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Aziridine as Emerging Scaffold: Focusing on Anti-diabetic Perspectives

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ABSTRACT

Aziridine, a three-membered nitrogen-containing heterocycle, has gained significant attention as a versatile scaffold in drug discovery due to its unique reactivity and structural rigidity. Its strained ring system allows for facile derivatization, enabling the synthesis of a wide range of bioactive molecules. In recent years, aziridine-based compounds have been explored for their potential in treating diabetes mellitus, a chronic metabolic disorder characterized by impaired glucose homeostasis. Several studies have highlighted the role of aziridine derivatives in modulating key molecular targets involved in diabetes, such as dipeptidyl peptidase-4 (DPP-4), α-glucosidase, aldose reductase, and peroxisome proliferator-activated receptors (PPARs). Additionally, aziridine scaffolds have demonstrated promising inhibitory activity against advanced glycation end-products (AGEs), which play a crucial role in diabetic complications. The ability of aziridine derivatives to enhance insulin sensitivity, improve glucose uptake, and regulate oxidative stress further strengthens their therapeutic potential. Moreover, their ease of synthetic modifications allows for fine-tuning of pharmacokinetic and pharmacodynamic properties, improving bioavailability and target selectivity. This review aims to provide a comprehensive insight into the recent advancements in aziridine-based anti-diabetic agents, focusing on their various synthetic routes, mechanistic approaches, structure-activity relationships, and future perspectives. By elucidating the potential of aziridine as a promising scaffold, this study underscores its significance in the development of novel therapeutic agents for diabetes management.

Keywords: Aziridine, Diabetes, Anti-diabetic agents, Inhibitors, Targets, Synthesis

INTRODUCTION

Diabetes mellitus is derived from the Greek term "diabetes," which means "siphon" or "to pass through," and the Latin word "mellitus," which means "sweet" [1]. Upon reviewing the historical records, it seems evident that the term "diabetes" was initially employed by

Apollonius of Memphis between 250 and 300 BC [2]. In 1922, Banting et al. extracted and refined the insulin from bovine pancreas at the University of Toronto, resulting in the development of a viable therapy for diabetes [3]. Throughout the years, significant achievements have been made and numerous breakthroughs, along with effective management approaches, have been developed [4]. DM is a metabolic disorder characterized by abnormally high amounts of glucose in the blood. It encompasses various classifications: type 1 [5], type 2 [6], maturity-onset diabetes of the young (MODY) [7], gestational diabetes [8], neonatal diabetes [9], secondary causes resulting from endocrinopathies [10], steroid use [11], and other factors [12]. The primary subcategories of DM are Type 1 and Type 2, which typically arise from impaired insulin production and/or function. Type 1 typically occurs in children or teenagers, whereas type 2 diabetes mellitus is commonly seen in middle-aged and older adults who have experienced long-term high blood sugar levels as a result of unhealthy lifestyle and dietary habits. The etiology of Type 1 and Type 2 differs significantly, resulting in distinct causes, symptoms, and management strategies [13,14].

Etiology

The pancreas has two main types of endocrine cells located in the islets of Langerhans: beta cells, responsible for insulin production, and alpha cells, which release glucagon. Beta and alpha cells dynamically adjust their hormone production in response to changes in the glucose environment [15]. When there is an imbalance between insulin and glucagon, the levels of glucose become disproportionately skewed. In the context of DM, there is a lack of insulin and/or a reduced effectiveness of insulin (insulin resistance), resulting in elevated blood sugar levels (hyperglycemia). Type 1 DM is defined by the loss of beta cells in the pancreas, usually as a result of an autoimmune reaction. The outcome is the complete annihilation of beta cells, leading to the absence or extreme scarcity of insulin [16]. Type 2 diabetes mellitus (T2DM) is characterized by a gradual and hidden beginning, in which an imbalance between insulin release and its sensitivity leads to a deficiency in the functioning of insulin. Insulin resistance is a complex condition that typically arises from a combination of factors, with obesity and age being the most prevalent contributors [17].

MODY is a diverse condition characterized by the occurrence of non-insulin-dependent diabetes that is diagnosed in individuals who are typically less than 25 years old. The condition is inherited in an autosomal dominant manner and does not involve the presence of autoantibodies, as is the case in Type 1 Diabetes Mellitus (T1DM). Multiple genes are involved in this condition, specifically mutations in hepatocyte nuclear factor-1-alpha and the glucokinase gene. These mutations are present in 52–65% and 15–32% of MODY cases, respectively [18]. The genetic basis of this disease remains uncertain, as some patients exhibit mutations without ever developing the disease, while others display clinical symptoms of MODY but lack any identified mutation. Gestational diabetes refers to the occurrence of diabetes during pregnancy. The cause of its development is still uncertain. Excessive levels of proinsulin are believed to contribute to the progression of gestational diabetes. Additionally, there is speculation that proinsulin may cause stress to beta cells [19]. Glucose intolerance and diabetes mellitus are commonly observed in individuals with various endocrinopathies. This is because these conditions involve excessive secretion of endogenous hormones that have a glucogenic effect. Idiopathic hemochromatosis is linked to diabetes mellitus because it causes an excessive buildup of iron in the pancreas, leading to the death of beta cells [20].

Epidemiology

On a global scale, approximately 1 in 11 persons are affected by diabetes mellitus, with 90% of them having type 2 DM. The development of Type 1 DM exhibits a progressive growth starting from infancy and reaches its highest point between the ages of 4–6, and then again between ages 10–14. Roughly 45% of youngsters exhibit symptoms prior to reaching the age

of ten. The incidence rate among individuals aged below 20 is approximately 2.3 per 1000. Although most autoimmune disorders are more prevalent in females, there is no observable disparity in the occurrence of childhood T1DM based on gender [21]. Among certain populations, particularly older European males aged 13 and above, there is a higher likelihood of developing T1DM compared to females. The prevalence of Type 1 DM has been steadily rising on a global scale. Annually, rates in Europe, Australia, and the Middle East are experiencing a steady increase of 2% to 5%. T1DM rates in the United States have experienced an annual increase of approximately 2% across various age and ethnic groups, with higher prevalence observed among Hispanic kids. The precise cause of this pattern remains undisclosed [22].

Pathophysiology

A patient diagnosed with diabetes mellitus (DM) is at risk of developing hyperglycemia, which refers to abnormally high levels of glucose in the blood. The etiology of DM might be ambiguous as multiple variables can frequently contribute to the disease. Hyperglycemia by itself can hinder the functioning of pancreatic beta-cells and lead to a decrease in insulin production. As a result, there is a harmful cycle of high blood sugar levels leading to a compromised metabolic condition. In this setting, blood glucose levels exceeding 180 mg/dL are commonly classified as hyperglycemic. However, due to the diverse range of mechanisms involved, there is no definitive threshold. At increased blood glucose levels, patients experience osmotic diuresis because the glucose transporters in the nephron become saturated. While the impact may vary, blood glucose levels exceeding 250 mg/dL are likely to result in symptoms of polyuria and polydipsia [23].

