VER
Vascular & Endovascular Review

Oxindole-Based α-Glucosidase Inhibitors: A Comprehensive Review

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ABSTRACT

α-Glucosidase is a crucial therapeutic target in type 2 diabetes mellitus due to its key role in carbohydrate metabolism, making the inhibition of this enzyme an effective strategy to control postprandial hyperglycaemia. Currently prescribed α-glucosidase inhibitors, such as Acarbose, Miglitol, and Voglibose, slow down glucose absorption and help manage blood sugar levels. However, their clinical use often limited by undesirable gastrointestinal side effects. Therefore, there is a need to develop more safer and effective alternatives. In recent years, oxindole-based derivatives have emerged as a highly promising scaffold for the development of new α-glucosidase inhibitors. These compounds offer remarkable structural diversity, a favourable pharmacological profile, and excellent potential for structural optimization. Advances in this area have focused on the synthesis, design, and biological evaluation of oxindole derivatives. The structure–activity relationship (SAR) studies showing that specific substitutions on the oxindole core can significantly enhance inhibitory potency. Hybridization of oxindoles with heterocyclic systems such as thiazoles, oxadiazoles, and spiro frameworks has further improved biological activity and drug-like properties. Molecular docking studies have provided valuable mechanistic insights into the binding interactions within the α-glucosidase active site, enabling more rational and targeted drug design. Overall, oxindole scaffolds are highly promising chemical class that holds significant potential to yield next-generation α-glucosidase inhibitors.

KEYWORDS: Oxindole derivatives, Alpha-glucosidase, Alpha-glucosidase inhibitors.

How to Cite: Mr. V. Rajasekhar Reddy[1], Dr. K. Aruna[2*], (2025) Oxindole-Based α-Glucosidase Inhibitors: A Comprehensive Review, Vascular and Endovascular Review, Vol.8, No.16s, 126-145.

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycaemia, which may occur in both fasting and postprandial states due to defects in insulin secretion, insulin action, or a combination of both (American Diabetes Association, 2021)[1]. Long-term exposure to elevated blood glucose levels in diabetes is significantly associated with progressive damage, dysfunction, and ultimate failure of various organs, including the eyes, kidneys, nerves, heart, and blood vessels, resulting in serious complications such as retinopathy, nephropathy, neuropathy, and cardiovascular disease[2-3]. The American Diabetes Association (ADA) classifies diabetes into various types according to etiology and clinical characteristics. Type 1 diabetes mellitus (T1DM) is predominantly an autoimmune disorder characterized by the destruction of pancreatic β-cells, leading to complete insulin deficiency; it usually presents in childhood or adolescence but may arise at any age [4]. Type 2 diabetes mellitus (T2DM), constituting over 90% of global cases, is defined by insulin resistance in peripheral tissues alongside progressive β-cell dysfunction; it is significantly linked to obesity, a sedentary lifestyle, and genetic predisposition [5]. Gestational diabetes mellitus (GDM) is characterized by glucose intolerance identified during pregnancy, linked to maternal and neonatal complications, and an increased lifetime risk of developing type 2 diabetes mellitus (T2DM) for both mother and child[6]. In addition to these, there are other specific types of diabetes that have known causes. For example, Maturity-Onset Diabetes of the Young (MODY) is a monogenic form of diabetes that caused by mutations in genes that control insulin secretion. Secondary diabetes can happen when diseases of the exocrine pancreas (like pancreatitis or cystic fibrosis) or when drugs or chemicals (like glucocorticoids or thiazide diuretics) cause diabetes[7, 8]. Diabetes is now seen as one of the most important global health problems because it is becoming more and more common. In 2021, there were an estimated 537 million adults with diabetes, and by 2045, that number is expected to rise to 783 million (International Diabetes Federation, 2021)[9]. To stop or slow down the progression of complications, it is important to make an early diagnosis, correctly classify the condition, and manage it well. At the same time, learning more about the underlying mechanisms of the different subtypes will help create more targeted and personalized treatment plans.

EPIDEMIOLOGY AND GLOBAL BURDEN

Epidemiological data indicate that type 2 diabetes mellitus (T2DM) accounts for approximately 90–95% of all diabetes cases, while type 1 diabetes mellitus (T1DM) and other less common forms make up the remainder (American Diabetes Association

[ADA], 2023)[10]. Despite advances in diagnosis and care, global diabetes prevalence remains highly uneven, with about 50% of cases still undiagnosed, particularly in low- and middle-income countries where access to healthcare resources is limited[11]. Diabetes has emerged as a leading cause of morbidity and mortality worldwide, contributing to nearly 6.7 million deaths in 2021, equivalent to one death every five seconds. In addition to its devastating health toll, diabetes imposes a significant financial burden, with healthcare expenditures projected to exceed USD 1 trillion annually by 2030, placing unsustainable pressure on resource constrained health systems[12] The epidemiology of diabetes further complicated by the rising incidence of gestational diabetes mellitus (GDM), which not only increases the risk of adverse pregnancy outcomes but also confers a long-term predisposition to T2DM for both mothers and their offspring [13]. Moreover, diabetes often coexists with other non-communicable diseases (NCDs), including hypertension, dyslipidemia, and cardiovascular disease, creating a syndemic that amplifies health risks and complicates management. Collectively, the global diabetes epidemic represents not only a pressing clinical and biomedical challenge but alson a societal, economic, and public health crisis. With rising obesity rates and increasingly sedentary lifestyles contributing to the surge of diabetes across all age groups show in (fig. 1), the economic impact extends beyond healthcare costs to encompass productivity losses and reduced workforce capacity. Addressing this escalating burden requires comprehensive, Multisectoral strategies that integrate prevention, early detection, and effective management, supported by coordinated efforts from individuals, healthcare professionals, communities, and policymakers to build a healthier future.

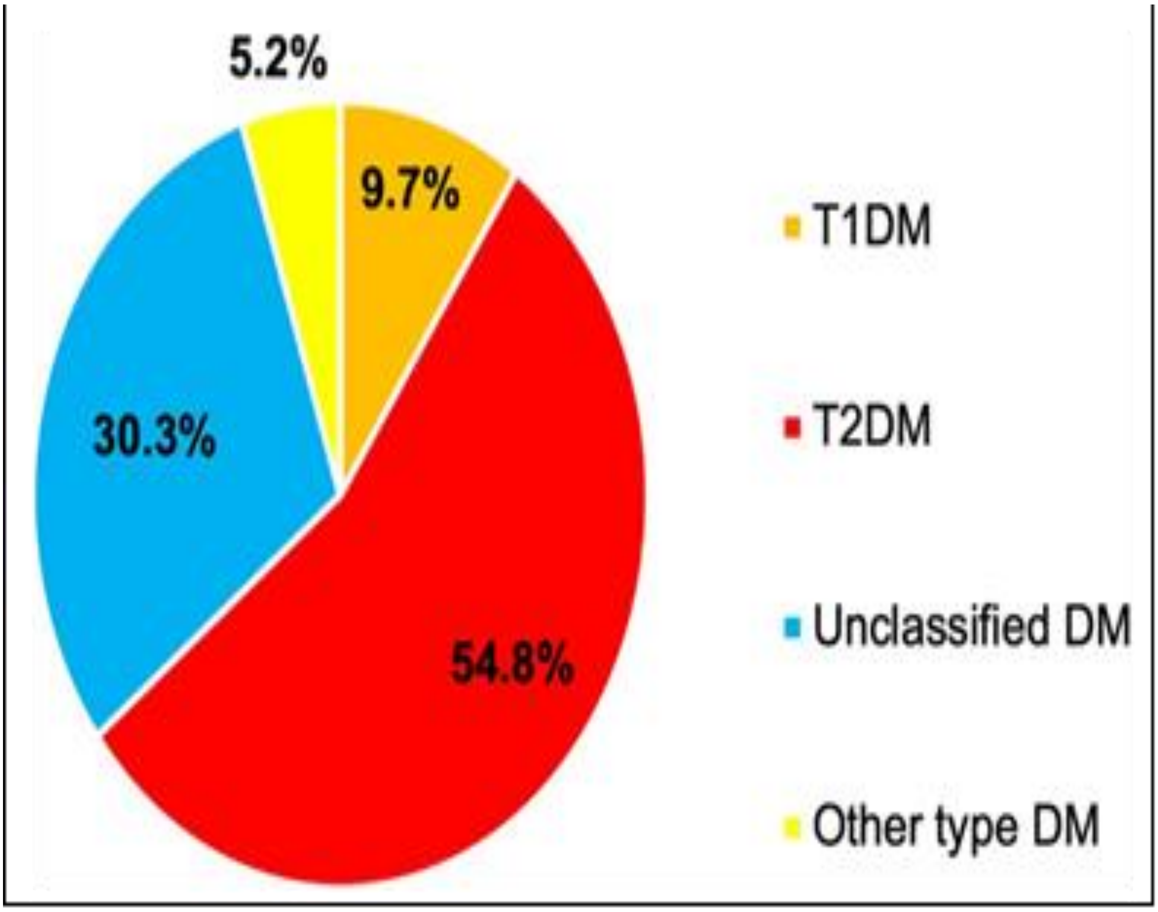


Figure 1: Epidemiology and global burden of diabetes mellitus, highlighting its prevalence, associated complications, and impact on global health.

TREATMENT OF DIABETES

In addition to controlling hyperglycaemia, the goals of diabetes mellitus management are to increase quality of life, increase survival, and avoid long-term complications. Although the keystone of treatment in the past were insulin therapy and older oral hypoglycaemic medications like biguanides and sulfonylureas, developments in diabetes research have significantly broadened the range of available treatments. Novel drug classes that target several pathophysiological mechanisms of type 2 diabetes have been developed in recent years. Among these, α-glucosidase inhibitors (AGIs) are special and important, especially for populations whose diets are high in carbohydrates. Acarbose, miglitol, and voglibose are examples of AGIs that work by competitively and reversibly inhibiting intestinal α-glucosidase enzymes found in the small intestine's brush border. When used alone, this inhibition lowers postprandial hyperglycemia (PPHG) without producing hypoglycemia by delaying the hydrolysis of complex carbohydrates into glucose[14]. Given that PPHG is closely linked to the emergence of cardiovascular complications in type 2 diabetes, their capacity to precisely target postprandial glucose excursions makes them particularly pertinent[15]. Acarbose was shown in the STOP-NIDDM trial to significantly lower cardiovascular events in high-risk populations and the risk of progression from impaired glucose tolerance (IGT) to type 2 diabetes by about 25%. According to a different meta-analysis, AGIs can lower HbA1c by 0.5% to 0.8% while also lowering body weight and triglyceride levels [16]. The cost-effectiveness of AGIs in Asian nations, where high carbohydrate intake leads to significant PPHG spikes, was further highlighted in a 2021 report by the International Diabetes Federation (IDF).

In addition to AGIs, a number of other innovative drug classes are frequently employed to treat diabetes. These include dipeptidyl peptidase-4 (DPP-4) inhibitors, which increase incretin activity; sodium-glucose cotransporter-2 (SGLT-2) inhibitors, which lower blood glucose through increased urinary glucose excretion while also offering cardiovascular and renal benefits; thiazolidinediones, which improve insulin sensitivity in peripheral tissues; and glucagon-like peptide-1 receptor agonists (GLP-1 RAs), which improve insulin secretion and aid in weight loss [17,18]

According to current therapeutic guidelines, AGIs can be used as an adjuvant to metformin when more postprandial control is required, or as first-line treatment for patients with mild hyperglycemia or predominant postprandial hyperglycemia. Since they do not directly stimulate insulin secretion, they are especially appropriate for elderly patients and those who are at high risk of hypoglycemia. However, adherence may be hampered by their gastrointestinal side effects, which include diarrhea and flatulence.

