, structure-activity relationships, functional mechanisms, expression regulation, and pharmacological applications.

Keywords: Anti-diabetic drugs ,diabetes mellitus, oxadiazole, and heterocyclic ring

I. INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder that affects millions of people around the world. Diabetes was estimated to be prevalent in 366 million people in 2011, and it is projected to reach approximately 552 million cases by 2030.(1)As diabetes prevalence has increased, global health burdens have increased accordingly.(2) There are many chronic conditions and disorders associated with DM, such as obesity,(3) hypertension,(4) heart disease,(5) and atherosclerosis,(6) which contribute to a significant reduction in life expectancy. DM has a multifaceted etiology, making its management another challenge.(7-8)

Researchers in the fields of medicinal and pharmaceutical chemistry are interested in heterocyclic compounds containing nitrogen atoms, such as oxadiazole moiety.(9)Known as a heterocycle, an oxadiazole is a five-membered ring containing one oxygen, two carbon atoms, two nitrogen atoms, and two double bonds.(10) Due to its versatile biological effects, the oxadiazole heterocyclic ring is one of the most important heterocyclics.(11) Oxadiazole exists in four different isomers such as 1,2,4-oxadiazole, 1,2,3-oxadiazole, 1,2,5-oxadiazole, and 1,3,4-oxadiazole. Among these, 1,3,4-oxadiazoles and 1,2,4-oxadiazoles are better known and studied by researchers due to their wide range of chemical and biological properties.

There are currently more than ten classes of molecules used in DM treatment, and several new ones are in development.(12-13)Approximately 40 years ago (between the mid-1950s and the mid-1990s), the only treatments available were insulin, sulfonylureas, and biguanides.(13-14) 1995 brought the discovery and development of a new class of DM therapeutics. During this review, we will outline six types of pharmacological actions of oxadiazole derivative as anti-diabetic drugs: Peroxisome proliferator-activated receptor (PPAR) agonist, PPAR alpha and gammareceptoragonistG protein-coupled receptors 119 (GPR119) agonist and G protein-coupled receptors 40 (GPR40) agonist, inhibiting DPP-4**,** inhibiting α-amylase, inhibiting α-glucosidase, inhibiting advanced glycation end-product (AGEPs) formation.(15) We will also discuss some of the recent reports on Oxadiazole as a anti-diabetic agent with its multi-target pharmacological actions. Recent advances in Oxadiazole derivative as an anti-diabetes treatment are discussed about characteristics, structure-

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 3 May-June 2024, pp: 1541-1552 www.ijprajournal.com ISSN: 2456-4494

activity relationships, functional mechanisms, expression regulation, and applications in medicine.In this study, we have examined the anti-diabetic activity of different oxadiazole derivatives that
containamide, mercaptobenzimidazole, thiazolidine dione, pyridinyl, methoxyphenyl, benzothiazole, tr iphenyl, tetrahydroquinolin, benzofuran, fattacid, in dole, benzothiazole, thiazolidinone, trans-
acryliacid, pyrimidine, azaspirocycles groups in this regard

A REVIEW ON RECENT PROGRESS IN AN ANTI-DIABETIC ACTIVITY.

Xuet al (2005) (16)sythesized anti-substituted b-methylphenylalanine derived amides which proven to be potent DPP-IV (Dipeptidyl peptidase- IV) inhibitors which showhigh-quality selectivity over each DPP-VIII and DPP-IX. These are a number of the most potent compounds pronouncedto this pointmissing electrophilic traps. Authors further processed to improvise potency and selectivity over QPP (quiescent cell prolinedipeptidase) also tried substitution on phenyl group at 3-position by incorporating a heterocyclic ring with low potency. In authors suggested that there is a fine balance among lipophilicity, selectivity, and oral bioavailability. The incorporation of a polar group at the b-position led to further optimization of these properties. The most potent compound amongstthose is 5-oxo-1,2,4-oxadiazole, DPP-IV has shown in Figure1