Diagnosis

The diagnosis of T1DM is typically based on a distinct medical history and confirmed by high levels of glucose in the blood (>6.5%). This diagnosis may also involve the presence of antibodies to glutamic acid decarboxylase and insulin. Measuring fasting glucose levels and conducting HbA1c tests are valuable methods for promptly detecting Type 2 DM. If a person's glucose levels are on the borderline, a glucose tolerance test can be performed to assess both their fasting glucose levels and their serum response to an oral glucose tolerance test. Prediabetes, a condition that frequently occurs before the onset of Type 2 DM, is characterized by a fasting blood glucose level ranging from 100–125 mg/dL [24,25].

Prognosis

In 2015, diabetes mellitus ranked as the sixth most common cause of mortality in the United States. The prognosis of diabetes mellitus is greatly affected by the level of glucose control. Prolonged elevation of blood glucose levels significantly enhances the likelihood of developing problems associated with diabetes mellitus. A study revealed that persons with Type 1 DM and Type 2 DM have a higher occurrence of microvascular problems due to prolonged high blood sugar levels. Patients who are able to return to normal glucose levels during the transition from pre-diabetes to full-blown diabetes mellitus have a favorable prognosis and may have the potential to slow down the advancement of the disease [26,27].

Complications

Irrespective of the particular form of diabetes, complications encompass problems related to small blood vessels, large blood vessels, and nerves. These complications include nephropathy, retinopathy, neuropathy, and cardiovascular events, particularly when diabetes is accompanied by additional conditions such as dyslipidemia and hypertension. Approximately 66% of those with DM will succumb to either a myocardial infarction or stroke [28].

AZIRIDINE

Aziridines (Figure 1) are nitrogen-containing, three-membered ring heterocycles, which are widely known as useful reactive intermediates in the synthesis of amino acid derivatives, azomethine ylides or chiral amino alcohols [29–31]. In addition, they are used as chiral auxiliaries and chiral ligands in asymmetric synthesis [32–34] or in fused heterocycles [35]. Besides their importance as reactive intermediates, aziridine-containing compounds possess many biological activities especially antitumor and antibacterial ones, due to the presence of the aziridine ring [36].

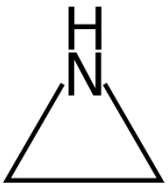


Figure 1. Chemical structure of Aziridine

Aziridines are powerful alkylating agents and there *in vivo* potency is based primarily on toxicity rather than specific activity. The toxicity of aziridine derivatives depends on their structure, and several important natural products, such as mitomycin C [37], porfiromycin [38], and carzinophilin A [39] are well known in the literature as biologically active agents. Physiological effect of mitomycin C relies on aziridine ring opening and interaction with guanine nucleobase of DNA in the alkylation reaction. This leads to covalent interstrand DNA–DNA crosslink formation, inhibition of replication and finally to cell death. Aziridines with the amide function are currently of special interest with Imexon as the well-known representative. Imexon is an anticancer agent active especially against human myeloma cells where it binds to cellular thiols, reduces the amount of glutathione and cysteine in target cells which leads to elevated levels of reactive oxygen species (ROS). As a result, mitochondria swell, cytochrome c is released, caspase-3 and caspase-9 are activated and the cells enter an apoptotic pathway [40,41]. Imexon is also known to disrupt the redox balance of the endoplasmic reticulum which inhibits protein translation and arrests cell growth [42]. In combination with docetaxel, it has been successfully applied in the trial treatment of different cancers [43]. Other work related its activity to suppression of B-lymphocyte activation which suggested Imexon to be useful in the treatment of B-cell or plasma cell lymphomas or neoplasias, certain autoimmune disorders and infection with Rauscher leukemia virus [44,45]. Natural aziridine alkaloids, as well as their lipophilic semi-synthetic, and synthetic analogs, in addition to antitumor activity, have also a strong antibacterial activity [46]. Well known mitomycin-A, mitomycin-C, and mitosane compounds show antimicrobial activity primarily against Gram-positive bacteria and *Klebsiella pneumoniae* [47]. Azirinomycin (3-methyl-2*H*-azirine-2-carboxylic acid) is most active against *Staphylococcus aureus* followed by *Streptococcus faecalis, Proteus vulgaris*, and *Bacillus subtilis*. The methyl ester of azirinomycin exhibited broad spectrum antibiotic activity *in vitro* against both Gram-positive and Gram-negative bacteria. The alkaloidal antibiotic ficellomycin produced by Streptomyces ficellus inhibited growth of Gram-positive bacteria *in vitro* and *in vivo* during treatment of experimental *Staphylococcus aureus* infections in mice. Some naturally occurring peptides containing an aziridine ring, for example madurastatin A1 and B1, consisting of Ser and salicylic acid moieties exhibit antibacterial activity against *Micrococcus luteus* [48]. Anticancer drugs, azinomycin A and B are active against both Gram-positive and Gram-negative bacteria. Two other aziridine derivatives, azicemicin A and B demonstrate strong antibacterial activity mainly against *Mycobacterium smegmatis*, *Escherichia coli* NIHJ, *Corynebacterium bovis*, and *Micrococcus luteus*. A chromoprotein antitumor drug maduropeptin exhibits inhibitory activity against Gram-positive bacteria [49]. There are also known some aziridine, 2-aminoethylaziridine and azirine

complexes of copper (II) and palladium (II) with potent antimicrobial properties against Gram-positive bacteria (*S. aureus, S. epidermidis*, and *E. faecalis*) [50]. Moreover, one derivative of diaziridinyl quinone isoxazole hybrid showed good antibacterial and anti-biofilm activities with very low MIC values against *S. aureus* and *B. subtilis* and it also exhibited antifungal activity against *Candida albicans*. Many other natural or synthesized compounds with different structures like lipids, steroids, amino acids and peptides containing the aziridine moiety have also shown biological activity and are promising candidates for the development of new drugs against several diseases.

Preparation of aziridines

Several methodologies have been described for the preparation of aziridine derivatives. Kappe and co-workers reported a continuous flow bromodimethylsulfonium bromide (2, BDMS) generation/alkene sulfobromination/aziridination sequence for preparing functionalized aziridines (4). BDMS (2) is a versatile reagent employed in organic synthesis as a stoichiometric reagent or as a catalyst. However, upon storage, it has to be treated as a hazard since it is corrosive and sensitive to heat and moisture, releasing molecular bromine (Br_2) upon contact with water. For this reason, the authors decided to develop a continuous flow procedure for the safe generation and utilization of BDMS (2). In addition, by using a flow chemistry approach, the potential hazard from the accumulation of this reagent in batch can be overcome, as the reagent is immediately consumed upon generation. Thus, BDMS (2) was prepared for the first time in flow, starting from HBr and DMSO, and was then further reacted with primary amines (3) to yield 2-phenyl aziridines (4) in a 3-step sequential process [51].

Gonnade and co-workers documented the syntheses of aziridine 7 which was then used for the preparation of the well-known Tamiflu (8), also called oseltamivir phosphate, which is used as a medicine to cure both influenza A and B and to prevent the spread of influenza. In one of the described procedures, cis-aziridine (7) was employed as a chiral synthon (Figure 2) [52].