α-glucosidase inhibitors continue to be an important component of the current diabetes treatment regimen, particularly for Asian and low-resource populations. AGIs work in tandem with other innovative therapeutic classes to target postprandial glucose excursions and lower the risk of diabetes progression. This helps to achieve complete glycaemic control.

In addition to their established role in postprandial glucose regulation, α-glucosidase inhibitors (AGIs) exert broader metabolic and clinical effects that support their continued relevance in diabetes management. By delaying carbohydrate digestion in the proximal intestine, AGIs redistribute glucose absorption to the distal segments of the gut, which has been associated with enhanced secretion of incretin hormones such as glucagon-like peptide-1 (GLP-1). This incretin-mediated effect contributes to improved insulin sensitivity, suppression of inappropriate glucagon release, and modest improvements in β-cell function, thereby complementing their primary enzymatic inhibition mechanism.

From a cardiovascular perspective, postprandial hyperglycaemia is increasingly recognized as an independent risk factor for endothelial dysfunction, oxidative stress, and atherogenesis. By attenuating rapid glucose spikes after meals, AGIs may indirectly reduce oxidative stress and inflammatory signaling pathways implicated in vascular complications. Clinical and epidemiological studies have suggested potential benefits of AGIs in reducing surrogate markers of cardiovascular risk, including postprandial triglyceride levels and inflammatory mediators, particularly in populations consuming high-carbohydrate diets.

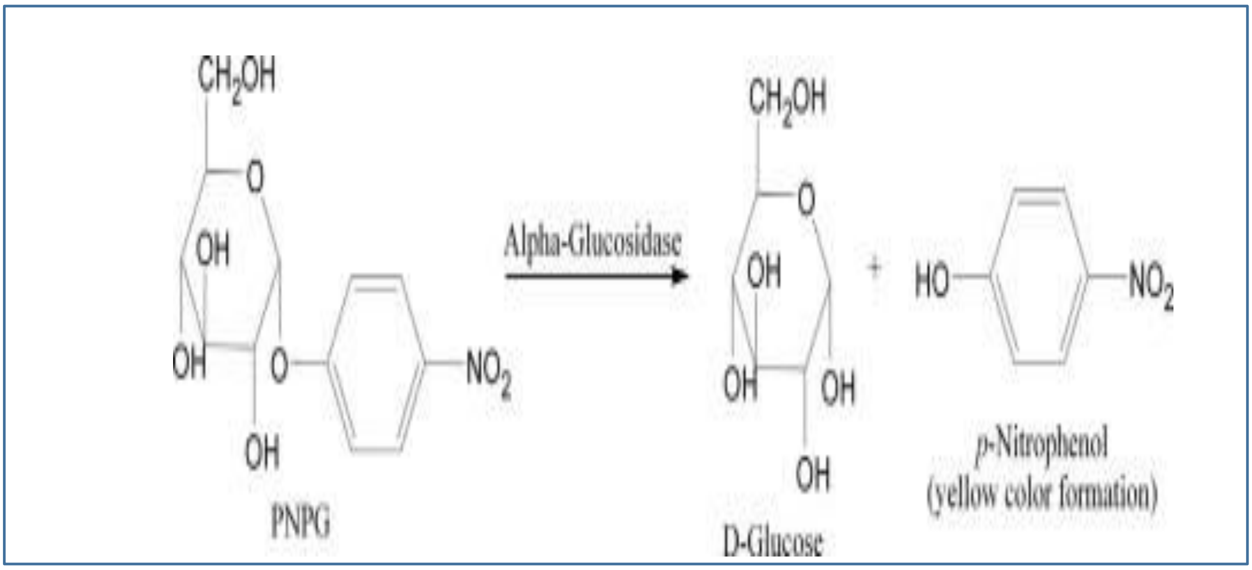
AGIs also demonstrate a neutral or modestly beneficial effect on body weight, as they do not promote insulin-mediated lipogenesis. This characteristic is advantageous in overweight or obese patients with type 2 diabetes mellitus, where weight gain associated with certain antidiabetic agents can negatively impact long-term outcomes. Furthermore, the insulin-independent mode of action of AGIs allows their safe use across different stages of disease progression and in combination with other antidiabetic drug classes such as metformin, DPP-4 inhibitors, SGLT-2 inhibitors, and insulin therapy.

Despite these advantages, ongoing research is focused on improving tolerability and patient adherence by developing next-generation AGIs with enhanced selectivity, improved pharmacokinetic profiles, and reduced gastrointestinal adverse effects. Advances in medicinal chemistry, including the exploration of novel scaffolds such as oxindole-based derivatives and hybrid molecules, aim to achieve potent α-glucosidase inhibition while minimizing fermentation-related side effects. Collectively, these efforts reinforce the significance of AGIs as a foundational and evolving component of comprehensive, patient-centered diabetes care.

3.1 Catalytic Mechanism of α-Glucosidase

The catalytic function of α-glucosidase operates via a traditional double-displacement (retaining) mechanism, maintaining the anomeric configuration of glucose during the entire reaction cycle. This two-step process involves making a covalent enzyme-substrate intermediate, which is then broken down by water (fig. 2).

Figure 2: Mechanism of hydrolysis of p-nitrophenyl alpha-D-glucopyranoside (pNPG) by -α - glucosidase.



The reaction starts when the carbohydrate substrate binds to the enzyme's active site pocket. This is where the key catalytic residues, usually aspartate or glutamate, are placed in a way that makes them work best. A nucleophilic residue (e.g., Asp) assaults the anomeric carbon of the glycosidic bond, leading to bond cleavage and the liberation of the leaving sugar moiety. At this point, a covalent glycosyl enzyme intermediate holds the transition state steady. In the second step, an acidic or basic residue (usually Glu acting as a general base) activates a water molecule, which then attacks the glycosyl enzyme intermediate. This hydrolytic step breaks the covalent bond, freeing up glucose and restoring the enzyme's catalytic residues, which makes the active site ready for the next cycle. As part of this two-step process, α-glucosidase breaks down disaccharides and oligosaccharides into monosaccharides that can be absorbed, mostly glucose. This is the last step in the digestion of carbohydrates in food. This mechanistic pathway underscores the vital function of α-glucosidase in modulating postprandial blood glucose concentrations, establishing it as a significant therapeutic target in type 2 diabetes mellitus [19,20]

INHIBITORS OF ALPHA-GLUCOSIDASE

Alpha-glucosidase inhibitors are oral, non-invasive therapeutic agents extensively utilized in the management of Type 2 Diabetes Mellitus (T2DM). Their primary mechanism of action entails the competitive and reversible inhibition of carbohydrate-digesting enzymes in the small intestine, specifically α-glucosidase and pancreatic α-amylase. AGIs lower the postprandial glucose surge by slowing down the breakdown of disaccharides and oligosaccharides into monosaccharides that can be absorbed. This improves glycemic control without directly stimulating insulin secretion[21].

At present, only a limited number of AGIs, specifically acarbose, miglitol, and voglibose, have received clinical approval. These agents not only slow down the absorption of glucose, but they also cause the release of glucagon-like peptide-1 (GLP-1), which helps control blood sugar levels and lower HbA1c levels even more. For example, the important STOP-NIDDM trial found that acarbose slowed the progression from impaired glucose tolerance to type 2 diabetes by about 25% and also lowered the number of cardiovascular events. Even though these are good things, gastrointestinal side effects like gas, diarrhea, and stomach pain still make it hard for patients to follow through.

To address these constraints, rigorous research focused on creating innovative scaffolds that exhibit improved α-glucosidase inhibitory activity and reduced adverse effects. Of these, the oxindole nucleus has become a very promising scaffold. Oxindole derivatives exhibit pharmacological versatility and are linked to a diverse array of biological activities, including antibacteri[22], anti-inflammatory[23], antihypertensive[24], anticancer[25], anti-angiogenic[26], and antiproliferative effects[27]. Oxindole-based medications, including sunitinib, nintedanib, ziprasidone, and ropinirole, exhibit therapeutic versatility in oncology, psychiatry, neurology, and respiratory disorders [28,29]. Moreover, various oxindole derivatives function as aldose reductase inhibitors, offering dual advantages in diabetes by enhancing glycemic regulation and mitigating complications such as neuropathy and retinopathy.

In addition to Oxindoles, several heterocyclic compounds have developed as potent α-glucosidase inhibitors. Thiazole and Oxadiazole derivatives have hydrogen bonding and hydrophobic contacts with it, while flavonoids and chalcones serve as natural competitive inhibitors with added antioxidant benefits[30]. Other chemotypes, including spiroindolones, coumarins, and pyridines, have shown selective inhibition with reduced toxicity. This structural diversity underscores the potential of hybrid design strategies, where oxindole frameworks are integrated with complementary bioactive motifs to achieve enhanced potency, selectivity, and drug-like properties.

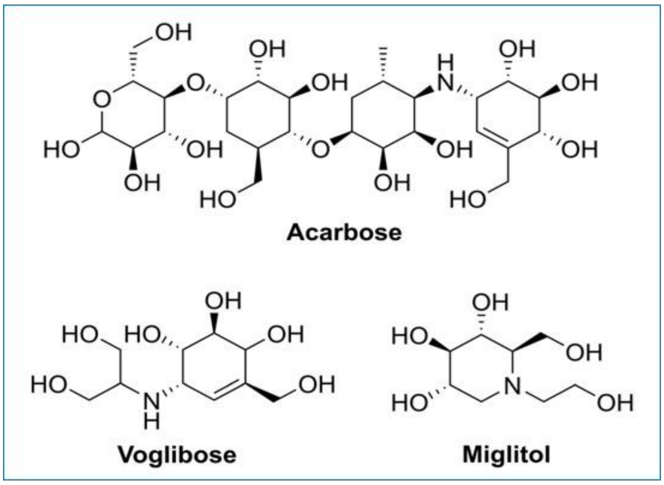


Figure 3: Clinically used α-glucosidase inhibitors for the treatment of T2DM.

α-glucosidase inhibitors (AGIs) (fig. 3) are still an important type of medicine for treating T2DM. However, oxindole derivatives have gotten a lot of attention because they can be used in many different ways and have shown promise as α-glucosidase inhibitors. Investigations into oxindole-based scaffolds highlight their promise as next-generation inhibitors that not only reduce postprandial glucose levels but may also confer additional advantages, including cardiovascular protection and the mitigation of diabetic complications.

In medicinal chemistry, the Oxindole scaffold is significant because it can take on many different shapes and can interact with many different biological targets. It has a rigid bicyclic structure with both an aromatic and a heteroaromatic ring, which gives it many places to add or change things. This makes it a good model for creating new drugs. In the last twenty years, scientists have studied oxindole derivatives a lot, and some of them have even become clinically approved drugs. This shows how important they are in modern pharmacotherapy.

Oxindole-based drugs like Sunitinib and Nintedanib (fig. 4) have been shown to be very effective at blocking multiple kinases and are approved for treating cancers and fibrotic lung diseases. Ziprasidone, on the other hand, has become very popular as an atypical antipsychotic. These examples show how the scaffold can be used in many different areas of medicine, including oncology, neurology, and respiratory medicine. Also, clinical candidates that have been dropped, like semaxanib, show that people have been interested in oxindoles as vascular endothelial growth factor (VEGF) pathway inhibitors for a long time.

Oxindoles are gaining popularity as antidiabetic agents, especially as α-glucosidase inhibitors (AGIs), in addition to their well-known clinical uses. α-Glucosidase is a crucial intestinal enzyme that degrades complex carbohydrates into glucose; its inhibition is an effective method for mitigating postprandial hyperglycemia in type 2 diabetes mellitus (T2DM). Acarbose and miglitol are two AGIs that are currently available. These compounds work well, but they can cause gastrointestinal side effects and aren't very effective. Recent studies have shown that substituted oxindole derivatives are very good at stopping α-glucosidase, and their IC_{50} values are often higher than those of traditional AGIs. Adding heterocyclic moieties like thiazoles, oxadiazoles, or spiro frameworks and optimizing functional groups on the oxindole core have greatly increased enzyme binding affinity and selectivity. Molecular docking studies also show that these compounds interact favorably with catalytic residues in the α-glucosidase active site. Some oxindole-based inhibitors also have multiple benefits, such as being antioxidants and anti-inflammatory agents. This could help lower the risk of complications from diabetes, such as oxidative stress ad inflammation of the blood vessels.