Figure1: 3-(4'-(3-amino-4-(3-fluoropyrrolidin-1-yl)-4-oxobutan-2-yl)-[1,1'-biphenyl]-3-yl)-1,2,4-oxadiazol-5(4H)-one

Xu et al (2006)researchers have developed a novel series of oxadiazole-based amides that exhibit excellent selectivity over a variety of DPP-4 homologs. Compound 43 exhibited excellent selectivity over a wide range of DPP-4 homologs. In authors suggested that The stereochemistry at the b-position plays an important role in the binding potency of this series because the anti-diastereoisomer of the corresponding syn-diastereoisomer is typically tenfold less potent. In the absence of an electrophilic trap, these compounds are among the most potent reported. Because of differences in binding modes, this series displays a change in stereochemistry (syn over anti) compared to biaryl derivatives.(17)

Figure 2: 2-amino-4-cyclopropyl-3-(3-(2-fluoro-4-(methylsulfonyl)phenyl)-1,2,4-oxadiazol-5-yl)-1-(pyrrolidin-1-yl)butan-1-one

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 3 May-June 2024, pp: 1541-1552 www.ijprajournal.com ISSN: 2456-4494

Shingalapuret al. (2010)author synthesized and tested 1,3,4-oxadiazoles 6 (a - j) containing a 2-mercaptobenzimidazole moiety for in vivo antidiabetic activity using the oral glucose tolerance test (OGTT). The active molecules (6c), (6d), (6h) and (6i) had excellent antidiabetic properties, and pharmacophore derived from them suggested a common feature of all active molecules: the presence of OH groups. These compounds (6c), (6d), (6h) and (6i) exhibited outstanding activity against Glibenclamide and were deemed significant in comparison to diabetic control groups.(18)

Figure 3: 4-(5-{[(1H-benzimidazol-2-yl)sulfanyl]methyl}-1,3,4-oxadiazol-2-yl)phenol

Iqbal et al (2012) in this research author claimed thatusing phenyl rings linked by a carbon atom, the researcher synthesized heteroatom-linked thiazolidinediones, similar to the pharmaceutical pioglitazone. Oxadiazole was tested in vivo for its effects on hypolipidemia and diabetes, and it was found to have insulin-sensitizing properties. Besides the standard compound, compounds 10h, 11c, and 11d were tested in hypoglycemic and hypolipidemic trials. Blood glucose levels and triglycerides are also decreased with 10h, 11c, and 11d, which are important for hyperglycemia as well as cardiovascular problems. According to these results, the combination of thioethyloxy linkage and oxadiazole may lead to the development of new potent drugs.(19)

.

Figure 4: E-5-(4-(2-((5-phenyl-1,3,4-oxadiazol-2-yl)thio)ethoxy)benzylidene)thiazolidine-2,4-dione

Shyma et al (2015) according to the author Three new series of 1,3,4-oxadiazole derivatives such as 2-[3-(6-methylpyridinyl)]-5-aryl-[1,3,4]-oxadiazole (3a-e), 2-[3-(6-methylpyridinyl)]-4-substitutedaminomethyl-[1,3,4]-oxadiazole-5-thione (5a-e) and 2-[3-(6-methyl pyridinyl)]-5-substituted benzylthio-[1,3,4]-oxadiazole (6a-e) were synthesized. The synthesized compounds were evaluated for their anti-diabetic and antioxidant properties. Compounds 3d and 5a are effective inhibitors of α-amylase and α-glucosidase compared to the standard.(20)

In conclusion, 1,3,4-oxadiazole derivatives with pyridine moiety may have therapeutic properties and should be investigated further.