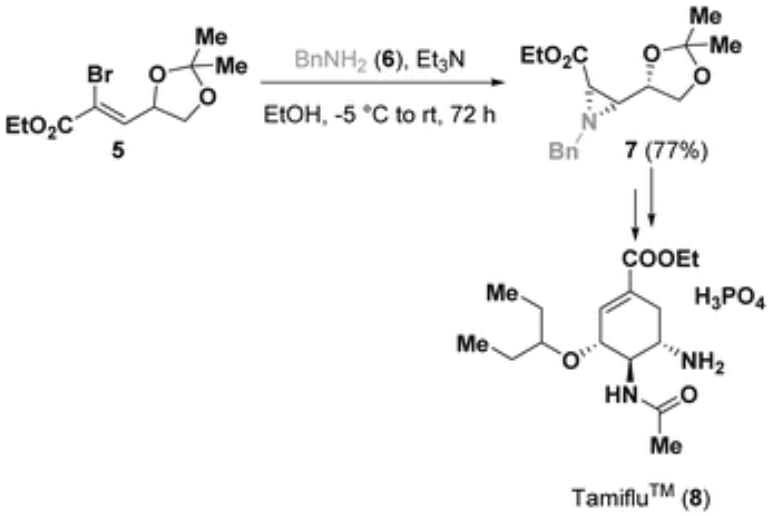


Figure 2. Aziridination of vinyl bromide 5 for preparing Tamiflu (8)

Watson and co-workers reported in 2022 the asymmetric synthesis of aziridines (13) via enantioselective protonation of catalytically generated enamines by using chiral Brønsted acids such as 11 ((S)-TCYP). The aziridine ring (13) is achieved after treating the so-formed α-chloroamine 12 with a base in a one-pot process (Figure 3) [53].

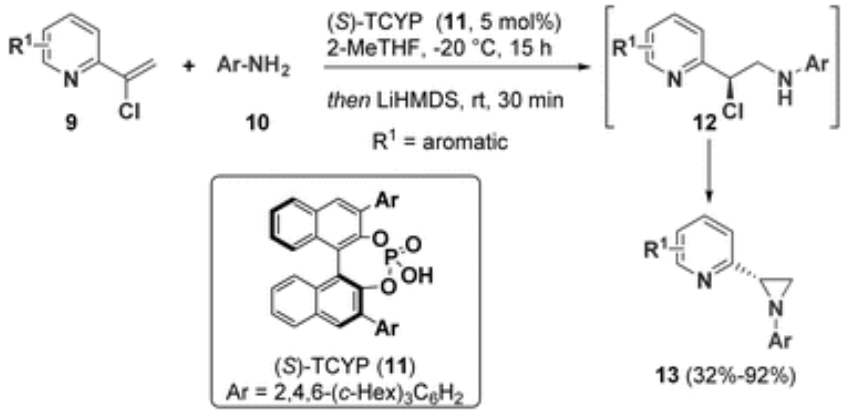


Figure 3. Asymmetric synthesis of aziridines.

Catalysis is one of the most used methodologies for preparing aziridine derivatives. Indeed, a lot of pathways have been described by using different catalysts [54]. Among them, nickel was employed and in 2022 Wu and co-workers reported a nickel-catalyzed aminofluoroalkylative cyclization of unactive alkenes (15) with iododifluoromethyl ketones (14) to afford versatile difluoroalkylated nitrogen-containing hetorocycles including aziridines (18). According to the authors, the transformation proceeds through a radical mechanism. Upon treatment with the Ni-catalyst and base, iododifluoromethyl ketones (14) are transformed into intermediates such as 16, which react with *N*-allyl anilines (15) to give radical species 17, from which the aziridine products (18) are obtained (Figure 4) [55].

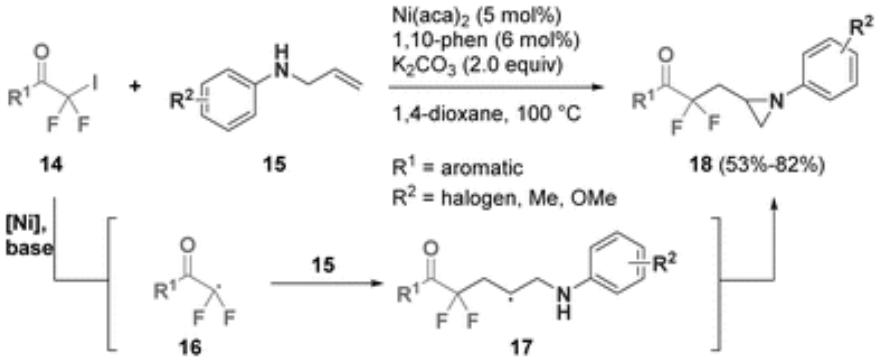


Figure 4. Nickel catalyzed aziridination of unactive alkenes.

Berhal *et al*. documented the iron-catalyzed reaction between alkenes (20) and hydroxylamine derivatives (19) to give aziridines (22). In particular, they used simple iron (II) sources and readily available ligands rendering the reaction conditions more sustainable (Figure 5) [56]. Considering the mechanism of the reaction, the *in situ* generated iron catalyst [Fe] provides an iron–nitrene intermediate (24 or 25) after reacting with the hydroxylamine derivative 19, releasing an equivalent amount of carboxylic acid (23). Since metal–nitrene complexes exist in two different spin states, the authors consider two possible reaction pathways. If the metal–nitrene complex predominantly exists in its singlet state (24), a concerted (2+1) cycloaddition could take place, leading to a stereospecific process. On the other hand, if the iron–nitrene complex is in its triplet state (25), a radical addition followed by a radical-based ring closure could occur. In this case, due to the multistep procedure, no stereoselectivity should be observed.

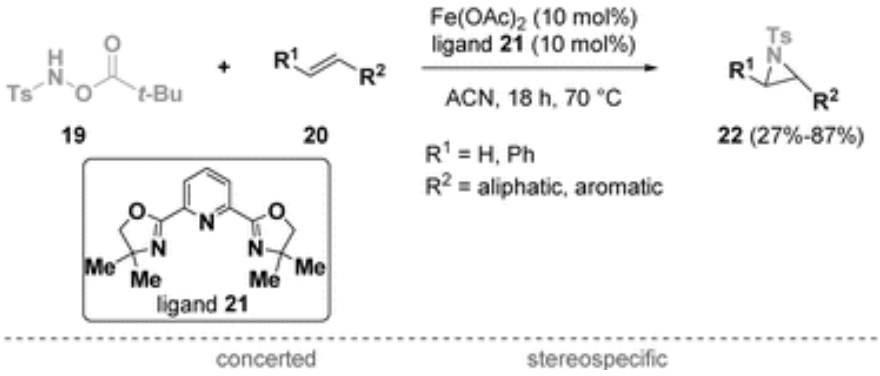


Figure 5. Reaction of alkenes with hydroxylamines for preparing aziridines.