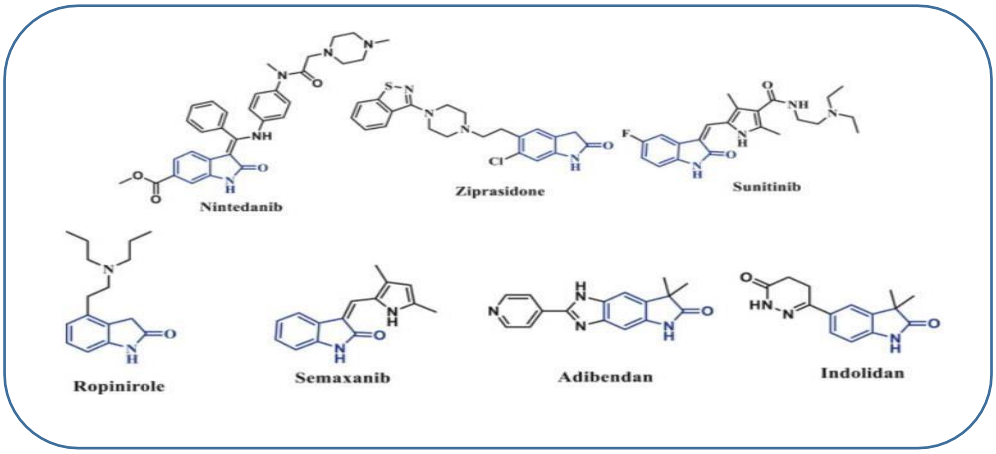


Figure 4: Structure of tetracyclic oxindole derivatives

4.1. Tetracyclic oxindole derivatives

In 2015, Kailin Han and colleagues published[31] the design and synthesis of a new group of tetracyclic oxindole derivatives that are strong α-glucosidase inhibitors. The synthetic approach commenced with isatin scaffolds, which were subsequently developed into tetracyclic frameworks through a tandem Suzuki coupling followed by a Michael addition (fig. 5). This route made it possible to build the stiff fused ring system that is typical of these derivatives, but the overall yields were low (8–20%). More diversity was achieved by adding different aryl substituents through Suzuki coupling. This made it possible to systematically study how electronic and steric effects affect enzyme inhibition. NMR and mass spectrometry fully characterized the resulting compounds, and twenty analogues were tested to see if they could stop α-glucosidase.

The structure-activity relationship (SAR) analysis showed clear patterns that linked substitution patterns to biological potency (fig. 6). The most impressive compound, 7i, had an IC_{50} of 4.8 µM, which is about 24 times stronger than the standard drug acarbose ($IC_{50} \approx 115.8$ µM). Other derivatives, such as 7d, 7e, and 7h, also showed strong inhibitory activity in the low micromolar range (12–16 µM), which was much better than acarbose. In contrast, analogues like 7c and 7g, which had less favorable substituents, showed weaker inhibition (about 30 µM), but they were still better than the reference drug. The SAR indicated that aryl substituents significantly influence activity: electron-withdrawing groups and optimally positioned hydrophobic substituents increased binding, whereas bulky or mismatched groups diminished potency.

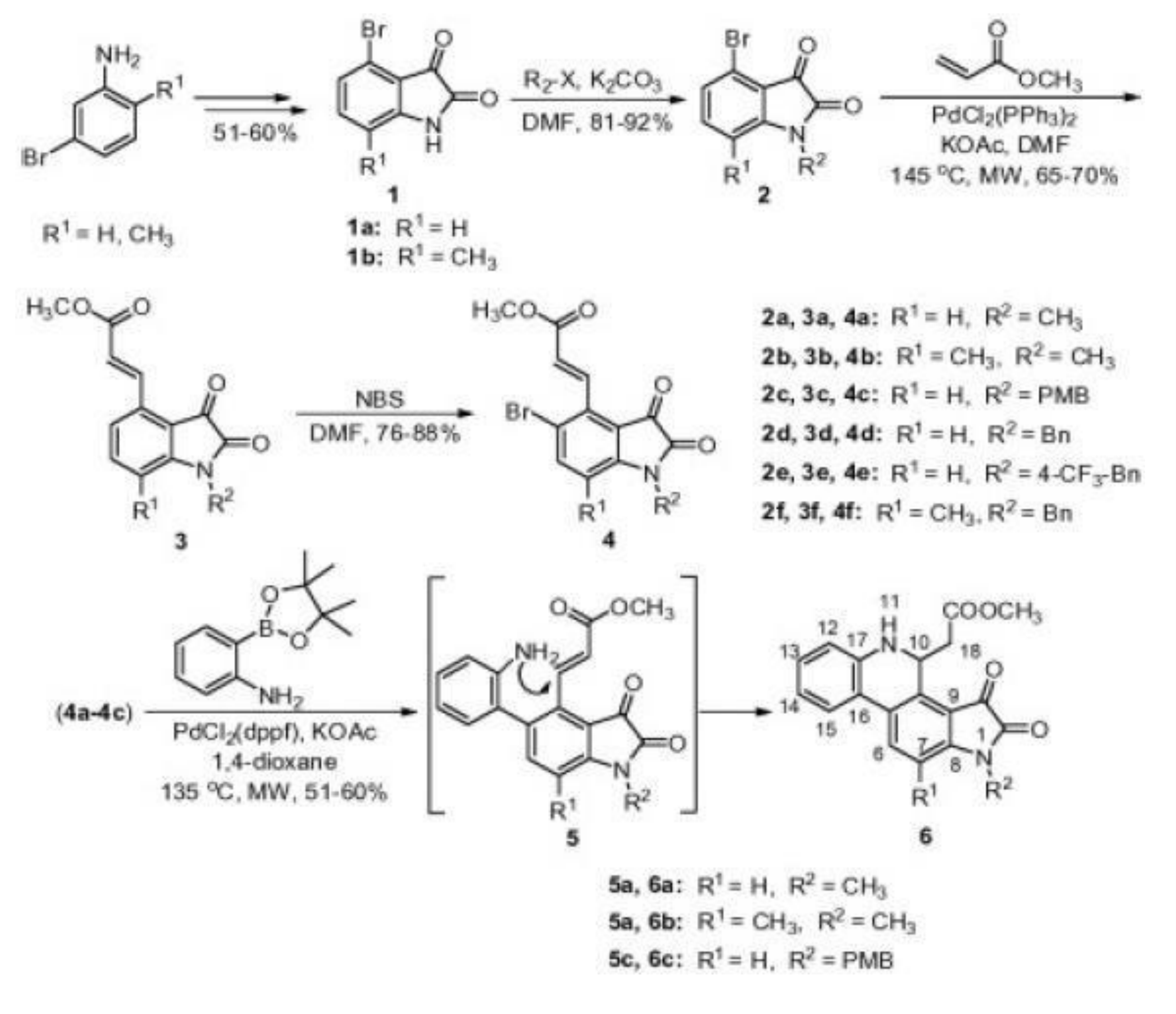


Figure 5: Synthesis of tetracyclic oxindole derivatives 6a-6c.

In (2016), H. Sun and colleagues[32] built on earlier research into oxindole-based scaffolds by publishing a full study of tetracyclic oxindole derivatives as α-glucosidase inhibitors, looking at both their inhibitory activity and how they work. This study offered both a synthetic investigation of these tetracyclic heterocycles and an enhanced mechanistic comprehension of their interaction with the α-glucosidase enzyme, a vital therapeutic target in the treatment of type 2 diabetes mellitus.

The research team created a library of tetracyclic oxindole analogues by making multi-step sequences that began with isatin derivatives. They used important tandem reactions, such as intramolecular cyclization strategies, to make three different series of tetracyclic frameworks with different aryl substituents. This scaffold design was inspired by the understanding that oxindole cores are privileged pharmacophores, and when they are made into rigid fused polycyclic systems,

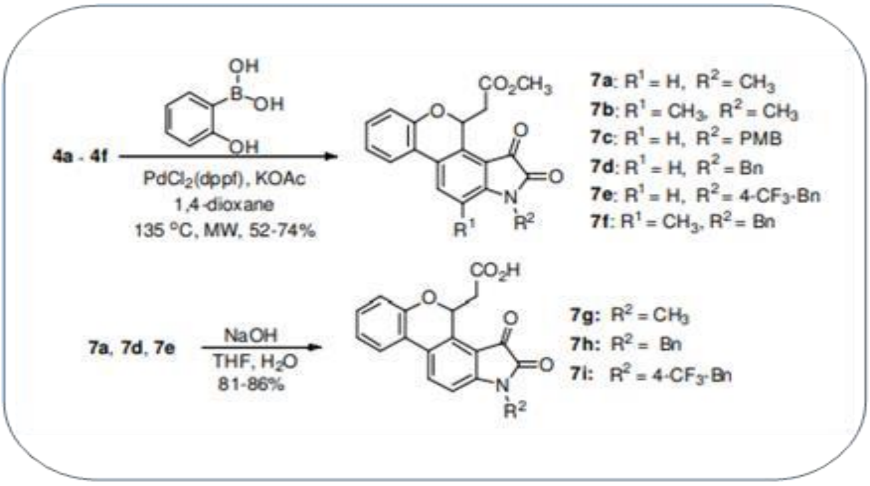


Figure 6: Synthesis of tetracyclic oxindole derivatives 7a-7i.

The biological assessment of these analogues demonstrated significant inhibitory activity against α-glucosidase. A number of compounds had low micromolar IC_{50} values, which was much better than the reference drug acarbose, which usually has an IC_{50} of about 116 µM under the same conditions. The lead derivative discovered in the study, commonly known as compound 6t, exhibited an IC_{50} value of 0.7 µM, indicating a potency increase exceeding 150-fold compared to acarbose. This remarkable activity highlighted the therapeutic potential of tetracyclic oxindole scaffolds as next-generation α-glucosidase inhibitors.

Mechanistic studies conducted utilizing enzyme kinetics and molecular docking simulations. Lineweaver–Burk plots showed that the most active derivatives had mixed-type inhibition. This means that these compounds can bind to both the catalytic site and an allosteric site of the enzyme. This dual binding mode is important because it makes inhibition more flexible and may lower the chance of resistance. Docking experiments further validated that the tetracyclic oxindole derivatives establish robust hydrogen bonds with critical residues in the α-glucosidase active site (notably Asp214, Glu276, and His348), while concurrently participating in hydrophobic and π–π stacking interactions with aromatic residues, thus stabilizing the inhibitor enzyme complex. The structure-activity relationship analysis showed that even small changes to the aryl substituents had a big effect on how well they worked as inhibitors. Compounds with electron-withdrawing groups (like halogens or nitro) at certain places made binding stronger, probably by making hydrogen bonding and electronic complementarity in the active site better. On the other hand, big or sterically hindered substituents made activity less likely, probably because of bad steric clashes. The tetracyclic structure's rigidity and planarity were very important because they made it possible for the aromatic residues in the enzyme pocket to stack perfectly.

In general, the study made a big difference in the search for new antidiabetic drugs by showing that tetracyclic oxindole derivatives (fig. 7,8) are one of the most promising chemotypes for α-glucosidase inhibition that has been reported so far. This study established the groundwork for further optimization and preclinical investigation of oxindole-based inhibitors by integrating robust inhibition, explicit structure-activity relationship (SAR) insights, and mechanistic evidence of mixed-type binding. The results indicate that further optimization of physicochemical properties may facilitate the development of these derivatives as innovative therapeutic agents for the management of postprandial hyperglycemia in type 2 diabetes.