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 3 May-June 2024, pp: 1541-1552 www.ijprajournal.com ISSN: 2456-4494

Zahanich et al (2015) in this research author mentioned thatOxadiazole derivatives were synthesized and studied for their GPR40 (G-protein receptor 40) agonistic activity. EC_{50} values of 0.0058μM and 0.30 μM were determined for oxiadiazole as the most potent GPR40 agonist. The compounds in each of these chemotypes could be identified, and then those with excellent properties in terms of solubility in water, microsomal stability, Caco-2 permeability, plasma protein binding, and inhibition of cytochrome P450 could be selected. As well as providing promising new starting points for further preclinical development, both lead compounds have similarities in potency with the clinical candidate TAK-875 (FLIPR EC50 0.014 m).(21)

Figure 5: 3-(4-(1-(3-phenyl-1,2,4-oxadiazol-5-yl)ethoxy)phenyl)propanoic acid

Taha et al (2015) in this research to identify potent anti-diabetic agents, compounds synthesized from 2-(2-methoxyphenyl)-5-phenyl-1,3,4-oxadiazole were evaluated for their antiglycation activity. The IC_{50} value for 1–6 and 8 was 295.09 * 1.04 m higher than rutin (IC_{50} values of 160.2 to 290.17 m). The compound 6 series is the second most active. These compounds are dihydroxylated analogs. The different number of hydroxyl groups on the phenyl ring causes minor differences in activity. If a compound only contains one hydroxyl group, its activity declines.The experimental data reveal that all compounds containing hydroxyl groups exhibit antiglycation properties.(22)

Figure 6: 4-[5-(2-methoxyphenyl)-1,3,4-oxadiazol-2-yl]benzene-1,3-diol

Rathore et al (2017) according to the author an oxadiazole moiety 6(a-l) was synthesized in analogous derivatives. The hypoglycemic activity of benzothiazole derivatives with oxadiazole was evaluated in rats induced with alloxan-induced diabetes. At 350 mg/kg body weight, compound 6f was able to lower glucose levels the most, while compound 6d was the least effective. It may be compound 6i that lowers glucose the most due to its heterocyclic amine (morpholine) content. Compound 6g's anti-diabetic effect was strongest at 350 mg/kg compared to all other synthesized derivatives. Summary Compound may have a maximum effect on lowering blood sugars due to its heterocyclic amine composition (morpholine).(23)

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 3 May-June 2024, pp: 1541-1552 www.ijprajournal.com ISSN: 2456-4494

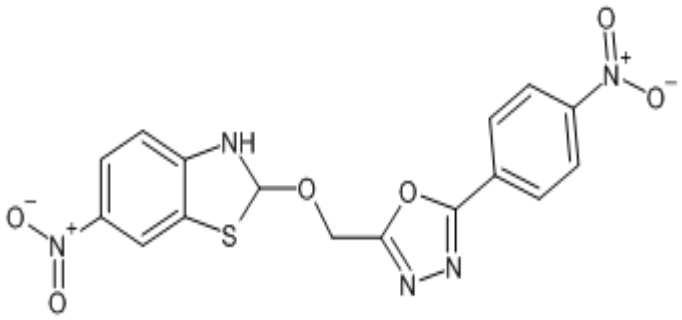

Figure 7: 6-nitro-2-{[5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl]methoxy}-2,3-dihydro-1,3-benzothiazole

Khosravi et al (2017)author stated thatin vitro screening was conducted for the activity of 3,4,5-triphenyl-4,5-dihydro-1,2,4-oxadiazole derivatives against α--glucosidase. Oxadiazole derivatives 6a-k were investigated for their ability to inhibit Saccharomyces cerevisiae α-glucosidase. The docking studies revealed that II-anion and II-alkyl interactions, such as lipophilic interactions, were distinct between 6c and 6d with the residue in the active site. The two compounds can bind freely to the active site of the enzyme and have important binding interactions as compared with acarbose, the reference standard. Molecular docking studies were also supportive of the in vitro results of compounds 6c and 6d. For the most active compounds, the IC_{50} values are 215± 3, 256 ±3, and 295 ± 4 μM. Kinetic analysis of compound 6c revealed that it is a competitive inhibitor of Saccharomyces cerevisiae α-glucosidase with a Ki of 122 μM. According to our study, our synthesized compounds have potential for development as new α-glucosidase inhibitors that can be used to treat postprandial hyperglycemia.(24)

