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A REVIEW ON THE ROLE OF 1,3,4-OXADIAZOLE HYBRID SCAFFOLDS IN ANTIDIABETIC DRUG DEVELOPMENT

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ABSTRACT

Heterocyclic compounds, especially those with heteroatoms like oxygen and nitrogen, make up a substantial share of drugs on the market today. Among these, the aromatic heterocycle 1,3,4-oxadiazole, featuring an N=C=O linkage, is particularly notable for its impressive biological activities. Oxadiazole is a five-membered heterocyclic organic compound containing two nitrogen atoms and one oxygen atom in its ring. Currently, diabetes mellitus is one of the most prevalent chronic diseases in almost every country, and its prevalence and importance are rising as a result of changing lifestyles characterised by a decline in physical activity and an increase in obesity. Between type 1 and type 2 diabetes, type 2 is regarded as one of the disorders with an increasing prevalence worldwide. As a result, the most crucial public health goals are appropriate treatment options for type 2 diabetes. The ability to lower fasting blood glucose levels, increase insulin sensitivity, and improve glucose tolerance has all been demonstrated by oxadiazole hybrids. The antidiabetic effects of oxadiazole are mediated through the modulation of molecular targets like peroxisome proliferator-activated receptor gamma (PPARγ), α-glucosidase, α-amylase, and GSK-3β, all of which play a key role in regulating glucose metabolism and insulin secretion. This review discusses various 1,3,4-oxadiazole derivatives as potential agents for targeting anti-diabetic activity.

KEYWORDS: Oxadiazole, antidiabetic, Targets, Diabetes.

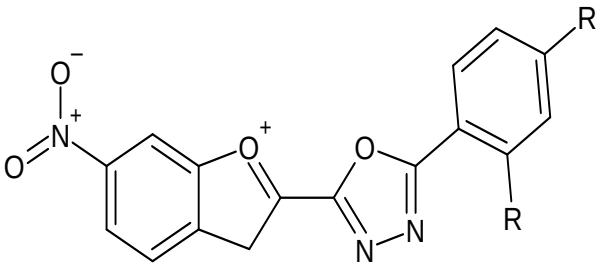
INTRODUCTION

Diabetes mellitus (DM) refers to a group of chronic metabolic disorders characterized by elevated glucose levels. It is one of the most significant global public health challenges of the 21st century, linked to various life-threatening conditions such as cardiovascular disease, cancer, stroke, kidney failure, and Alzheimer's disease. There are three primary types of diabetes—insulin-dependent (Type I), insulin-independent (Type II), and gestational DM—Type II diabetes is far more prevalent than the others. It was found that nearly 90% of all diabetes cases are diagnosed as Type II.[1]

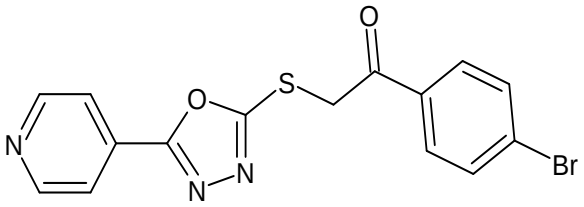
Oxadiazoles, also known as furadiazoles, are a class of heterocyclic compounds with significant relevance in medicinal chemistry. Specifically, 1,3,4-oxadiazole and its derivatives exhibit a broad spectrum of pharmacological effects.[2] The 1,3,4-oxadiazole derivative works on diabetes by blocking the enzymes that hydrolyze carbohydrates, such as α-amylase and α-glucosidase.[3] It is also thought that reducing oxidative stress is a workable way to control postprandial glucose levels in diabetic patients. By decreasing hydrolytic activity and the enzyme-substrate complex, 1,3,4-oxadiazole derivatives, either through orthosteric inhibition or allosteric inhibitors—which have been identified as α-glucosidase inhibitors in numerous molecular hybrid designs—cause a delayed release of the hydrolyzed product.[4] This may theoretically lead to a reduction in the concentration of glucose in the bloodstream, hence reducing postprandial hyperglycemia and the problems that accompany it. By increasing antioxidant enzyme activity, 1,3,4-oxidazole derivative and Nrf2 (nuclear factor E2-related factor or nuclear factor erythroid 2) limit free radical levels, encourage the pancreas to make insulin, and lower blood glucose levels.[5]

LITERATURE REVIEW

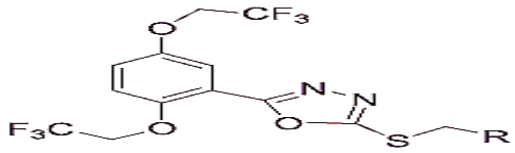
Muhammad Tukur Ibrahim *et al* has performed in-silico studies of 27 oxadiazole derivatives to investigate anti-diabetic potential. They concluded that some of the compounds exhibit excellent antidiabetic potential against alpha-glucosidase. Results of QSAR and molecular modelling reaveals that oxadiazole derivatives can be used to develop potent antidiabetic agents against alpha-glucosidase.[6]