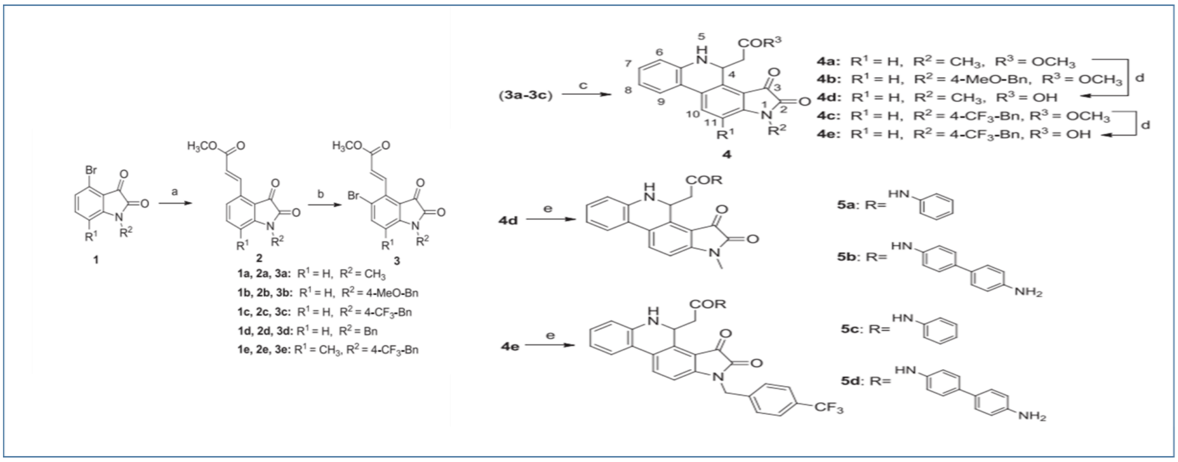


Figure 7: Synthesis of tetracyclic oxindole derivatives 4a-4e and 5a-5d.

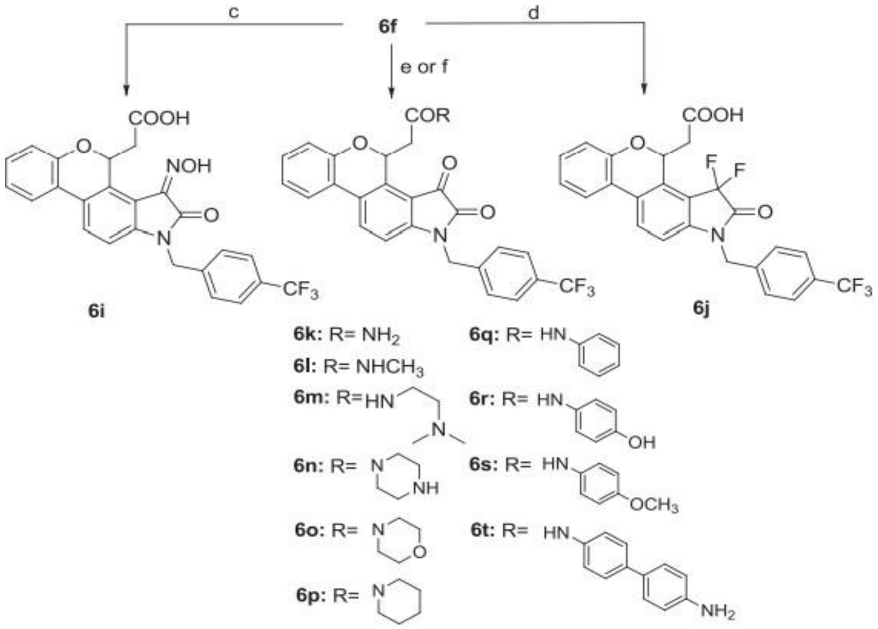


Figure 8: Synthesis of tetracyclic oxindole derivatives 6a-6t.

4.2 3,3-di(indolyl)indolin-2-ones derivatives:

Wang et al., 2017 found 3,3-di(indolyl)indolin-2-one derivatives as a new class of strong α-glucosidase inhibitors 33. The scientists made these molecules by changing the oxindole nucleus and adding two indolyl groups to the C-3 position of the indolin-2-one core. The synthesis was accomplished via a Fischer-type condensation reaction, utilizing isatin as the precursor, which was reacted with substituted indoles under acid-catalyzed conditions to produce the di(indolyl) framework (fig. 9). This synthetic method worked well and was flexible, making it possible to add different electron-donating and electron-withdrawing groups to the indole rings. This made a library of analogues that could be used for biological testing. Spectroscopic techniques, such as NMR and mass spectrometry, were used to confirm the structures of the products.

Biological assessment of these compounds demonstrated exceptional α-glucosidase inhibitory activity, with multiple analogues exhibiting low micromolar IC_{50} values, significantly surpassing the reference drug acarbose ($IC_{50} \approx 116$ μM). The most active derivative inhibited in the single-digit micromolar range, showing that this scaffold has a lot of potential for finding new antidiabetic drugs (Table. 1). The structure–activity relationship (SAR) analysis yielded significant insights: derivatives featuring electron-withdrawing substituents, such as halogens or nitro groups on the indole ring, exhibited significantly increased potency, which can be discribed to enhanced hydrogen bonding and superior electronic complementarity within the enzyme's active site. On the other hand, bulky substituents made activity less effective because they blocked the binding pocket. Fluorinated analogues worked especially well because replacing a halogen with a fluorine atom made hydrophobic interactions stronger and encouraged π–π stacking with aromatic residues in the α-glucosidase active site. The di(indolyl) substitution at C-3 of the oxindole scaffold gave it planarity and rigidity, which were also very important because they made stacking interactions more stable and helped the enzyme bind.

Overall, study showed that 3,3-di(indolyl)indolin-2-ones are a promising and structurally new scaffold for inhibiting α-glucosidase. They are much more potent than other inhibitors. The simple way to make it, along with the good SAR trends, gives us a lot of chances to improve the structure even more. These results not only showed that di(indolyl)oxindole derivatives could be used to treat postprandial hyperglycemia, but they also added a new type of heterocyclic scaffold to the medicinal chemistry toolbox that could be used to make new antidiabetic drugs in the future.

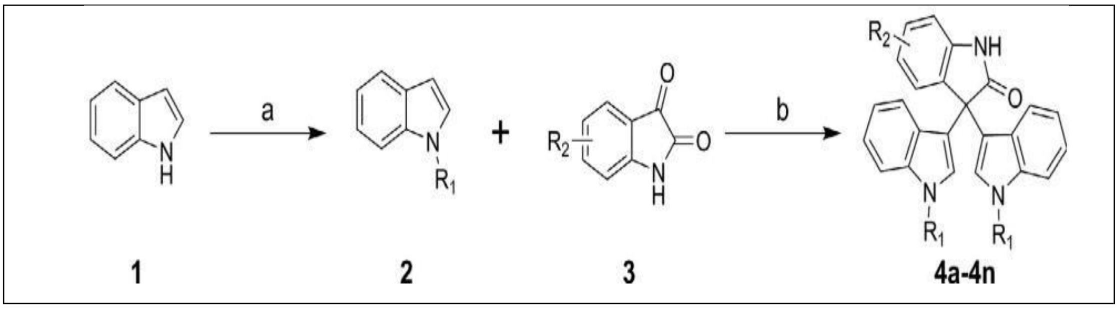
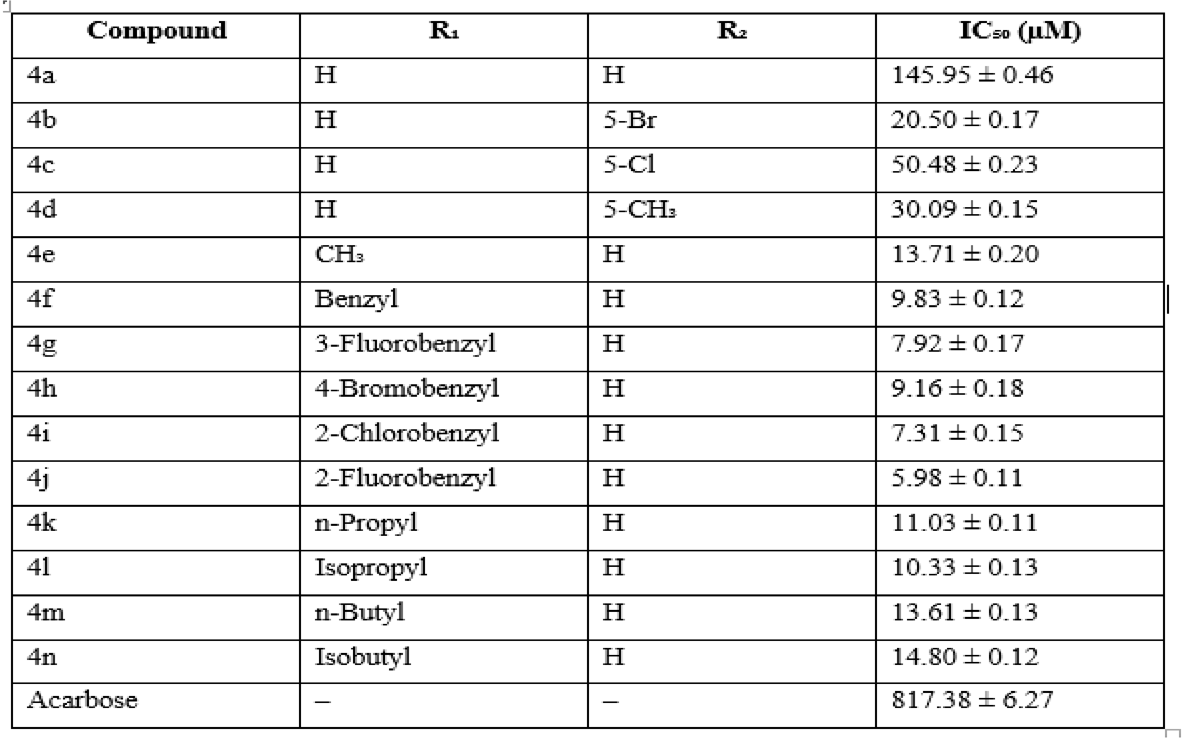


Figure 9: Reagents and conditions: (a) RX (X = Br or Cl), KOH, DMF, 12 h, room temperature; (b) pTsOH, CH2Cl2, 2 h, room temperature.

Table 1: α-Glucosidase inhibitory activity of 3,3-di(indolyl)indolin-2-ones (4a–4n).



Compound	R_1	R_2	IC_{50} (μM)
4a	H	H	145.95 ± 0.46
4b	H	5-Br	20.50 ± 0.17
4c	H	5-Cl	50.48 ± 0.23
4d	H	5-CH_3	30.09 ± 0.15
4e	CH_3	H	13.71 ± 0.20
4f	Benzyl	H	9.83 ± 0.12
4g	3-Fluorobenzyl	H	7.92 ± 0.17
4h	4-Bromobenzyl	H	9.16 ± 0.18
4i	2-Chlorobenzyl	H	7.31 ± 0.15
4j	2-Fluorobenzyl	H	5.98 ± 0.11
4k	n-Propyl	H	11.03 ± 0.11
4l	Isopropyl	H	10.33 ± 0.13
4m	n-Butyl	H	13.61 ± 0.13
4n	Isobutyl	H	14.80 ± 0.12
Acarbose	–	–	817.38 ± 6.27

4.3 Spiroindolone analogues:

In 2019, M.S. Altowyan and colleagues[34] reported the development of spiroindolone analogues as potential hypoglycemic agents, emphasizing their inhibitory activity against α-glucosidase and supportive evaluation against α-amylase. The team chose the spiroindolone scaffold because it is structurally strong and has an oxindole nucleus that is known to interact with many different biological systems. The synthesis of these analogues was accomplished via a one-pot multicomponent reaction, where in substituted isatins were reacted with active methylene compounds and appropriate nucleophiles under mild catalytic conditions. This strategy facilitated the efficient synthesis of a broad array of spirooxindole derivatives featuring various substituents and exhibiting high stereochemical control, as validated by NMR and mass spectrometry (fig. 10).