Figure8: 3-(4-chlorophenyl)-4-(4-fluorophenyl)-5-phenyl-4,5-dihydro-1,2,4-oxadiazole

Wang et al (2018) 5-(2-((1-(phenylsulfonyl)-1,2,3,4-tetrahydroquinolin7-yl)oxy)pyridin-4-yl)-1,2,4-oxadiazoles as novel agonists of GPR119. Increasing the substituent size (larger than 3 carbons: 36 and 37) and substituents at the 3-position of the 1,2,4-oxadiazole moiety CF_3 group adversely affects the efficacy on the cyano receptor. As a result of its reduced activity on the cyano receptor, 1,2,4-oxadiazole is well tolerated compared to 1,3,4-oxadiazole. Fluoro- or chloro-substituents are added to the oxygen on the tetrahydroquinoline ring to maintain potency yet reduce in vivo clearance in rats. 5-(2-((1-(phenylsulfonyl)-1,2,3, 4-tetrahydroquinolin-7-yl)oxy)pyridin-4-yl)-1,2,4-oxadiazoles as a novel class of GPR119 agonists, and presented the SAR in detail.(25)

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 3 May-June 2024, pp: 1541-1552 www.ijprajournal.com ISSN: 2456-4494

Figure 9: 5-(2-chloro-6-((1-((4-chlorophenyl)sulfonyl)-1,2,3,4-tetrahydroquinolin-7-yl)oxy)pyridin-4-yl)-3-cyclopropyl-1,2,4-oxadiazole

Ibrahim et al (2018)author mentioned thatThe anti-diabetic activities of 27 Oxadiazole derivatives were studied in-silico. This study may lead to the design of new anti-diabetic compounds that have better inhibitory activity against α-glycosidase, an enzyme responsible for hydrolyzing carbohydrates to produce excess glucose. The results of this study show that the binding affinity generated is in accordance with the work done by other researchers on this series of compounds.(26)

Figure 10: 2-[5-(6-nitro-1-benzofuran-2-yl)-1,3,4-oxadiazol-2-yl]phenol

Kapooret al (2018)This research focused on designing, synthesizing, performing docking, and testing whether the selected synthesized derivatives of fatty acid and oxadiazole moiety could reduce glucose level in normal rats and anti-diabetic effect on diabetic rats. A total of twenty-two compounds showed good activity, with compound M_{15} more potent than the standard drug due to the presence of an electron-withdrawing group fluoro, and therefore may be explored further in search of potential new agents for type II diabetes. Thus, by substituting amines with modified fatty acids that have a polar chain and an oxadiazole moiety at the end, new mannich base derivatives were synthesized that have this type of model. (27)

Nazir et al (2018) Oxadiazole scaffolds containing 8a-l N-substituted acetamides were synthesized in good yields and inhibited yeast α-glucosidase enzyme with an IC_{50} as low as that of the reference compound. Compound 8 l bearing the methyl-substituted pyridine ring showed excellent inhibitory potential and was found to be most active among all synthetic derivatives (IC_{50} = 9.37 * 0.03 m) not related to its involvement with the enzyme's active site. Compound 8e with ethoxy group at para position had greater activity as compared to the standard, however, a decrease in the activity was observed when the position of ethoxy was shifted from para to ortho in 8d may be due to the increased steric factors.(28)

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 3 May-June 2024, pp: 1541-1552 www.ijprajournal.com ISSN: 2456-4494

Figure 11:2-({5-[(1H-indol-3-yl)methyl]-1,3,4-oxadiazol-2-yl}sulfanyl)-N-phenylacetamide