Driver *et al*. described an intermolecular Rh_2(II)-catalyzed aziridination of olefins (28) using anilines (27) as non-activated nitrogen atom precursors and an iodine (III) reagent (30) as the stoichiometric oxidant. During the process, the *N*-aryl nitrene fragment is transferred from the intermediate iminoiodinane (31) to the Rh (II) carboxylate catalyst (29). The reaction proved to be stereospecific and chemo- and diastereoselective to produce *N*-aryl aziridine (33) as the only amination product (Figure 6) [57].

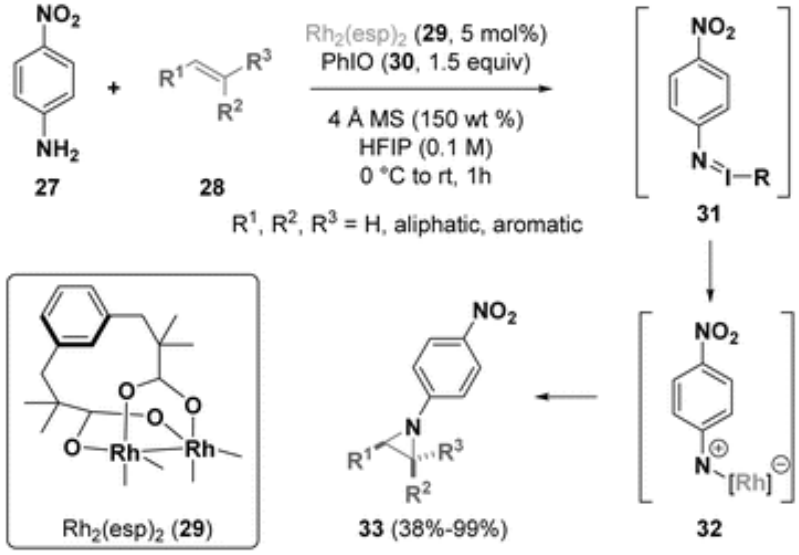


Figure 6. Intermolecular Rh2(II)-catalyzed aziridination of olefins.

After describing in 2022 the use of (NHC)M (M = Cu, Ag, Au) cores as catalysts for the olefin aziridination reaction [58], recently, Perez and co-workers reported the copper-catalyzed aziridination of olefins (Figure 7) [59]. The authors highlighted the important role of the halide characterizing the copper catalyst. Indeed, they demonstrated via mechanistic studies that the employed copper(I) complexes (TTM) CuCl (35) and [(TTM)Cu-(NCMe)]PF_6 (36) (TTM = tris(triazolyl)methane ligand) possess different behaviors, from catalytic and mechanistic points of view, depending on the presence or absence of the chloride ligand bonded to the metal center. If coordination is present, the limiting step of the reaction concerns the formation of the carbon–nitrene bond (39). In case the chlorine atom is not present, the highest barrier corresponds to the formation of the copper–nitrene intermediate (40). Chen and co-workers selected bis(pyrazolyl)borate Cu(I) complexes (43) as catalysts for the aziridination of olefins. The reaction was carried out starting from a suitable styrene (41) and [*N*-(sulfonyl) imino]phenyliodinane (42). During the catalytic process, a nitrene is generated and added to the double bond.

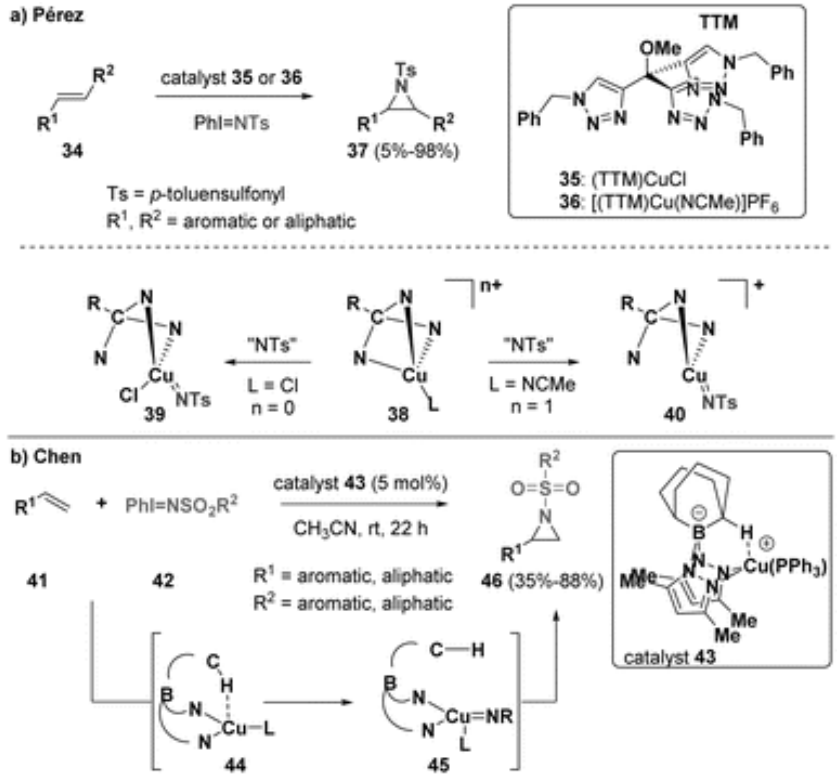


Figure 7. Copper-catalyzed olefin aziridination.

Dauban *et al*. employed C4-symmetrical dirhodium (II) tetra carboxylates (48) as catalysts for the asymmetric intermolecular aziridination of substituted alkenes (47) with *p*-tBu-phenylsulfamates 49 ($TBPhsNH_2$). The authors proposed a two-spin-state mechanism, involving a triplet Rh–nitrene species as the key intermediate (50) to direct the approach with stereo control and for the activation of the substrate. DFT studies support the proposed mechanism. An enantiomeric excess of up to 99% was observed (Figure 8) [60].

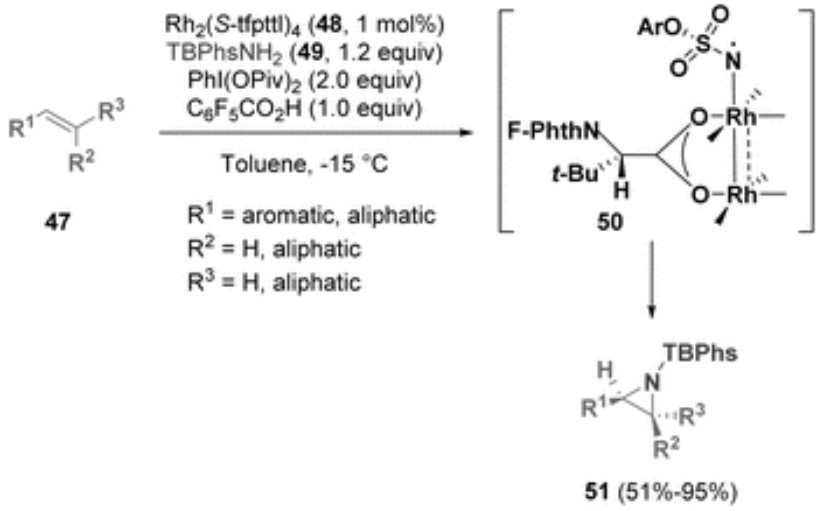


Figure 8. Asymmetric intermolecular aziridination of substituted alkenes.