The biological assessment of these compounds indicated that numerous spiroindolone derivatives displayed low micromolar IC_{50} values against α-glucosidase, often surpassing the efficacy of the standard drug acarbose ($IC_{50} \approx 116$ μM). Some compounds had IC_{50} values below 10 μM, which is important because it shows how strong their inhibitory potential is. However, when tested against α-amylase, most compounds only showed moderate to weak activity, which suggests that they are more selective for α-glucosidase. This selectivity is therapeutically beneficial, as excessive α-amylase inhibition is linked to gastrointestinal side effects that frequently restrict clinical use.

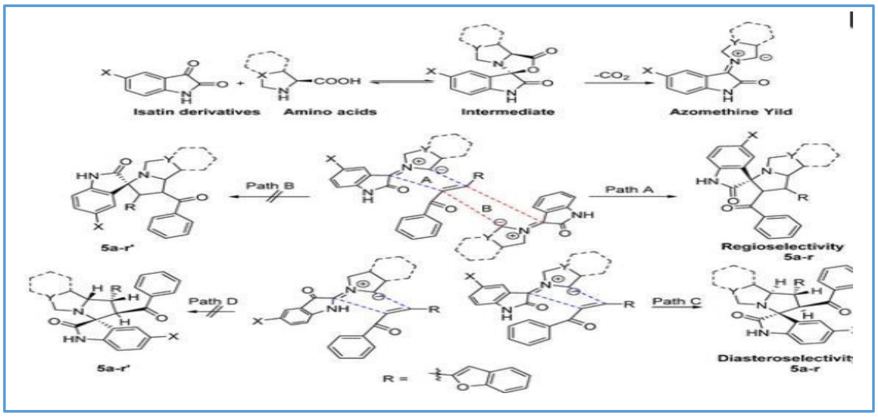


Figure 10: The synthesized compounds 5a–r.

The structure activity relationship (SAR) analysis elucidated the function of substituents. Derivatives containing electron-withdrawing groups, such as halogens (Cl, F, Br), on the aromatic ring exhibited increased α-glucosidase inhibition, presumably due to enhanced hydrophobic interactions and electronic complementarity within the active site. On the other hand, analogues with electron-donating groups (–OCH_3, –CH_3) were not as effective, which suggests that rings that are short on electrons are better at binding to enzymes. Bulky substituents usually made activity go down because they made it harder for the narrow catalytic pocket to work. The spiro-fused structure was very important for positioning functional groups in a way that encouraged strong π–π stacking interactions with aromatic residues and hydrogen bonding with catalytic residues like Asp and Glu. Molecular docking studies corroborated these findings, validating that the most effective compounds interacted with both catalytic and peripheral sites of α-glucosidase, aligning with competitive or mixed-type inhibition.

Overall, the study established spiroindolone analogues as potent, selective α-glucosidase inhibitors with strong antidiabetic potential. Their relatively weak α-amylase inhibition further highlighted their clinical promise by minimizing the likelihood of gastrointestinal complications. The combination of a straightforward synthetic route, clear SAR insights, and favorable selectivity profile positions spiroindolones as a valuable scaffold for future development of next-generation antidiabetic drugs.

4.4 5-fluoro-2-oxindole derivatives

In 2022, J. Lin and colleagues[35] published a significant study regarding the synthesis and biological assessment of 5-fluoro-2-oxindole derivatives as prospective α-glucosidase inhibitors (Table 2), thereby augmenting the oxindole-based antidiabetic scaffold series. The design's purpose was to add a fluorine atom to the C-5 position of the oxindole core. This is because fluorination often makes molecules more stable in the body, changes their lipophilicity, and increases their binding affinity by changing the electronic effects and adding non-covalent interactions. The synthetic route started with 5-fluoroisatin, which is easy to find on the market. A variety of oxindole derivatives made by combining nucleophilic substitution, condensation, and cyclization reactions. For instance, 5-fluoroisatin was reacted with active methylene compounds using Knoevenagel condensation to make oxindole scaffolds with functional groups. More changes, like N-alkylation, esterification, or amide coupling, made it possible to add structural diversity at the nitrogen and carbonyl positions. This modular synthetic strategy was very flexible and made a lot of different derivatives for biological testing. The yields were usually high and the purification was easy, which made the route synthetically appealing.

Biological testing showed that many of the synthesized derivatives had strong α-glucosidase inhibitory activity. Some compounds had IC_{50} values in the low micromolar range, which was much better than the reference drug acarbose ($IC_{50} \approx 116$ µM). The structure–activity relationship (SAR) analysis showed clear patterns: derivatives with electron-withdrawing substituents, especially halogens and nitro groups on the oxindole ring or attached aromatic moieties, were more potent because they made better hydrogen bonds and hydrophobic interactions with the enzyme's active site. On the other hand, derivatives with big or very electron-donating groups didn't work as well, probably because they were too big or didn't bind as well. The fluorine atom at the C-5 position was found to be very important because it changed the electron density across the oxindole ring, made the scaffold more polar, and made stabilizing interactions like halogen bonding and dipole–dipole contacts easier to form in the α-glucosidase binding pocket. Molecular docking studies validated that the most active compounds established numerous hydrogen bonds with catalytic residues (Asp, Glu, His) while concurrently participating in π–π stacking interactions with aromatic residues, thereby stabilizing the ligand enzyme complex.

This study confirmed that the 5-fluoro-oxindole scaffold is a very promising template for stopping α-glucosidase. The effective and adaptable synthetic method enabled systematic substitution, and the biological outcomes underscored the advantageous impact of fluorine incorporation in modulating both activity and selectivity. Research yielded significant insights into the formulation of next-generation oxindole-based antidiabetic agents, integrating robust inhibitory efficacy, advantageous drug-like characteristics, and a synthetically accessible scaffold amenable to further medicinal chemistry enhancement.

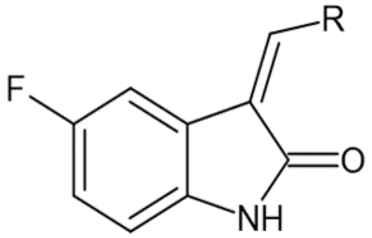
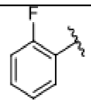
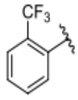
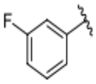
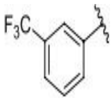
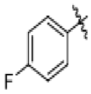
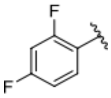
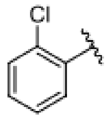
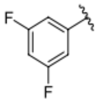
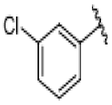
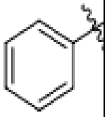
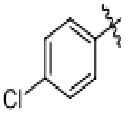
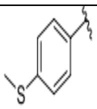
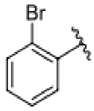
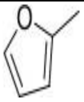
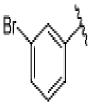
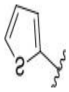
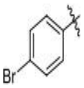
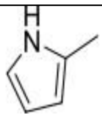
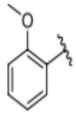
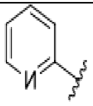
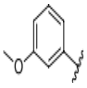
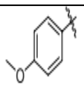


Table 2: α-Glucosidase inhibitory activities of compounds (3a ~ 3v).

Compound	R	Inhibition rate at a concentration of 100 µM (100%)	IC50 (µM)	Compound	R	Inhibition rate at a concentration of 100 µM (100%)	IC50 (µM)
3a		7.29 ± 0.16	>100a	**3m**		8.43 ± 1.14	>100a
3b		5.19 ± 0.79	>100a	**3n**		52.79 ± 1.68	96.78 ± 0.72

3c		9.55 ± 0.13	>100a	**3o**		18.78 ± 1.15	>100a
3d		89.19 ± 0.14	49.89 ± 1.16	**3p**		55.89 ± 1.71	92.62 ± 0.45
3e		21.64 ± 0.78	>100a	**3q**		10.01 ± 1.75	>100a
3f		90.52 ± 0.27	35.83 ± 0.98	**3r**		60.8 ± 1.27	90.56 ± 1.87
3g		53.71 ± 0.47	95.68 ± 0.28	**3s**		4.49 ± 1.88	>100a
3h		31.61 ± 0.21	>100a	**3t**		5.67 ± 1.11	>100a
3i		92.86 ± 0.32	56.87 ± 0.42	**3u**		3.77 ± 1.35	>100a
3j		19.17 ± 1.21	>100a	**3v**		3.99 ± 1.28	>100a
3k		27.25 ± 1.47	>100a	**5-Fluoro-2-oxindole**			(7.51 ± 0.17) × 10 3
3l		15.70 ± 0.71	>100a	Acarbose			569.43 ± 43.72

Inhibitory activity of test compounds at 100 μM is less than 50%.

4.5. 1,3,4-oxadiazole derivatives:

Ullah Hayat et al. on the synthesis and α-glucosidase inhibitory evaluation of a set of 1,3,4-oxadiazole derivatives intended as potential antidiabetic agents[36]. The synthesis consisted of two steps: first, the condensation of the right hydrazides with different carboxylic acids to make hydrazide intermediates, and then the cyclization of those intermediates under the right conditions to make the 1,3,4-oxadiazole core. The reaction conditions were fine-tuned to get high yields and pure structures. Spectroscopic techniques like ^{1}H-NMR, ^{13}C-NMR, and high-resolution mass spectrometry to fully characterize all of the synthesized derivatives. This showed that the oxadiazole ring had formed correctly and that the aromatic moieties had the right substitution patterns. The in vitro assessment of α-glucosidase inhibitory activity demonstrated that the derivatives displayed a wide spectrum of potencies, with IC_{50} values ranging from 0.80 ± 0.1 μM to 45.1 ± 1.7 μM. Several compounds exhibited inhibitory activity markedly superior to that of the standard inhibitor acarbose, which demonstrated an IC_{50} of 38.45 ± 0.80 μM. Compound 14 was the strongest inhibitor in the series, with an IC_{50} of 0.80 ± 0.1 μM. This shows that changing the structure of a compound can make it work better. SAR analysis showed that having electron-withdrawing substituents, like nitro and halogen groups, on the aromatic ring was important for increasing potency. This is probably because they made the active site residues of α-glucosidase interact better with each other. The position of the substituents also had a big effect on activity. Para-substituted derivatives usually inhibited better than ortho- or meta-substituted analogs. Molecular docking studies corroborated these findings, demonstrating that the most active compounds effectively bound within the α-glucosidase active site, establishing critical hydrogen bonds and hydrophobic interactions that stabilized the enzyme–ligand complex. These computational insights aligned effectively with the experimental findings, elucidating the mechanistic basis of the inhibitory activity. In general, the study shows that 1,3,4-oxadiazole derivatives are a good starting point for making strong α-glucosidase inhibitors. This is useful information for the rational design and further improvement of antidiabetic drugs. This work is an important contribution to the field of enzyme-targeted diabetes therapeutics because it uses effective synthetic methods, thorough SAR analysis, and docking studies.

4.6 Oxindole based oxadiazole hybrid analog :

Taha et al. (2018)[37] detailed the design, synthesis, and biological assessment of a novel series of oxindole-derived oxadiazole hybrid analogs functioning as α-glucosidase inhibitors. The authors combined oxindole and oxadiazole into hybrid scaffolds to make them more useful as antidiabetic drugs. Oxindole is useful for many different types of drugs, and oxadiazole is stable in the body. The synthetic strategy was well-planned. It started with making oxindole intermediates and then used cyclization reactions to make the oxadiazole ring. This modular method allowed for substitutions at important spots, which led to a wide range of derivatives with different electronic and steric properties. . The reactions produced good yields, showing that robustness of the synthetic pathway.