Bhutani et al (2018) A small library of new benzothiazole clubbed oxadiazole-Mannich bases (M-1 to M-22) were synthesized compounds, nine compounds were selected based on docking score and evaluated for their in vivo anti-diabetic activity using Oral Glucose Tolerance Test (OGTT) in normal rats followed by Streptozotocin (STZ) – induced diabetes. The results showed that compound M-14 (161.39 * 4.38) showed the greatest reduction of blood glucose in the STZ model comparable to that of the standard drug glibenclamide (140.29 * 1.24). Other compounds exhibited moderate to good antihyperglycaemicactivity.The compounds under study showed significant anti-diabetic activity in oral glucose tolerance tests in normal rats and in streptozotocin-induced rats, with the best results observed with compounds containing two electron-withdrawing groups and lacking phenyl rings.(29)

Figure 12: 3-[5-(2,3-dihydro-1,3-benzothiazol-2-yl)-1,3,4-oxadiazol-2-yl]-2-methyl-1,3-thiazolidin-4-one

Bhutaniet al (2019) To search for potential anti-diabetic agents, a series of new benzothiazole-1,3,4-oxadiazole-4-thiazolidinone hybrid analogs (Tz1-Tz28) were synthesized. Compounds Tz21 (with diethylamine group at para position and hydroxyl group at ortho position of phenyl ring at 2^{nd} position of 4-thiazolidinone), Tz17 (having methoxy substituent at para position of phenyl ring at 2^{nd} position of 4-thiazolidinone), Tz10 (with dimethyl amine group at para position of phenyl ring at 2^{nd} position of 4-thiazolidinone) caused significant lowering in blood glucose level. Compounds containing electron-withdrawing groups such as 4-chloro, 4-nitro and 4-trifloromethyl also displayed good anti-diabetic effect but a decrease in blood glucose level was less as compared to compounds having a substitution of electron-donating groups on the phenyl ring of 4-thiazolidinone.(30)

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 3 May-June 2024, pp: 1541-1552 www.ijprajournal.com ISSN: 2456-4494

Figure 13: 3-(5-(benzo[d]thiazol-2-yl)-1,3,4-oxadiazol-2-yl)-5-(4-(diethylamino)-2-hydroxyphenyl)-2-methylthiazolidin-4-one

Kaur et al (2020) These compounds possess aryl/methylene linkers linking the pharmacophore head to the lipophilic tail to create PPAR (peroxisome proliferator-activated receptor) alpha/gamma agonists. It has been concluded that the electron-withdrawing group shown to be over active at the 4th position on 1,2,4-oxadiazole based and trans-acrylic acid derivatives can serve to be an alternative treatment in better management of type 2 diabetes mellitus. These compounds possess an aryl/methylene linker between the pharmacophore head and the lipophilic tail so they are capable of acting as dual PPAR alpha and PPAR gamma agonists.(31)

Figure 14: (2Z)-3-{4-[2-oxo-2-(3-phenyl-1,2,4-oxadiazol-5-yl)ethoxy]phenyl}prop-2-enoic acid

Lalparaet al (2020)This study synthesized pyrimidine derivatives containing 1,3,4-oxadiazole condensations and tested their antidiabetic activity in vitro. A-amylase inhibition assays of synthesized compounds and acarbose are performed. The synthesized compounds show moderate to good a-amylase activity. Compounds were screened for their anti-diabetic activity in vitro; many of them had very good potency compared to acarbose, a standard reference drug.(32)

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 3 May-June 2024, pp: 1541-1552 www.ijprajournal.com ISSN: 2456-4494

Figure 15: N-(2-chlorophenyl)-2-mercapto-6-methyl-4-(4-((5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methoxy)phenyl)-1,2-dihydropyrimidine-5-carboxamide

Radia et al (2021) In vitroantidiabetic screening of 1,3,4-oxadiazole derivatives containing azaspirocycles synthesized by the author. In vitroantidiabetic screening of synthesized compounds by α-amylase inhibition. The compound 6a has a high activity and an inhibition percent very close to acarbose. The synthesis of bioactive and potent heterocycles using the combination of two different pharmacophores, 1,3,4-oxadiazole and azaspirocycles, was tested for antidiabetic activity to obtain significant results. (33)