Zirconium has also been employed as a catalyst for the synthesis of aziridine derivatives. Moura-Letts and co-workers described the aziridination of alkenes (41) by using chloramine T [61] (52) as the quantitative source of nitrogen. Supported by kinetics and model reaction studies, the authors propose that the reaction mechanism involves the formation of a zirconooxaziridine complex (53) as the active catalyst (Figure 9) [62].

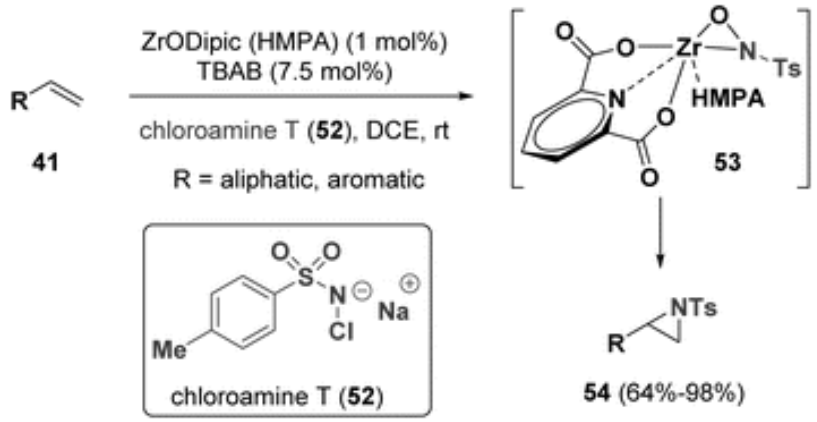


Figure 9. Zirconium catalyzed synthesis of aziridines.

Jat and co-workers reported the iron (II) catalyzed direct N–H/N–Me aziridination of olefins (55) employing *O*-aryl sulfonyl hydroxylamines (56). The one-pot methodology proved to be stereo- and regioselective, yielding a variety of unactivated aziridines (57) in good to excellent yields (Figure 10) [63].

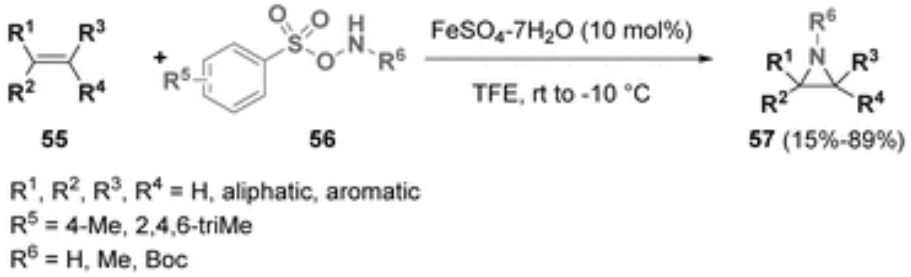


Figure 10. Iron (II) catalyzed direct N–H/N–Me aziridination of olefins.

Mixed approaches of photo- and metal-catalysis have also been reported for the synthesis of aziridines [64]. Koenigs *et al*. described the preparation of trifluoro methylated aziridines (62) starting from fluorinated olefins (58) and iodinanes (59), which undergo oxidative quenching in the presence of a Ru(bpy)3Cl_2 catalyst (60), releasing a nitrene radical anion (61). Computational studies confirmed that the nitrene radical (61) serves as a reactive intermediate in direct aziridination reactions (**Figure 11**) [65].

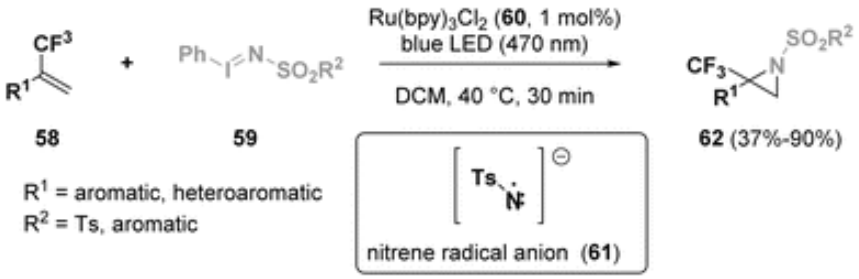


Figure 11. Photocatalytic amination reaction for preparing trifluoro methylated aziridines.

Zhang and co-workers employed the carbonyl azide TrocN3 (65, 2,2,2-trichloroethoxycarbonyl azide), which is a potent nitrogen radical precursor for the aziridination of olefins (64). Chiral *N*-carbonyl aziridines (66) were prepared at room temperature in high yields with excellent enantioselectivities. The obtained *N*-Troc-aziridines (66) can be opened by different nucleophiles, achieving a variety of chiral amines with excellent stereospecificity (89–100% es) (Figure 12) [66].

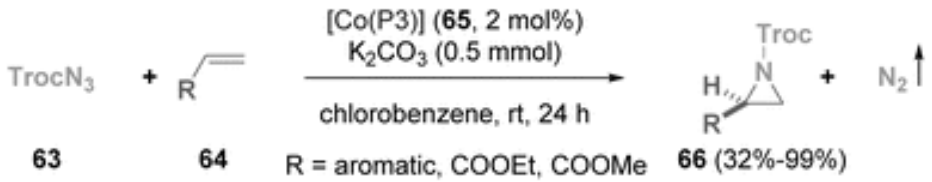


Figure 12. Olefin aziridination via Co (II)-based Metallo radical catalysis.

The major part of the reported methodologies for synthesizing aziridines relies on the transition-metal catalyzed reactions of alkenes with nitrene precursors or imines with carbene precursors [67]. However, these pathways are limited by the use of hazardous and explosive carbene and nitrene precursors as well as additional steps for diazo synthesis and transition-metal residue removal. For these reasons, the development of more sustainable methodologies has been pursued by scientists [68]. Different pathways employing electrochemical activation to facilitate oxidative cyclization were developed [69]. Nevertheless, significant limitations and challenges are still to be overcome. Recently, the employment of thianthrenium salts was reported to be an alternative methodology [70]. In 2021, Wickens *et al*. documented the electrochemical transformation of non-activated alkenes (67) into metastable, dicationic intermediates 69 and 70 that undergo aziridination with primary amines (71) under basic conditions. This new approach allows the preparation of diverse aziridine building blocks (72) bearing sensitive functional groups, such as allyl and cyano groups, that are challenging to access through more conventional approaches (Figure 13) [71].