The biological assessment of these hybrids demonstrated a wide range of α-glucosidase inhibitory activity, with IC_{50} values varying from 1.25 ± 0.05 μM to 268.36 ± 4.22 μM. The broad range of activity shows how sensitive enzyme inhibition is to small changes in structure. It's important to note that some compounds worked in the low micromolar range, which is similar to or better than the reference drugs used in the clinic. SAR analysis showed that the patterns of substitution on both the oxindole and oxadiazole parts were very important for changing how strong the inhibition was. Electron-withdrawing substituents, especially halogens and nitro groups, increased inhibitory activity, probably because they interacted more strongly with polar residues in the enzyme active site. On the other hand, large hydrophobic groups usually made the potency lower, which suggests that steric hindrance and poor accommodation in the catalytic pocket were to blame.

In general, the study shows that combining oxindole and oxadiazole scaffolds in a smart way is a good way to make strong α-glucosidase inhibitors. The authors offered significant SAR insights that may direct subsequent optimization through a methodical examination of various substituents. The most active compounds from this series show promise as lead molecules for the development of antidiabetic drugs. However, more research, such as molecular docking, pharmacokinetic evaluation, and in vivo validation, would make their therapeutic relevance stronger. This research highlights the significance of scaffold hybridization in contemporary medicinal chemistry and identifies oxindole-oxadiazole hybrids as a promising category of enzyme inhibitors with considerable potential for diabetes management.

4.7 Indolo[2,3-a] quinolizidine and spiro[indolizidine-1,3′-oxindole] derivatives

Punlop Kuntiyong et al. (2024)[38] introduced a sophisticated synthetic methodology for the synthesis of indolo[2,3-a]quinolizidine and spiro[indolizidine-1,3′-oxindole] derivatives, utilizing L-glutamic acid as the chiral precursor. A significant advancement in their methodology was the incorporation of the dibenzylamino group for stereocontrol, guaranteeing the synthesis of optically pure intermediates that were later cyclized into intricate heterocyclic frameworks. This strategy shows how important chiral auxiliaries are for directing stereoselective synthesis, especially in scaffolds inspired by natural products that could be used for medicine. The anti-α-glucosidase assessment of these compounds demonstrated considerable inhibitory activity, with one indoloquinolizidine derivative (IC_{50} = 18.06 μM) and one spiro[indolizidine-1,3′-oxindole] derivative (IC_{50} = 13.83 μM) exhibiting significant potential. These results underscore the pharmacological significance of rigid heterocyclic frameworks, wherein stereochemistry and conformational locking are critical determinants of enzyme binding. The SAR implications indicate that the spirocyclic configuration may augment steric complementarity and binding affinity within the α-glucosidase catalytic site, elucidating its enhanced potency relative to the indoloquinolizidine analogs.

Simultaneously, the synthesis of aryl-oxadiazole Schiff bases has been extensively documented in the literature as a promising strategy for α-glucosidase inhibition. The usual way to make these compounds is to condense substituted aromatic aldehydes with oxadiazole-linked amines. This makes hybrids that contain imines and have longer conjugation. The Schiff base functionality not only adds more places for hydrogen bonding, but it also makes the structure flatter, which makes it easier for π–π stacking interactions to happen with the enzyme's active site residues. Biological screening of these derivatives has consistently demonstrated that electron-withdrawing substituents (e.g., nitro, chloro, fluoro) augment inhibitory potency by reinforcing polar interactions, whereas electron-donating groups (e.g., methoxy, methyl) generally diminish activity. The oxadiazole core also gives metabolic stability, which could lead to better pharmacokinetic profiles.

The research conducted and the investigations into aryl-oxadiazole Schiff bases highlight the extensive variety of heterocyclic scaffolds systematically engineered for the inhibition of α-glucosidase. Some stereo controlled frameworks, like spiro[indolizidine-1,3′-oxindole], use conformational rigidity to increase potency. Others, like aryl-oxadiazole Schiff bases, are simpler but more flexible and have tunable electronic and structural features that drive activity. Future research that combines stereochemical precision with electronically modulated Schiff base hybrids may produce more effective antidiabetic candidates.

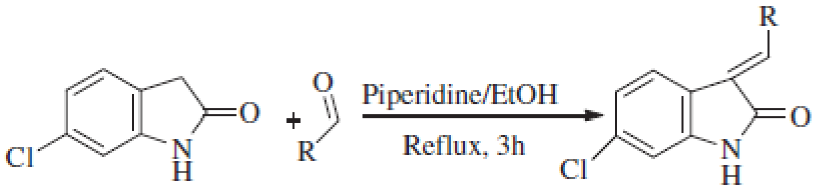
4.8. 6-chloro-3-oxindole derivatives :

Momin Khan et al. (2014)[39] conducted a study that detailed the design and synthesis of a new series of oxindole-based compounds intended to create strong α-glucosidase inhibitors for diabetes treatment. Oxindole is a favored scaffold in medicinal chemistry due to its adaptable binding characteristics and its extensive occurrence in bioactive compounds. The researchers chose 6-chloro-oxindole as the starting point and used a simple method to make Schiff base derivatives. The oxindole nucleus combined with a variety of substituted aromatic aldehydes in the presence of a small amount of piperidine, resulting in a wide range of compounds. This method was effective, gave good yields, and made it possible to make systematic structural changes by adding both electron-donating and electron-withdrawing groups to the aromatic ring. All the synthesized compounds 420 were isolated with E configuration (fig. 11). For the determination of the structures of the synthesized twenty five compounds, 1H NMR, and EI spectroscopy used and observed satisfactory CHN analysis

All twenty-five compounds tested for synthesized derivatives in vitro to see how well they could stop yeast α-glucosidase and Acarbose used as the standard reference drug. The biological findings were very promising because many of the oxindole derivatives showed very strong inhibitory power. Compound 2, which has a hydroxyl group at the para-position of the aromatic ring, had an IC$_{50}$ value of 2.71 ± 0.007 µM, which was much higher than acarbose's IC$_{50}$ value of about 38 µM under the same conditions (Table 4). This finding underscored the potential of oxindole Schiff bases as promising lead compounds in the pursuit of effective α-glucosidase inhibitors. Also, the selectivity of these compounds showed that improving the structure of the oxindole scaffold could lead to better pharmacological profiles with fewer side effects.

The SAR analysis gave us more information about what makes something inhibit activity. It was noted that electron-donating substituents, such as hydroxyl and methoxy groups on the aromatic aldehyde moiety, typically augmented α-glucosidase inhibition, presumably by enhancing the likelihood of hydrogen-bond interactions with the enzyme's active site. On the other hand, strong electron-withdrawing groups like nitro or chloro substituents had different effects, and some made the potency weaker. Substituents that could participate in π–π stacking interactions or additional hydrogen bonding were also advantageous for enzyme affinity, demonstrating that both steric and electronic properties substantially affect activity. The oxindole core was essential for bioactivity, as its planar structure and capacity to establish stabilizing interactions with the enzyme pocket formed the basis for potent inhibitory effects.

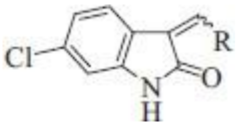
The authors effectively demonstrated that oxindole-derived Schiff base derivatives constitute a novel and potent category of α-glucosidase inhibitors, exhibiting enhanced efficacy relative to the conventional drug acarbose. The research exhibited a straightforward and adaptable synthetic methodology while also elucidating distinct SAR trends that may facilitate the subsequent optimization of this scaffold.

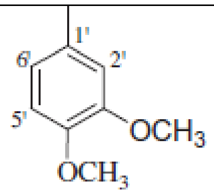
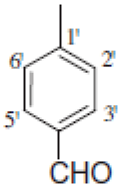
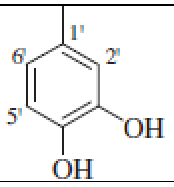
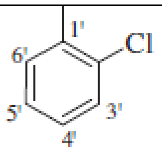
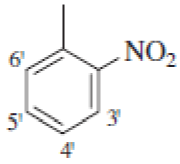
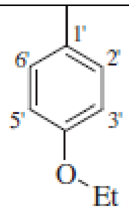


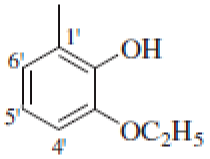
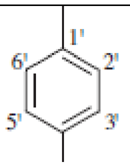
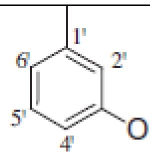
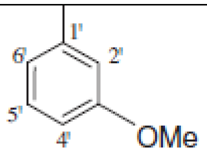
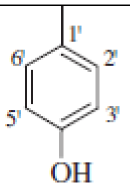
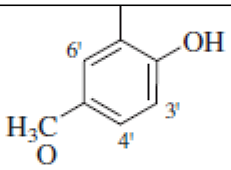
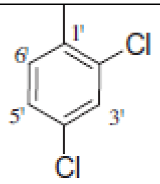
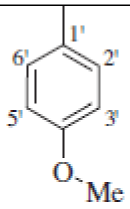
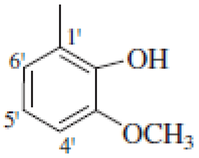
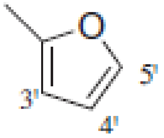
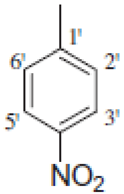
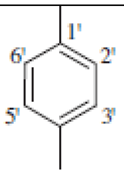
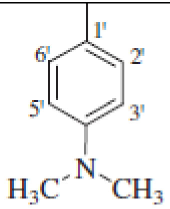
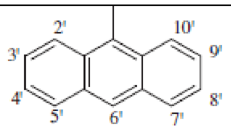
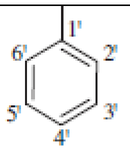
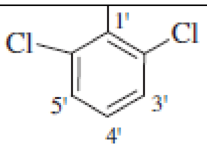
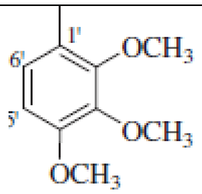
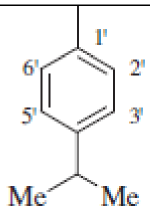
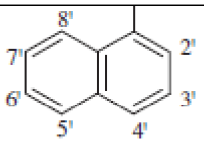
1-25

Figure 11: Synthesis of 6-chloro-3-oxindole derivatives 1–25.

Table 4 : Inhibition studies of α -glucosidase of compounds 1–25



Compound	R	IC50 ± SEM (µM)	Compound	R	IC50 ± SEM (µM)
1		410.55 ± 0.91	14		109.98+/-0.07
2		2.71+/-0.007	15		73.11+/-0.001
3		11.41+/-0.005	16		99.72+/-0.04

4		37.93+/-0.002	17		51.81+/-003
5		15.19+/-0.004	18		139.23+/-0.02
6		24.71+/-0.007	19		82.15+/-0.02
7		55.64+/-0.09	20		108.31+/-0.04
8		72.19+/-0.008	21		173.32+/-0.003
9		84.35+/-0.001	22		114.73+/-0.02
10		91.22+/-0.009	23		17.33+/-0.001
11		195.59+/-0.05	24		52.87+/-0.004
12		341.11+/-0.12	25		14.27+/-0.002
13		102.32+/-0.003	Acarbose	Standard inhibitor	38.25+/-0.12

A-AMYLASE INHIBITION AND THE POTENTIAL OF OXINDOLE AND OXADIAZOLE DERIVATIVES IN ANTIDIABETIC DRUG DISCOVERY

The enzymatic hydrolysis of dietary carbohydrates is an essential process in the release of glucose after eating, primarily facilitated by α-amylase and α-glucosidase. By stopping these enzymes, carbohydrate digestion and glucose absorption are slowed down, which helps prevent postprandial hyperglycemia, a common sign of type 2 diabetes mellitus (T2DM). Acarbose and miglitol are two examples of α-amylase and α-glucosidase inhibitors that are currently used in medicine. However, they often cause gastrointestinal side effects like gas and diarrhea, which is why researchers are looking for inhibitors that are more selective, powerful, and easier to take. Oxindoles and oxadiazoles have become important heterocyclic systems for targeting metabolic enzymes in medicinal chemistry.