Figure 16: 2-(1-{[5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl]methyl}piperidin-4-yl)-1,3-oxathiolan-5-one

II. CONCLUSION

Currently, there are several diabetes drugs on the market, and scientists are conducting extensive research to determine whether these drugs are effective or not novel anti-diabetes drugs. However, we have not yet been able to cure diabetes.The challenge for medicinal chemists is to diagnose or treat diseases efficiently. Thus, oxadiazole is safer, more effective, and safer is always in demand in medicinal chemistry. The current review has highlighted seven major types of oxadiazole as anti-diabetes drugs, namely Peroxisome proliferator-activated receptor (PPAR) agonist, PPAR alpha and gamma receptoragonistG protein-coupled receptors 119 (GPR119) agonist and G protein-coupled receptors 40 (GPR40) agonist, inhibiting DPP-4**,** inhibiting α-amylase, inhibiting α-glucosidase, inhibiting advanced glycation end-product (AGEPs) formation. A comparison of different oxadiazole derivatives as anti-diabetic drugs' multi-target pharmacological actions was also reported. All of these agents reveal the effects on all of the major targets of diabetes, such as-Peroxisome proliferator-activated receptor (PPAR) agonist, PPAR alpha and gammareceptoragonistG protein-coupled receptors 119 (GPR119) agonist and G protein-coupled receptors 40 (GPR40) agonist, inhibiting DPP-4**,** inhibiting α-amylase, inhibiting α-glucosidase, inhibiting advanced glycation end-product (AGEPs) formation etc. and showed effective and promising activities towards

diabetes disease. With their promising activities and mechanism of action against diabetes, most of the discussed oxadiazole derivatives as can help to synthesize novel oxadiazole derivatives and also help to design oxadiazole derivatives as novel anti-diabetes drugs.

CONFLICT OF INTEREST

The authors state that the publishing of this paper does not include any conflicts of interest.

ACKNOWLEDGEMENT

The authors are thankful to the management and Principal of PES Modern College of Pharmacy, Moshi , Pune ,Maharashtra,India,for providing infrastructure and other research facilities.

REFERENCES

[1]. Patel S, Srivastava S, Singh MR, Singh D. Mechanistic insight into diabetic wounds: Pathogenesis, molecular targets and treatment strategies to pace wound healing. Biomedicine & Pharmacotherapy. 2019 Apr 1;112:

[2]. Federation ID. IDF diabetes atlas 8th edition.International diabetes federation. 2017:905-11.

[3]. Bugger H, Abel ED. Molecular mechanisms of diabetic cardiomyopathy. Diabetologia. 2014 Apr;57:660-71

[4]. Kostev K, Rathmann W. Diabetic retinopathy at diagnosis of type 2 diabetes in the UK: a database analysis. Diabetologia. 2013 Jan;56:109-11.

[5]. Gray SP, Cooper ME. Alleviating the burden of diabetic nephropathy.Nature Reviews Nephrology. 2011 Feb;7(2):71-3.

[6]. Martin CL, Albers JW, Pop-Busui R, DCCT/EDiC research Group. Neuropathy and related findings in the diabetes control and complications trial/epidemiology of diabetes interventions and complications study. Diabetes care. 2014 Jan 1;37(1):31-8.

[7]. a)Leung MY, Pollack LM, Colditz GA, Chang SH. Life years lost and lifetime health care expenditures associated with diabetes in the US, National Health Interview Survey, 1997–2000. Diabetes care. 2015 Mar 1;38(3):460-8.
(b) Gifford JA, O'Connor HT, Honey AL, Caterson ID. 12 Nutrients, Health and Chronic.Nutrition and Performance in Masters Athletes. 2014 Oct 15:213.

[8]. Guariguata L, Whiting DR, Hambleton I, Beagley J, Linnenkamp U, Shaw JE. Global estimates of diabetes prevalence for 2013 and projections for 2035.Diabetes research and clinical practice. 2014 Feb 1;103(2):137-49.