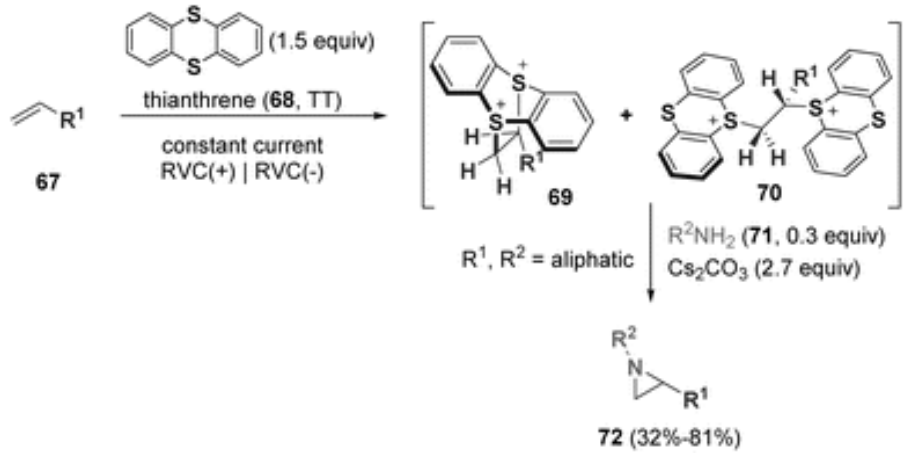


Figure 13. Electrochemical transformation of unactivated alkenes into aziridines.

In 2022, Shu and co-workers developed a straightforward aziridination pathway using primary amines (73) with alkenes substituted with thianthrenes (74). The methodology works well for terminal, internal, aromatic, and aliphatic alkenes [72]. In comparison with the electrochemical thianthrene-mediated aziridine formation, which only allows functionalization of terminal olefins with primary amines [73], this conventional approach allows aziridination of both terminal and internal alkenes. Furthermore, it is not limited to the use of primary amines, but also tolerates primary amides, carbamates, and sulfonamides. The use of active methylene instead leads to cyclopropanation, making the methodology even more versatile (Figure 14) [74].

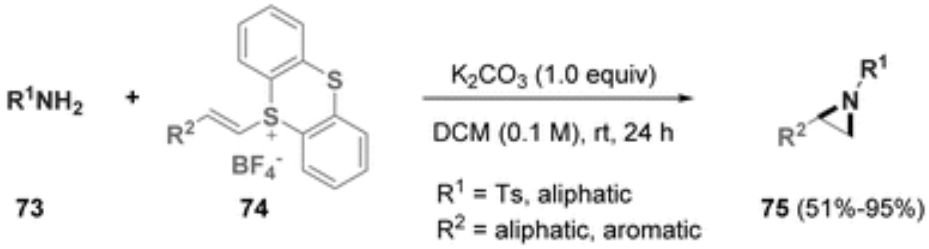


Figure 14. Aziridination pathway using free primary amines and alkenes substituted with thianthrenes.

The chemo selective aziridination of styrenes (76) performed in the presence of hydroxylamine derivatives (77) via cobalt single-atom catalysis was reported by Tang and co-workers in 2023. The developed methodology is carried out under mild conditions and has a wide scope and high atom economy. Several natural products and drug-derived olefins have also been subjected to aziridination (Figure 15) [75].

Figure 15. Aziridination pathway via cobalt single atom catalysis.

Recent Reports

Qazi *et al*., 2023 analyzed the antihyperglycemic and antioxidant roles of the 1,3,4-oxadiazole derivative with its toxicity. Diabetes was induced through intraperitoneal administration of alloxan monohydrate at 150 mg/kg in rats. Glimepiride and acarbose were used as standards. Rats were divided into groups of normal control, disease control, standard, and diabetic rats (treated with 5, 10, and 15 mg/kg of 1,3,4-oxadiazole derivative). After 14 days of oral administration of 1,3,4-oxadiazole derivatives (5, 10, and 15 mg/kg) to the diabetic group, the blood glucose level, body weight, glycated hemoglobin (HbA1c), insulin level, antioxidant effect, and histopathology of the pancreas were performed. The toxicity was measured by estimating liver enzyme, renal function, lipid profile, antioxidative effect, and liver and kidney histopathological study. The blood glucose and body weight were measured before and after treatment. Alloxan significantly increased blood glucose levels, HbA1c, alanine transaminase, aspartate aminotransferase, urea, cholesterol, triglycerides, and creatinine. In contrast, body weight, insulin level, and antioxidant factors were reduced compared to the normal control group [76].

Jagadeesan *et al*., 2023 indole-3-heterocycles were synthesized via functionalizing of 3-(4-chlorobutyl)-1*H*-indole-5-carbonitrile with different triazoles, tetrazole, thiazole and mercapto benzothiazole with a base. Analytical techniques like ^{1}H, ^{13}C-NMR, HRMS, and FTIR spectroscopy characterized the newly synthesized indole heterocycles. These indole compounds functionalized were investigated for antidiabetic properties and antioxidant potentials on varying the side-chain. The synthesized indole compounds exhibited varying inhibition compared to α-amylase standard with IC_{50} values ranging between 6.44±1.14 µg/mL and 29.27±1.06 µg/mL competing with standard acarbose (IC_{50} = 5.7 ± 0.99 µg/mL). Among the series of eleven compounds, higher activity of IC_{50} = 6.44 ± 1.14 µg/mL was exhibited by compound against α-amylase [77].

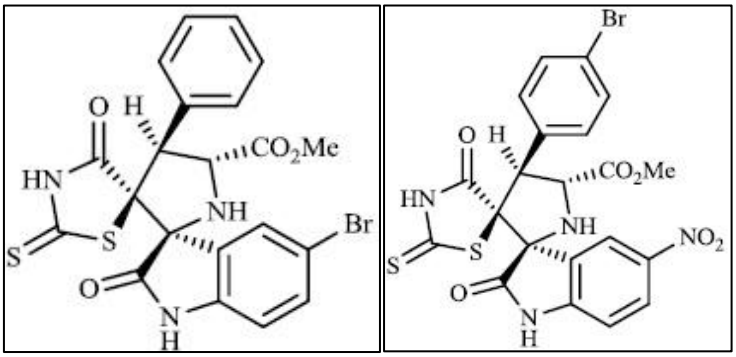
Waheed *et al*., 2022 reported that three ketone derivatives of succinimides were synthesized based on Michael addition and characterized using NMR. All the synthesized compounds were checked for their *in vitro* α-amylase and α-glucosidase inhibitory activities. Further the synthesized compounds were also explored for their antioxidant activities, *i.e.*, DPPH and ABTS assays. Based on the *in vitro* results, the synthesized compounds were further evaluated for *in vivo* antidiabetic activity. The synthesized compounds were (2-oxocyclohexyl)-1-phenylpyrrolidine-2,5-dione (BW1), benzyl-3-(2-oxocyclohexyl) pyrrolidine-2,5-dione (BW2), and (4-bromophenyl)-3-(2-oxocyclohexyl) pyrrolidine-2,5-dione (BW3). BW1 showed the highest inhibitory activity for DPPH causing 83.03 ± 0.48 at 500 μg/mL with IC_{50} value of 10.84 μg/mL and highest inhibitory activity for ABTS causing 78.35 ± 0.23 at 500 μg/mL with IC_{50} value of 9.40 μg/mL against ascorbic acid used as standard. BW1 also exhibited the highest activity against α-amylase and α-glucosidase inhibition causing 81.60 at concentrations of 500 μg/mL with IC_{50} value of 13.90 μg/mL and 89.08 ± 1.04 at concentrations of 500 μg/mL with IC_{50} value of 10.49 μg/mL, respectively, against the standard drug acarbose [78].