The oxindole (2-indolinone) nucleus is a flexible pharmacophore with a wide range of biological effects, such as anticancer, anti-inflammatory, antimicrobial, and antidiabetic effects. The oxindole core's structural flexibility makes it easier to add new functional groups, which makes it easier for biomolecular targets to interact with it. Recent molecular docking and quantitative structure-activity relationship (QSAR) studies have demonstrated that oxindole-based analogues can effectively engage with the catalytic pocket of α-glucosidase and α-amylase enzymes through hydrogen bonding, π–π stacking, and polar interactions. For instance, Khaldan et al. 2022[40] and Luthra et al. (2018)[41] showed that oxindole derivatives could be more powerful than standard inhibitors, showing that the scaffold has promise as a treatment. Researchers have also looked into fluorinated oxindoles, and they found that substituting fluorine for an electron-withdrawing group increased inhibitory activity, which gave them useful SAR information. All of these results show that oxindoles can be used as flexible frameworks for the logical design of new antidiabetic drugs.

5.1 1,3,4-Oxadiazole Derivatives as Potent α-Amylase Inhibitors

Chavan et al. (2023)[42] created, synthesized (fig. 12), and tested a library of 1,3,4-oxadiazole derivatives to see how well they could stop α-amylase. The authors employed computational pre-screening to identify analogues exhibiting advantageous ADMET profiles and drug-like characteristics. Two promising compounds, SC2 and SC8, using a multi-step process that included condensation and cyclization reactions. NMR and MS methods used to confirm the structure.

In vitro assays indicated that SC2 and SC8 demonstrated IC_{50} values of 36.5 ± 1.5 µg/mL and 45.2 ± 2.1 µg/mL, respectively, surpassing the standard drug acarbose (IC_{50} = 68.9 ± 3.2 µg/mL). This big improvement shows that the scaffold could make stronger α-amylase inhibitors. Molecular docking (PDB: 6Z8L) demonstrated that both SC2 and SC8 established stabilizing hydrogen bonds and hydrophobic interactions within the enzyme's catalytic pocket. The observed structure-activity relationship (SAR) indicated that substituents facilitating polar interactions enhanced inhibitory potency, which is consistent with the experimental findings. The authors determined that oxadiazoles offer a favorable chemical framework for the optimization of antidiabetic leads, especially targeting α-amylase.

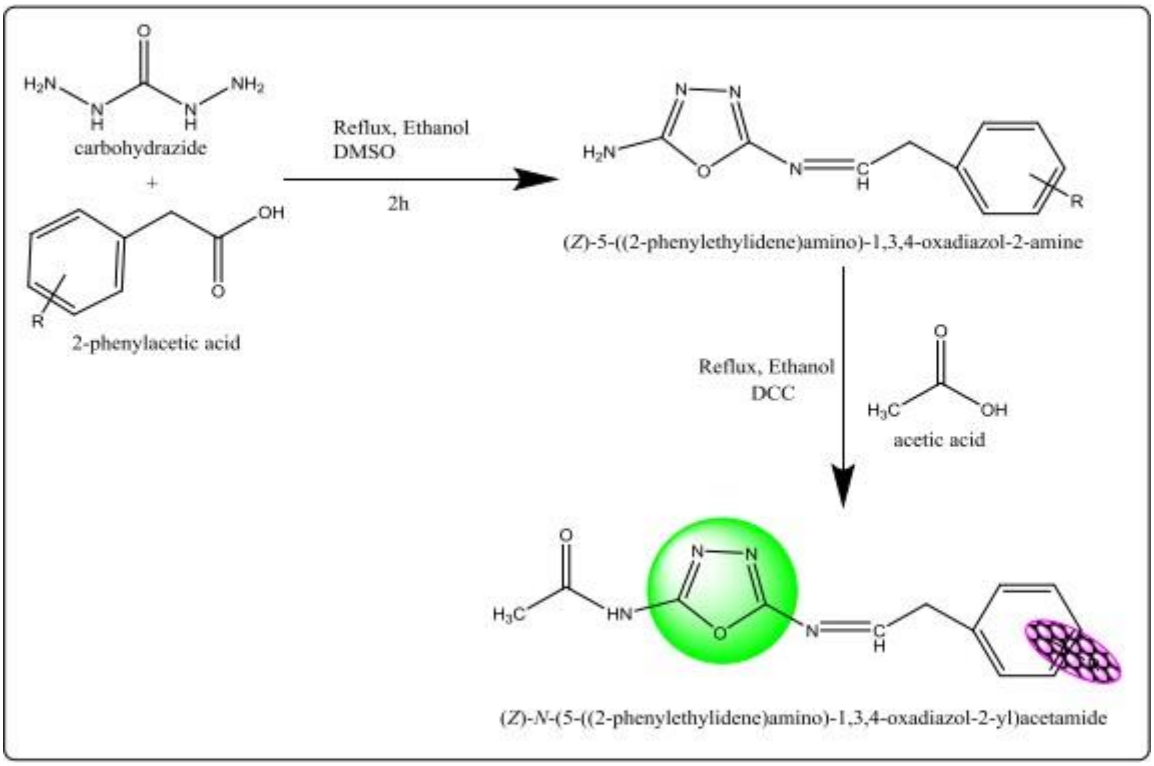


Figure 12: Proposed scheme of synthesis of 1,3,4-Oxadiazole derivatives.

5.2 2-thione-1,3,4-oxadiazole derivatives as Dual α-Amylase and α-Glucosidase Inhibitors

Bukhari et al., (2021)[43] made another important contribution by making a series of 2-thione-1,3,4-oxadiazole derivatives through the condensation of hydrazide carboxylic acid and then cyclization. FTIR, NMR, and elemental analysis used to figure out the structure (fig. 13). The synthesized analogues tested against both α-amylase and α-glucosidase, which increased their potential for use in medicine.

Compound 5g among the derivatives showed strong α-amylase inhibition (IC_{50} = 13.09 ± 0.06 µg/mL), which is very close to acarbose (IC_{50} = 12.20 ± 0.78 µg/mL). For α-glucosidase, derivatives like 5a and 4a(a) had IC_{50} values of 12.27 ± 0.41 µg/mL and 15.45 ± 0.20 µg/mL, respectively. Miglitol had an IC_{50} value of 11.47 ± 0.02 µg/mL. SAR analysis demonstrated that hydroxyl substitution markedly increased inhibitory activity, presumably due to hydrogen bond formation with essential catalytic residues. On the other hand, substituents that gave electrons made the potency lower, while thione functionality made the activity better. Molecular docking confirmed these findings, showing that active analogues bind strongly to enzyme catalytic residues. Show value in the table below (Table 5).

Table 5: Shows the IC50 and % of Inhibition of α-glucosidase derivatives

Compound	**Alpha -glucosidase IC_{50} (µg/ml ± SEM)**	**Alpha-amylase IC_{50} (µg/ml ± SEM)**
5a	12.27 ± 0.41	60.02 ± 0.08
5b	62.01 ± 0.92	64.8 ± 1.07
5c	69.04 ± 0.27	68.45 ± 0.15
5d	73.61 ± 0.02	89.77 ± 0.91
5e	68.02 ± 0.43	97.1 ± 0.80
5f	273.06 ± 0.04	208.54 ± 0.14
5g	80.8 ± 0.52	13.09 ± 0.06
4a(a)	15.45 ± 0.20	291.12 ± 0.02
4a(b)	No effect	185.44 ± 0.36
4a(c)	299.11 ± 0.31	394.34 ± 0.63
Miglitol	11.47 ± 0.02	Not applicable
Acarbose	Not applicable	12.20± 0.78

This dual inhibitory profile is particularly important because targeting both α-amylase and α-glucosidase may provide synergistic control of postprandial hyperglycemia. Thus, the therapeutic versatility of oxadiazole derivatives in addressing T2DM through multi-target inhibition.

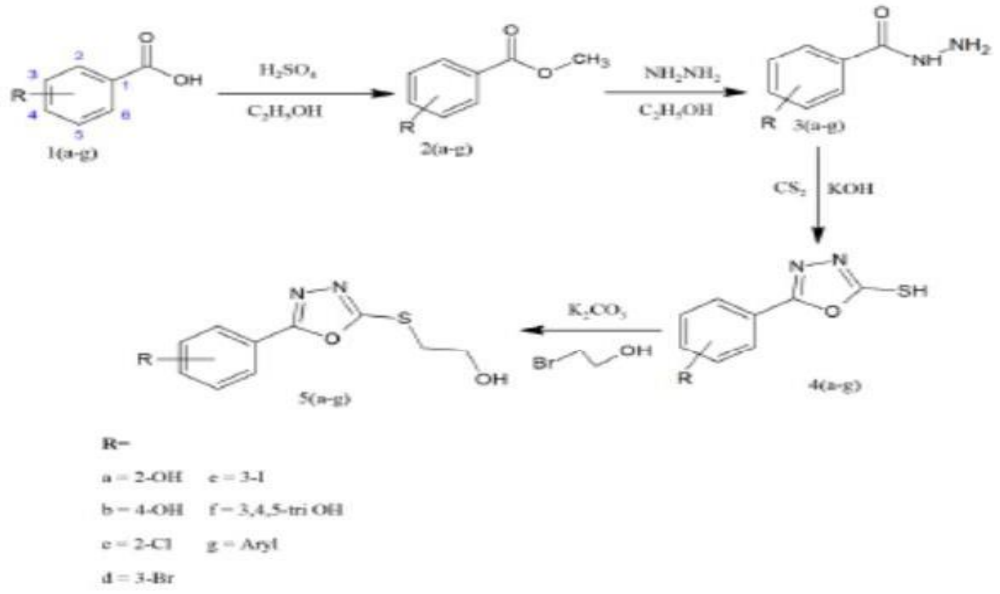


Figure 13: Synthesis of 2-substituted phenyl -1, 3, 4-oxadiazole-2- thion derivatives.

GLUCAGON-LIKE PEPTIDE-1 (GLP-1) RECEPTOR:

Glucagon-like peptide-1 (GLP-1) is an incretin hormone released by intestinal L-cells in reaction to food consumption. It is pivotal in glucose homeostasis by enhancing glucose-dependent insulin production, inhibiting glucagon release, postponing stomach emptying, and fostering satiety. These activities facilitate the reduction of postprandial blood glucose levels and enhance overall glycemic regulation. Native GLP-1 possesses a brief plasma half-life of 1–2 minutes, attributable to swift enzymatic breakdown by dipeptidyl peptidase-4 (DPP-4) and neutral endopeptidases. To address this constraint, various long-acting GLP-1 receptor agonists (GLP-1RAs), including exenatide, liraglutide, dulaglutide, and semaglutide, have been formulated and are extensively utilized in the treatment of type 2 diabetes mellitus (T2DM).

GLP-1 receptor agonists replicate the physiological functions of endogenous GLP-1 and have exhibited significant antihyperglycaemic benefits in both clinical and preclinical research. In addition to reducing HbA1c by around 0.8–1.5%, these medicines also facilitate weight loss and offer cardiovascular and renal protection. Clinical trials like LEADER (liraglutide) and SUSTAIN-6 (semaglutide) have demonstrated substantial decreases in major adverse cardiovascular events and the advancement of diabetic kidney disease, respectively [45,-47]. Due to these diverse advantages, GLP-1 receptor agonists currently regarded as fundamental in the treatment of type 2 diabetes mellitus, especially in patients with obesity and cardiovascular comorbidities.