[9]. Siwach A, Verma PK. Therapeutic potential of oxadiazole or furadiazole containing compounds. BMC chemistry. 2020 Dec;14:1-40.

[10]. Ahsan MJ. Synthesis and cytotoxicity evaluation of [(2, 4-dichlorophenoxy) methyl]-5-aryl-1, 3, 4-oxadiazole/4$ H $-1, 2, 4-triazole analogues.Turkish Journal of Chemistry. 2018;42(5):1334-43.

[11]. Wang PY, Shao WB, Xue HT, Fang HS, Zhou J, Wu ZB, Song BA, Yang S. Synthesis of novel 1, 3, 4-oxadiazole derivatives containing diamides as promising antibacterial and antiviral agents. Research on Chemical Intermediates. 2017 Nov;43:6115-30.

[12]. Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, Kravitz BG, Lachin JM, O'Neill MC, Zinman B, Viberti G. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. New England Journal of Medicine. 2006 Dec 7;355(23):2427-43.

[13]. DCCT Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl j Med. 1993;329:977-86.

[14]. LeRoith D, Taylor SI, Olefsky JM, editors. Diabetes mellitus: a fundamental and clinical text. Lippincott Williams & Wilkins; 2004.

[15]. Dowarah J, Singh VP. Anti-diabetic drugs recent approaches and advancements. Bioorganic & medicinal chemistry. 2020 Mar 1;28(5):115263.

[16]. Xu J, Wei L, Mathvink R, He J, Park YJ, He H, Leiting B, Lyons KA, Marsilio F, Patel RA, Wu JK. Discovery of potent and selective phenylalanine based dipeptidyl peptidase IV inhibitors. Bioorganic & Medicinal Chemistry Letters. 2005 May 16;15(10):2533-6.

[17]. Xu J, Wei L, Mathvink RJ, Edmondson SD, Eiermann GJ, He H, Leone JF, Leiting B, Lyons KA, Marsilio F, Patel RA. Discovery of potent, selective, and

orally bioavailable oxadiazole-based dipeptidyl peptidase IV inhibitors.Bioorganic & Medicinal Chemistry Letters. 2006 Oct 15;16(20):5373-7.

[18]. Shingalapur RV, Hosamani KM, Keri RS, Hugar MH. Derivatives of benzimidazolepharmacophore: Synthesis, anticonvulsant, antidiabetic and DNA cleavage studies. European journal of medicinal chemistry. 2010 May 1;45(5):1753-9.

[19]. Iqbal AM, Khan AY, Kalashetti MB, Belavagi NS, Gong YD, Khazi IA. Synthesis, hypoglycemic and hypolipidemic activities of novel thiazolidinedione derivatives containing thiazole/triazole/oxadiazole ring.European journal of medicinal chemistry. 2012 Jul 1;53:308-15.

[20]. Shyma PC, Balakrishna K, Peethambar KS, Vijesh MA. Synthesis, characterization, antidiabetic and antioxidant activity of 1, 3, 4-oxadiazole derivatives bearing 6-methyl pyridine moiety. Der Pharma Chem. 2015;7(12):137-45.

[21]. Zahanich I, Kondratov I, Naumchyk V, Kheylik Y, Platonov M, Zozulya S, Krasavin M. Phenoxymethyl 1, 3-oxazoles and 1, 2, 4-oxadiazoles as potent and selective agonists of free fatty acid receptor 1 (GPR40). Bioorganic & Medicinal Chemistry Letters. 2015 Aug 15;25(16):3105-11.

[22]. Taha M, Ismail NH, Jamil W, Imran S, Rahim F, Kashif SM, Zulkefeli M. Synthesis of 2-(2-methoxyphenyl)-5-phenyl-1, 3, 4-oxadiazole derivatives and evaluation of their antiglycation potential. Medicinal Chemistry Research. 2016 Feb;25:225-34.