Vaddiraju *et al*., 2021 stated the utility of new series of novel pyrazoline fused indole derivatives were synthesized from indole and substituted acetophenone by the 4-step process. In the first step indole and dimethyl formamide were coupled by using phosphorous oxychloride and NaOH to prepare the compound Indole-3-aldehyde. In the second step, compound 1 was condensed with substituted aetophenone to synthesis the compound 2 chalcones. In the third step chalcones were coupled with semicarbazide or thiosemicarbazide to synthesis the compound 3. In the final step, compound 3 were coupled with indole-3-aldehyde to prepare the final product of R-substituted *N*-((1*H*-indol-3-yl)methylene)-5-(1*H*-indol-3-yl)-3-phenyl-4,5-dihydro-1*H*-pyrazole-1-carboxamide and R-substituted *N*-((1*H*-indol-3-yl)methylene)-5-(1*H*-indol-3-yl)-3-phenyl-4,5-dihydro-1*H*-pyrazole-1-carbothioamide. The compounds were screened for anti-diabetic activity by *in-vitro* and *in-vivo* methods. In *in-vivo* method, compounds have exhibited moderate anti-diabetic activity as that of standard drug, glibenclamide [79].

Kanwal *et al*., 2021 within the sight of the coupling reagent 1,1-carbonyldiimidazole, indole-3-acetamides were delivered by joining indole-3-acidic corrosive with various subbed anilines. Distinctive spectroscopic strategies, for example, electron ionization-mass spectroscopy was utilized to find the designs of manufactured mixtures (High-Resolution Electron Ionization Mass Spectrometry (HREI-MS). The anti-hyperglycemic and cell reinforcement properties of these substances were examined. Compound (IC_{50} = 1.09 μM) was the most dynamic of the gathering, with IC_{50} (Half-maximal Inhibitory Concentration) upsides of 0.35 μM and 0.81 μM in DPPH (2,2-diphenyl-1-picrylhydrazyl). *In silico* tests affirmed the restricted interchanges of created particles with the compound's powerful site. Different lead particles were distinguished as potential anti-hyperglycemic and cell support experts in the flow research [80].

Fattaheian-Dehkordi *et al*., 2021 found that restorative plants, including extricates and cleansed dynamic parts, have a significant capacity in blood glucose guideline. In view of the great to-brilliant results depicted in the writing, they've turned into a significant hotspot for making and delivering against Diabetes mellitus prescriptions and enhancements. The positive outcomes incited us to return to their viability to prepare for the making of home-grown enemy of diabetic drugs [81].

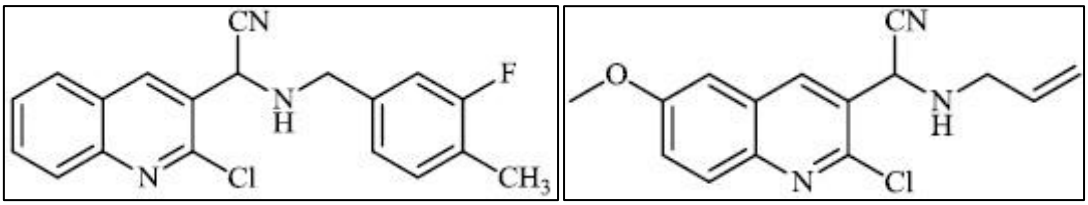
Toumi *et al*., 2021 synthesized rhodamine-fused Spiro oxindole pyrrolidine hybrids with IC_{50} values of 1.49±0.10, 1.50±0.07, and 1.57±0.10 μM, respectively, as new α-amylase inhibitors. The majority of the synthesized compounds demonstrated high α-amylase inhibition [82].



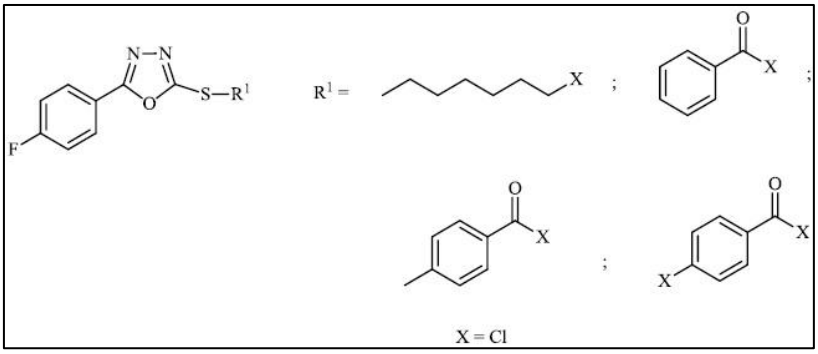
Mohamed *et al*., 2020 under green science conditions, a progression of new sulfonamide and Thiazolidinedione subsidiaries were delivered from amino acids connected triazole subordinates. The previously mentioned substances had solid enemy of diabetic activity *in vitro* and *in vivo*. The range and natural information were utilized to portray the constructions of the newfound mixtures [83].

Jia *et al*., 2020 produced and tested highly effective sesquiterpene lactone parthenolide against cancer. Several semicarbazone and thiosemicarbazone derivatives of parthenolide were tested for their anticancer efficacy to see if they may enhance the compound's already impressive biological activity. Many of the derivatives evaluated *in vitro* exhibited more cytotoxicity than parthenolide when used against 5 human tumor cell lines. The anticancer efficacy of five substances was further investigated in mice. Positive anticancer activity against mouse colon tumors and minimal immunological toxicity were observed for compound in an *in vivo* study. Compound's effects on cell apoptosis and cell cycle distribution were also investigated. Multiple interactions between compound and NF-κβ were found through molecular docking studies. Our results highlight semicarbazones as a novel class of chemicals with intriguing anticancer action [84].

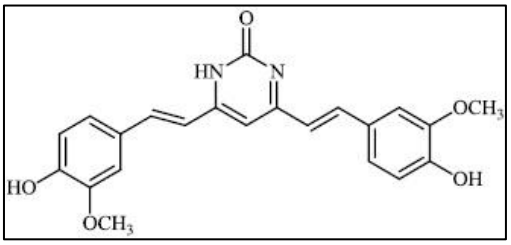
Dalavai *et al*., 2020 synthesized quinolinyl amino nitriles and evaluated them for different biological properties. Compounds demonstrated promising antidiabetic activity with IC_{50} value of 100 µg/mL [85].



Mamatha *et al*., 2020 synthesized mercaptooxadiazole derivatives as antidiabetic agents with 62% inhibitory potency and anti-tubercular agents with an MIC value of 1.6 µg/mL. Compounds with benzoyl, *p*-chlorobenzoyl, heptyl, and *p*-methylbenzoyl substituents displayed moderate activity against diabetes [86].