Notwithstanding their clinical efficacy, GLP-1 receptor agonists exhibit certain limitations, such as gastrointestinal adverse effects (nausea, vomiting), the necessity for parenteral administration, and comparatively elevated treatment expenses. These limitations have necessitated the pursuit of orally bioavailable, cost-effective small-molecule GLP-1 receptor agonists that are simpler to produce. The GLP-1 receptor is a member of the Class B G-protein-coupled receptor (GPCR) family, which poses structural difficulties for small-molecule design owing to its intricate extracellular domain that interacts with peptide ligands. Nevertheless, other tiny non-peptidic agonists and positive allosteric modulators (PAMs), including TT-OAD2 and BETP, have been identified, indicating that the activation of GLP-1R by small molecules is feasible, albeit still in the preliminary research phase [48-50].

DIPEPTIDYL PEPTIDASE-4 (DPP-4)

Dipeptidyl peptidase-4 (DPP-4) is a serine protease that quickly breaks down incretin hormones like glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP). These hormones are very important for keeping blood sugar levels stable because they make insulin release and stop glucagon release. By blocking DPP-4, these incretins stay active for longer, which helps people with type 2 diabetes mellitus (T2DM) control their blood sugar levels better. Linagliptin, saxagliptin, sitagliptin, alogliptin, and vildagliptin are clinically approved DPP-4 inhibitors that can lower HbA1c levels by about 0.5–0.7% while keeping DPP-4 activity inhibited for more than 95% of the time for up to 12 hours [51]. It is important to note that these drugs do not directly change insulin [52] sensitivity or secretion, so they are generally weight-neutral. However, some people have reported side effects like nasopharyngitis, upper respiratory infections, headaches, and very rare cases of pancreatitis.

Heterocyclic scaffolds have become important templates for finding new DPP-4 inhibitors, and oxindole derivatives are looking more and more promising. The oxindole nucleus, a favored framework in medicinal chemistry, has been thoroughly investigated for its diverse pharmacological attributes, encompassing anticancer, anti-inflammatory, and antidiabetic effects. In recent years, oxindole-based compounds designed and tested to see if they can stop DPP-4, usually with the help of molecular docking and SAR analyses. For instance, oxindole analogues with dimethyl and thiomethyl substitutions showed significant DPP-4 inhibitory activity in vitro, with potency differing based on substitutions at the C-3 and C-5 positions of the oxindole ring [53]. These results suggest that adding electron-donating groups can make the DPP-4 catalytic site bind better, which will make the enzyme work better overall. Comparative studies underscore the potential of oxindoles in conjunction with other heterocyclic scaffolds. For example, benzothiazole derivatives have produced highly effective inhibitors, such as compound 2f with an IC_{50} of 1.266 ± 0.264 nM, which outperformed the standard drug sitagliptin (IC_{50} = 4.380 ± 0.319 nM). Related derivatives (2g, 2o, and 2k) showed IC_{50} values in the low nanomolar range [54].

SODIUM GLUCOSE COTRANSPORTER-2 (SGLT-2)

Sodium glucose cotransporter-2 (SGLT-2) inhibitors represent a relatively new category of oral antidiabetic medications that operate via a mechanism different from most conventional treatments, which generally increase insulin secretion, enhance insulin sensitivity, or depend on external insulin supplementation. SGLT-2 inhibitors work by selectively blocking the reabsorption of glucose in the proximal tubules of the kidney. This causes more glucose to be excreted in the urine and lowers blood glucose levels in people with type 2 diabetes mellitus (T2DM). This insulin-independent mechanism not only helps control blood sugar levels, but it also has other benefits, such as helping people lose weight and protecting their hearts.

The FDA approved canagliflozin in 2013 as the first SGLT-2 inhibitor. Dapagliflozin and empagliflozin followed, and they now commonly prescribed alone or in fixed-dose combinations, such as canagliflozin–metformin. Dapagliflozin has an IC_{50} of about 1.1–1.2nM for human SGLT-2 and is more than 1200 times more selective for SGLT-1[55]. Canagliflozin has IC_{50} values of 2.2–4.4 nM and >250-fold selectivity, which means it is a little less effective at stopping things. Empagliflozin, on the other hand, is one of the most selective inhibitors, with IC_{50} values of 1.3–3.1 nM and an amazing >2500-fold selectivity for SGLT-1. Recent data indicate that empagliflozin exhibits enhanced potency (IC_{50} = 0.88 nM) and approximately 2000-fold selectivity, underscoring its superior clinical profile [56].

Although marketed SGLT-2 inhibitors have shown considerable effectiveness, there is a growing interest in investigating novel scaffolds, such as oxindole derivatives, as potential regulators of renal glucose transport. The oxindole nucleus is a special structure in medicinal chemistry because it can interact with biological targets in many different ways that don't involve covalent bonds. Recent in silico and synthetic investigations have discovered oxindole-derived analogues that can bind to the glucose recognition pocket of SGLT-2, exhibiting moderate to strong inhibitory activity. For instance, oxindole derivatives hybridized with aryl or heteroaryl substituents at the C-3 position demonstrated favorable docking scoreagainst SGLT-2, indicating binding interactions akin to those seen with dapagliflozin and canagliflozin[57, 58].

Modifications to the C-3 position of the oxindole scaffold have produced many bioactive compounds with enzyme inhibitory capabilities, including inhibitors of α-glucosidase, α-amylase, and GSK-3β. Nevertheless, a comprehensive examination of the existing literature and patent databases reveals that no oxindole-derived compounds documented as GLP-1 receptor agonists, DPP4 inhibitors, or SGLT-2 antagonists or modulators. In conclusion, although oxindole scaffolds have demonstrated potential as inhibitors of enzymes such as α-glucosidase, α-amylase, and GSK-3β, no oxindole-derived compounds identified as GLP-1 receptor agonists, DPP-4 inhibitors, or SGLT-2 antagonists, underscoring an uncharted yet potentially significant domain for future pharmacological exploration.

CONSEQUENCES OF DIABETES MANAGEMENT

Today, managing diabetes is about more than just keeping blood sugar levels in check. It also includes strategies to lower long-term complications, improve quality of life, and deal with the growing health and economic costs of diabetes worldwide. Recent evidence indicates that effective glycemic management can substantially diminish the risk of microvascular complications, including retinopathy, nephropathy, and neuropathy, as well as alleviate macrovascular risks, such as cardiovascular disease and stroke. New treatments not only lower blood sugar levels, but they also make insulin more effective, help beta cells work better, and help people lose weight. This shows a more complete view of how to treat diabetes.

Recent pharmacological advancements, including GLP-1 receptor agonists, SGLT-2 inhibitors, DPP-4 inhibitors, and innovative α-glucosidase inhibitors featuring oxindole-based scaffolds, have revolutionized treatment paradigms by providing cardiovascular protection, renal benefits, and a diminished risk of hypoglycemia, alongside glucose regulation. These agents are progressively incorporated into personalized combination therapies designed to optimize efficacy and mitigate side effects, signifying a transition from a "one-size-fits-all" methodology to individualized precision medicine.

Nutraceuticals and functional foods, including polyphenols, flavonoids, and natural α-glucosidase inhibitors, are concurrently being investigated as adjunct therapies, providing safer, patient-friendly alternatives that can enhance standard pharmacological treatments [59]. These kinds of approaches are in line with the growing need for integrative care that combines traditional drugs with dietary and natural treatments. Lifestyle changes are still the most important part of managing diabetes. Regular physical activity, dietary changes that focus on foods with a low glycemic index, weight control, and quitting smoking are still the best ways to improve metabolic outcomes and lower the need for medication. Current guidelines also stress the importance of technology-based interventions like continuous glucose monitoring (CGM), insulin pumps, and AI-driven digital health tools that help patients manage their own health, stick to their treatment plans, and make decisions about their care [60].

From a global health standpoint, the increasing incidence of diabetes, particularly in low- and middle-income nations, highlights the critical necessity for cost-effective and accessible interventions. Modern diabetes management has big effects: the future lies in patient-centered care that includes advanced pharmacological therapies like oxindole-based α-glucosidase inhibitors, changes in lifestyle, digital technologies, and public health programs. This kind of broad approach is necessary to stop the diabetes epidemic, lower the risk of complications, and improve the long-term health of people all over the world.

CONCLUSION

Oxindole derivatives have attracted considerable interest as next-generation α-glucosidase inhibitors (AGIs) owing to their enhanced potency, selectivity, and structural versatility relative to traditional agents like acarbose. The oxindole nucleus is a special structure that medicinal chemists use to make small changes that can have big effects on biological activity. Studies on the structure–activity relationship show that adding aryl, alkyl, or heteroaryl groups to the C-3 position makes hydrophobic interactions stronger. On the other hand, adding halogens to the C-5 or C-6 positions makes lipophilicity and binding affinity stronger. Methoxy groups and other electron-donating substituents make hydrogen bonding even stronger. Spiro- or fused-oxindole frameworks also make α-glucosidase much more selective.

The oxindole framework is very flexible when it comes to making things. Recent developments in green chemistry, one-pot methods, and microwave-assisted synthesis have added to classical methods like Fischer indole synthesis and palladium-catalyzed cross-coupling. These methods not only make it easier to make functionalized oxindole libraries, but they also improve efficiency, yield, and scalability, which makes oxindoles appealing for drug development. Oxindoles have more effects on the body than just blocking α-glucosidase. Docking and mechanistic studies validate their stable interaction with essential catalytic residues (Asp, Glu, His), whereas experimental evidence indicates supplementary antioxidant, anti-inflammatory, and cardioprotective advantages that are highly beneficial in the management of type 2 diabetes and its systemic complications.

Even with these improvements, more in vivo validation, ADMET profiling, and toxicity studies are needed before they can be used in clinical settings. Through combined work in synthesis, computer modeling, and pharmacological testing, oxindole derivatives are ready to change AGI therapy by providing safer, more effective, and more versatile ways to manage diabetes.

CONSTRAINTS AND PROSPECTIVE PATHWAYS

Even though diabetes treatment has come a long way, there are still some problems that make it hard to get the best and most long-lasting disease control. Present pharmacological strategies predominantly focus on glycemic control yet fail to eradicate the risk of chronic complications, including neuropathy, nephropathy, and cardiovascular diseases. Additionally, commonly prescribed medications, such as α-glucosidase inhibitors (AGIs) like acarbose and miglitol, are constrained by gastrointestinal adverse effects (flatulence, diarrhea, bloating), which hinder patient adherence. These agents also show some effectiveness in lowering HbA1c, which shows that we need stronger and more tolerable inhibitors.

New scaffolds like oxindole derivatives could help us get past these problems. Changes to the structure of the oxindole nucleus have shown stronger α-glucosidase inhibition, better selectivity, and possible extra benefits like antioxidant and anti-inflammatory effects. Nonetheless, research is predominantly preclinical, exhibiting deficiencies in comprehending their toxicity, pharmacokinetics, and in vivo efficacy. Without this information, it is still not clear how to turn laboratory findings into therapies that work in the real world.

Future strategies should concentrate on SAR studies and molecular modeling to discern substitution patterns that enhance potency while reducing side effects. Oxindole-based AGIs may work better when used with other types of drugs, like SGLT-2 or DPP-4 inhibitors. This could improve glucose control after meals and have other benefits as well. Personalized medicine, utilizing genetic and metabolic profiling, could enhance the customization of AGI-based therapies for particular patient demographics, especially those with carbohydrate-rich diets where AGIs demonstrate optimal efficacy.

Also, using digital health technologies like continuous glucose monitoring and AI-assisted treatment algorithms can help fine-tune dosing strategies and predict bad events, which will help people stick to their treatment plans. To have a global impact, it is important to find cost-effective ways to make oxindole derivatives and to do clinical trials that focus on the patient. In conclusion, the development of oxindole-derived α-glucosidase inhibitors presents a promising avenue for enhancing the safety, efficacy, and accessibility of diabetes treatments, contingent upon future research that aligns preclinical advancements with practical clinical requirements.

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