[23]. Kumar S, Rathore DS, Garg G, Khatri K, Saxena R, Sahu SK. Synthesis and evaluation of some 2-((benzothiazol-2-ylthio) methyl)-5-phenyl-1, 3, 4-oxadiazole derivatives as antidiabetic agents. Asian Pacific Journal of Health Sciences. 2016;3(4):65-74.

[24]. Khosravi A, Vaezi G, Hojati V, Abdi K. Study on the interaction of triaryl-dihydro-1, 2, 4-oxadiazoles with α-glucosidase. DARU Journal of Pharmaceutical Sciences. 2020 Jun;28:109-17.

[25]. Wang Y, Yu M, Zhu J, Zhang JK, Kayser F, Medina JC, Siegler K, Conn M, Shan B, Grillo MP, Liu JJ. Discovery and optimization of 5-(2-((1-(phenylsulfonyl)-1, 2, 3, 4-tetrahydroquinolin-7-yl) oxy) pyridin-4-yl)-1, 2, 4-oxadiazoles as novel gpr119 agonists.Bioorganic & Medicinal Chemistry Letters. 2014 Feb 15;24(4):1133-7.

[26]. 26. Ibrahim MT, Uzairu A, Shallangwa GA, Ibrahim A. In-silico studies of some oxadiazoles derivatives as anti-diabetic compounds. Journal of King Saud University-Science. 2020 Jan 1;32(1):423-32.

[27]. Kapoor G, Pathak DP, Bhutani R, Husain A, Jain S, Kant R, Iqbal MA. Newly Synthesized Oxadiazole Based Mannich Base Derivatives of Fatty Acid: In silico Study and In vivo Anti-Hyperglycaemic Estimation. Oriental Journal of Chemistry. 2018 Sep 1;34(5).

[28]. Nazir M, Abbasi MA, Siddiqui SZ, Khan KM, Salar U, Shahid M, Ashraf M, Lodhi MA, Khan FA. New indole based hybrid oxadiazole scaffolds with N-substituted acetamides: As potent anti-diabetic agents. Bioorganic chemistry. 2018 Dec 1;81:253-63.

[29]. Bhutani R, Pathak DP, Kapoor G, Husain A, Kant R, Iqbal MA. Synthesis, molecular modelling studies and ADME prediction of benzothiazole clubbed oxadiazole-Mannich bases, and evaluation of their anti-diabetic activity through in vivo model. Bioorganic chemistry. 2018 Apr 1;77:6-15.

[30]. Bhutani R, Pathak DP, Kapoor G, Husain A, Iqbal MA. Novel hybrids of benzothiazole-1, 3, 4-oxadiazole-4-thiazolidinone: Synthesis, in silico ADME study, molecular docking and in vivo anti-diabetic assessment. Bioorganic chemistry. 2019 Mar 1;83:6-19.

[31]. Kaur P, Bhat ZR, Bhat S, Kumar R, Kumar R, Tikoo K, Gupta J, Khurana N, Kaur J, Khatik GL. Synthesis and evaluation of new 1, 2, 4-oxadiazole based trans-acrylic acid derivatives as potential PPAR-alpha/gamma dual agonist. Bioorganic Chemistry. 2020 Jul 1;100:103867.

[32]. Lalpara JN, Hadiyal SD, Radia AJ, Dhalani JM, Dubal GG. Design and rapid

microwave irradiated one-pot synthesis of tetrahydropyrimidine derivatives and their screening in vitro antidiabetic activity. Polycyclic Aromatic Compounds. 2022 Jul 3;42(6):3063-78.

[33]. Radia AJ, Lalpara JN, Modasiya IJ, Dubal GG. Design and synthesis of novel 1, 3, 4-oxadiazole based azaspirocycles catalyzed by NaI under mild condition and evaluated their antidiabetic and antibacterial activities. Journal of Heterocyclic Chemistry. 2021 Feb;58(2):612-21.