Nabil *et al*., 2018 synthesized curcumin-based heterocyclic compounds with IC_{50} values of 200.2 μM and 95.5 μM, respectively, as potent antidiabetic agents. The authors revealed that pyranone and pyrimidinone derivatives of curcumin exhibited high potential against diabetes [87].

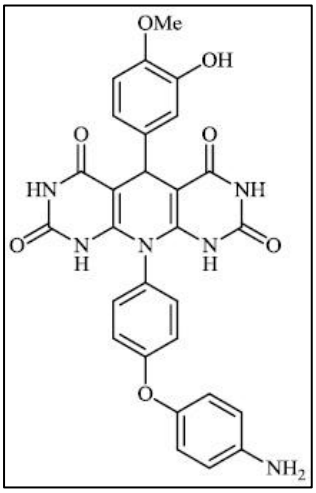


Kumar *et al*., 2017 studied spiro carbon in their molecules have proven their biological activity in agriculture and medicine. The present paper describes the synthesis, characterization of five newly synthesized Spiro- compounds characterized by means of chromatography, FTIR, ^{1}H-NMR and Mass spectral analysis. The author carried *in vitro* anti diabetic methods like alpha amylase and alpha glucosidase methods for anti-diabetic activity of tilted compounds. The investigation of anti-diabetic activity revealed that the test compounds of Spiro compounds showed favorable anti diabetic activity. Among the titled compounds some were having potent antidiabetic activity [88].

Manoharan *et al*., 2017 found the counter diabetic impact of indoline subordinates was shown in this review utilizing-amylase restraint movement. The forerunner *N*-(4-aminophenyl) indoline-1-carbothiamide was utilized to make a progression of indoline subordinates. Fourier-Transform Infrared Spectroscopy (FT-IR) was utilized to affirm the created compounds. The norm-amylase restraint test was utilized to test the anti-diabetic adequacy of created indoline subsidiaries *in vitro* [89].

Elham *et al*., 2016 utilized analytical and spectroscopic techniques, including elemental analysis, infrared spectroscopy, and nuclear magnetic resonance spectroscopy, were used to confirm the structures of a series of hydroxyl semicarbazone derivatives of substituted diaryl ketones and acetophenones that were produced. Excellently pure hydroxysemicarbazones were obtained via a condensation reaction between *N*-hydroxy semicarbazide and substituted diaryl ketones or acetophenones. *S. aureus, E. coli, Pseudomonas aeruginosa, Klebsiella pneumoniae*, and *Micrococcus luteus* were some of the bacterial strains tested after the produced hydrazones were tested for their inhibitory activity. Compounds showed the most bioactivity among the derivatives examined [90].

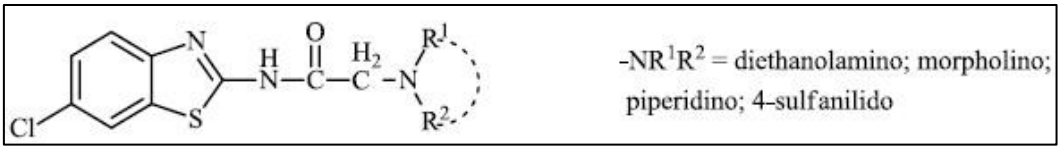
Panahi *et al*., 2013 synthesized novel pyrimidine-fused hybrids with IC_{50} values of 148 μM and 9 μM, respectively, as strong antidiabetic α-glucosidase inhibitors. Both compounds displayed excellent inhibitory activity against yeast α-glucosidase. In addition, compound also exhibited inhibitory activity against mouse α-glucosidase [91].



Ali *et al*., 2012 tested vanillin semicarbazone for its anticancer effects in a study using Swiss albino mice bearing the Ehrlich ascites carcinoma (EAC) cell line. The effectiveness of VSC was evaluated by measuring the inhibition of cell growth, the reduction of tumor weight, the extension of survival time, and the changes in depleted hematological parameters after intraperitoneal administration of the compound at three doses (5, 7.5, and 10 mg/kg i.p.). All of these measures were also analyzed using a typical medication dose of 0.3 mg/kg (i.p.) bleomycin. The most effective dose was 10 mg/kg (i.p.), which was shown to be quite similar to the effectiveness of 0.3 mg/kg (i.p.) bleomycin. VSC was shown to have low toxicity toward the host organism [92].

Islam *et al*., 2012 synthesized two Schiff bases, acetophenone semicarbazone (ASC) and benzophenone semicarbazone (BSC) and described in order to investigate their anti-inflammatory and analgesic properties in swiss albino mice. Throughout the course of the investigation, two doses of the test substances, 25 and 50 mg/kg (p.o.) for each, were selected. The 'carrageenan induced mice paw edema inhibition' approach was used to assess the compounds' ability to reduce inflammation. Both the 'acetic acid induced writhing' and the 'tail immersion' tests were used to ascertain the analgesic efficacy. All information was compared to those for reference medications given at a dose of 10 mg/kg (p.o.). Anti-inflammatory and analgesic effects have been observed with both ASC and BSC. At 50 mg/kg (p.o.), the test compounds' anti-inflammatory and analgesic actions were quite like those of conventional medicines at 10 mg/kg (p.o.). Both ASC and BSC have been shown to be effective painkillers and anti-inflammatory [93].

Mariappan *et al*., 2012 synthesized benzothiazole derivatives and explored their antidiabetic activity. In diabetic rats, the synthesized compounds caused a greater drop in blood glucose compared to other compounds. The LD_{50} values of the synthesized compounds were estimated to be in the range of 100-1000 mg/kg, respectively [94].



CONCLUSION

Aziridine has emerged as a promising scaffold in the design and development of novel anti-diabetic agents due to its unique structural and pharmacological attributes. The inherent ring strain of aziridine facilitates diverse chemical modifications, enabling the synthesis of potent bioactive derivatives with enhanced selectivity and efficacy. Numerous studies have

demonstrated the potential of aziridine-based compounds in targeting key pathways associated with diabetes mellitus, including dipeptidyl peptidase-4 (DPP-4) inhibition, α-glucosidase modulation, aldose reductase suppression, and peroxisome proliferator-activated receptor (PPAR) activation. Furthermore, their ability to mitigate oxidative stress and prevent the formation of advanced glycation end-products (AGEs) highlights their role in managing diabetic complications. Despite these advancements, challenges remain in optimizing the safety, stability, and pharmacokinetics of aziridine derivatives. Concerns related to cytotoxicity, metabolic stability, and off-target effects must be addressed through rational drug design and rigorous preclinical evaluations. Future research should focus on structure-activity relationship (SAR) studies to fine-tune the biological properties of aziridine analogs while minimizing adverse effects. Additionally, computational approaches, including molecular docking and in silico pharmacokinetic modeling, can facilitate the identification of lead candidates with enhanced drug-like properties. Overall, aziridine represents a versatile and innovative scaffold with immense therapeutic potential for diabetes management. With continuous advancements in medicinal chemistry and drug discovery strategies, aziridine-based compounds could serve as a foundation for next-generation anti-diabetic therapeutics, offering improved efficacy and patient outcomes.

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