Haroon khan *et al* has conducted Pharmacophore studies of 1, 3, 4-oxadiazole nucleus as α-glucosidase inhibitors. They investigated the preclinical efficacy of 1,3,4 oxadiazole derivatives as α-glucosidase inhibitors and anti inflammatory agents. The pharamacophore based virtual screening revealed promising results, suggesting that the 1,3,4 oxadiazole scaffold could be a valuable lead for developing novel α-glucosidase inhibitors.[7]



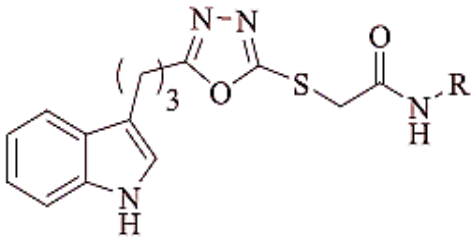
Asma Bukhari *et. al.,* evaluated novel oxadiazole derivatives as potent inhibitors of α-amylase and α-glucosidase enzymes. The newly synthesized derivatives were characterized using different spectroscopic techniques including FTIR, 1 H NMR, 13 C NMR, and elemental analysis data. Molecular docking studies were also carriedout. Two analogues exhibited strong inhibitory potential against the α-glucosidase enzyme in comparison with standard drug miglitol. One compound demonstrated outstanding inhibitory potential against the α-amylase enzyme in comparison with standard drug acarbose.[8]



Ramesh S. Gani *et. al.,* conducted a study on 5-(2,5-bis(2,2,2-trifluoroethoxy)phenyl)-1,3,4-oxadiazole-2-thiol derivatives. The structure of all the synthesized hybrids were confirmed by ^{1}HNMR and LC-MS. *In vitro* α-amylase and α-glycosidase inhibitory activity were performed. *In vivo* study was carried using a genetic model, Drosophila melanogaster, for assessing the antihyperglycemic effects.[9]

Muhammad Taha *et. al.,* synthesized tris-indole-oxadiazole hybrid analogs and assessed for their alpha-glucosidase inhibitory activity and were discovered to be significantly more effective than the common medication acarbose. The IC50 value is 895.09 ± 2.04 mM. To rationalize the structure-activity relationship and determine the structural components involved in the inhibitory action, an in silico analysis was conducted.[10]

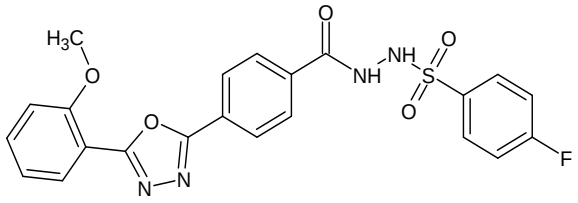
Majid Nazir *et. al.,* designed hybrid molecules of indole - oxadiazole scaffolds with N-substituted acetamides. The compound were screened to explore their enzyme inhibitory potential against α-glucosidase enzyme. *In silico* studies were also carried out to ascertain various kinds of interactions with active pocket of α-glucosidase enzyme. Cytotoxicity was also assessed to find their utility as possible drug candidates in drug discovery and development.[11]



Bharadwaj *et. al.,* efficiently synthesized and carriedout *in Silico* Studies of the benzimidazole hybrid scaffold with the quinolinyloxadiazole Skeleton. The study evaluates antidiabetic, anticoagulant, and antiplatelet activity of novel benzimidazole-containing quinolinyl oxadiazoles. These derivatives are synthesized and characterized using spectroscopy (FT-IR, ^{1}H NMR, and mass spectroscopy) and single crystal X-ray diffraction methods. The inhibitory effects of these compounds were evaluated by the α-glucosidase inhibitory assay.[12]

Sunil kumar *et. al.,* were synthesized 2-((benzothiazol-2-ylthio) methyl)-5- phenyl-1, 3, 4- oxadiazole derivatives and evaluated their anti-diabetic activity. Structures were characterized using ^{1}H NMR, ^{13}C NMR, FT-IR and Mass spectroscopy. Nitro derivatives were found to be more active among other compounds.[13]

Muhammad Taha *et. al.,* synthesized novel sulfonamides having oxadiazole ring and measured the inhibitory activity of β-glucuronidase in vitro and showed good inhibitory activity in the range of IC50 = 2.40 ± 0.01–58.06 ± 1.60 µM in comparison to the reference D-saccharic acid 1,4-lactone (IC50 = 48.4 ± 1.25 µM).[14]



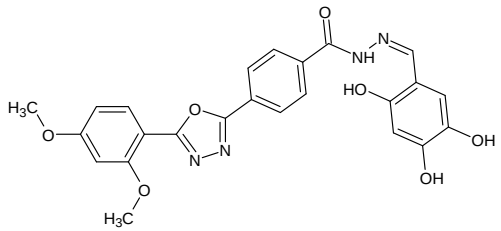
Kavitha Selvaraj *et. al.,* synthesized antidiabetic, anti-inflammatory, and anticancer properties of a number of novel 2,5-disubstituted 1,3,4-oxadiazole derivatives containing urea, amide, and sulphonamide were assessed

in vitro. The fifteen synthetic compounds exhibited moderate to good anti-inflammatory, anti-cancer, and anti-diabetic properties. The findings showed that adding urea and a sulphonamide group to oxadiazole increases its activity.[15]

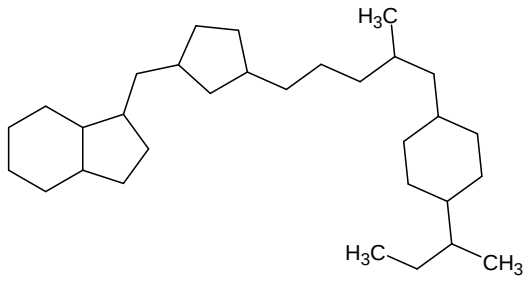
Muhammad Taha *et. al.*, synthesized Oxindole based oxadiazole hybrid analogs **(1**–**20)** were synthesized and evaluated their inhibitory potential against α-glucosidase enzyme. Comparing all analogs to the standard acarbose (IC50 = 895.09 ± 2.04 µM), the IC50 values for each analogue were within the range of 1.25 ± 0.05–268.36 ± 4.22).[16]

Di Xiao *et. al.*, identified 1,3,4-oxadiazolyl-containing β-carboline derivatives as new α-glucosidase inhibitors with antidiabetic properties. Of these derivatives, compound f26, which has an ortho-substituted benzene ring in its 1,3,4-oxadiazolyl moiety, exhibited favorable inhibitory activity toward α-glucosidase.[17]

Muhammad Taha *et. al.*, carried out Synthesis of new oxadiazole derivatives as α-glucosidase inhibitors. The IC50 values for inhibition activity vary in the range between 2.64 ± 0.05 to 460.14 ± 3.25 µM. The IC50 values were being compared to the standard acarbose (IC50 = 856.45 ± 5.60 µM).[18]



Muhammad Athar Abbasi *et. al.*, Synthesized and carried out molecular docking studies of novel biheterocyclic propanamides as Antidiabetic Agents. Compound shown promising enzyme inhibitory capability with an IC50 value lower than that of the standard acarbose. when these compounds were tested for their ability to inhibit the α-glucosidase enzyme. These compounds' molecular docking results aligned with their enzyme inhibitory potential data.[19]



Shuang Luo *et. al.*, conducted an investigation into the inhibitory properties of a family of new carbazole-oxadiazole compounds (6a–6n) against α-glucosidase and α-amylase. When compared to the positive control acarbose (IC50: 427.00 ± 9.56, 24.68 ± 1.10 µM, respectively), the majority of the synthesized compounds demonstrated inhibitory activities against α-glucosidase and α-amylase, with IC50 values ranging from 21.39 ± 0.69 to 92.05 ± 1.54 µM and 45.53 ± 1.50 to 126.14 ± 6.33 µM, respectively.[20]

Badrud Duza Mohammad *et. al.*, found Molecules having oxadiazole rings may offer an alternative method of treating diabetes, decreasing the advancement of atherosclerosis and other problems linked to the disease in addition to regulating blood sugar levels. Oxadiazole fusion with benzothiazole, 5-(2,5,2-trifluoroethoxy) phenyl, β-homophenylalanine, 2-methyl-2-{5-(4-chlorophenyl), diamine-bridged bis-coumarinyl, 5-aryl-2-(6′-nitrobenzofuran-2′-yl), nitrobenzofuran, and/or oxindole has been found to have possible anti-diabetic effects.[21]

Fahimeh Abedinifar *et. al.*, designed and synthesized a series of new benzofuran-1,3,4-oxadiazole containing 1,2,3-triazole-acetamides **12a**-**n** as potential anti-α-glucosidase agents. The α-glucosidase inhibition assay showed that all of the synthesized compounds 12a–n were more potent than the standard inhibitor acarbose (IC50 = 750.0 ± 12.5 µM), with half-maximal inhibitory concentration [IC50] values ranging from 40.7 ± 0.3 to 173.6 ± 1.9 µM. Compound 12c was the most effective of them all, with an inhibitory activity that was around 19 times greater than that of acarbose. A docking investigation of the most powerful chemical into the α-glucosidase active site was also conducted since it inhibited the enzyme in a competitive way. The title compounds' toxicity tests were also conducted in vitro and in silico.[22]

CONCLUSION

Modifications to Oxadiazole scaffolds have demonstrated promising biological effects. This review highlights a range of novel Oxadiazole derivatives that inhibit the enzymes α-amylase and α-glucosidase, which are known for their anti-diabetic properties. These findings could aid future research in the design of structure-activity relationship (SAR) studies on Oxadiazole-based compounds. Several drugs with potential anti-diabetic activity have already been introduced for the treatment of type II diabetes. Hence, the search for novel Oxadiazole pharmacophores that are potent, pharmacologically efficient, and secure as anti-diabetic medicines is encouraged.

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