# Review Of Benzothiazole-Coumarin Derivatives As Anti-Diabetic Agents

**Deepthy Chandran[1], Dr. Umamaheshwari[2*], Gomathi Vengatachalam[3]**

*[1*]Vinayaka mission's college of Pharmacy, Salem, Tamil Nadu, India*
*[2*]Department of Pharmaceutical Chemistry, Vinayaka missions college of pharmacy*
*[3]Department of pharmacology, Vinayaka Mission's College of Pharmacy, Vinayaka Mission's Research Foundation (Deemed to be university), Ariyanoor, Salem, Tamil Nadu -636008, India*

**KEYWORDS**
Benzothiazole, Coumarin, Diabetes Mellitus, α-Glucosidase Inhibition, Insulin Secretion

**ABSTRACT**
Diabetes mellitus is a chronic metabolic disorder characterized by insulin resistance, impaired insulin secretion, and persistent hyperglycemia. Conventional anti-diabetic therapies, including metformin, sulfonylureas, and DPP-IV inhibitors, effectively control blood glucose levels but have limitations such as side effects, long-term efficacy concerns, and lack of β-cell protection. As a result, novel multi-targeted compounds with improved pharmacological profiles are being explored. This review evaluates the potential of benzothiazole-coumarin derivatives as multi-targeted anti-diabetic agents, focusing on their mechanisms of action, enzyme inhibition, structure-activity relationships (SAR), pharmacokinetics, and therapeutic implications. A comprehensive literature review was conducted using databases such as PubMed, Scopus, Web of Science, and Google Scholar. Studies were selected based on their relevance to benzothiazole and coumarin derivatives, α-glucosidase and DPP-IV inhibition, insulin secretion, and antioxidant properties.
Benzothiazole-coumarin hybrids enhance insulin secretion via AMPK activation, inhibit α-glucosidase and DPP-IV, and improve insulin sensitivity. Their antioxidant and anti-inflammatory effects offer additional β-cell protection, making them superior to many existing treatments.
Benzothiazole-coumarin derivatives represent a promising therapeutic approach for diabetes management. However, further preclinical and clinical studies are required to establish their safety, efficacy, and pharmacokinetic stability.

## Introduction

The metabolic condition known as diabetes mellitus persists when blood glucose remains elevated because of problems with insulin release or insulin response or defects in both (American Diabetes Association, 2013). The number of adults living with diabetes has surged throughout the past decades based on International Diabetes Federation (IDF) projections of 537 million in 2021 which will grow to 643 million by 2030 and 783 million by 2045 (Kumar et al., 2024). The medical condition leads to serious health problems and death among patients because of cardiovascular disease alongside neuropathy nephropathy and retinopathy (Kulkarni et al., 2024).

The treatment of diabetes has been revolutionized by various available therapies including insulin therapy and metformin alongside sulfonylureas and thiazolidinediones (TZDs) and dipeptidyl peptidase-4 (DPP-IV) inhibitors and sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor (GLP-1R) agonists (Pathak et al., 2024; Su et al., 2023). The current anti-diabetic therapies have important drawbacks which include safety issues and side effects. Various anti-diabetic medications produce adverse effects for patients. The use of Metformin leads to gastrointestinal side effects yet sulfonylureas along with insulin create an elevated risk of hypoglycemia (Stoica, 2020). The use of TZDs leads to weight gain as well as edema and increases cardiovascular dangers (Chang et al., 2011). The long-term use of both DPP-IV inhibitors and SGLT2 inhibitors requires increased dosage adjustments or medicinal combinations because their effectiveness wanes over time according to Makrilakis et al. (2019) and Yin et al. (2022). The current treatment approaches only achieve glycemic control without addressing β-cell preservation or regeneration needs for long-term disease modification (Marchetti et al., 2009). The high cost of GLP-1 receptor agonists and insulin analogs restricts their accessibility to patients in low- and middle-income countries according to Hamed et al. (2024) and Silver et al. (2018). New compounds with improved efficacy levels, reduced side effects and extended therapeutic advantages such as β cell protection, antioxidant and enzyme inhibition capabilities are needed to overcome the existing therapeutic constraints.

Natural along synthetic small molecules are the subjects of current research as potential treatments for anti-diabetic therapy deficiencies (Uppal et al., 2018). The research on diabetes is mainly on the development of multi-targeted drugs to control blood glucose and provide additional therapeutic benefits such as β cell regeneration and enzyme inhibition with oxidative stress reduction (Sivakumar et al., 2021). Strong anti-

diabetic effects of the heterocyclic compounds including benzothiazole and coumarin derivatives have been reported through different mechanisms of action. It is known that heterocyclic compounds have pharmacological activity that inhibits essential glucose metabolism enzymes α-glucosidase and DPP-IV (Lacroix et al., 2013). Enhancement of insulin sensitivity and glucose uptake in peripheral tissues (Morley et al., 2015). They have antioxidant and anti-inflammatory properties that protect β cells against oxidative stress (Li et al., 2014). Properties of the drug encourage β cell regeneration and sustained disease modifications (Wang & Wang, 2017). These compounds have multiple pathway targeting capabilities and are therefore important drug candidates for the development of anti diabetic therapy. Benzothiazole and coumarin heterocyclic scaffolds have gained positions in medicinal chemistry due to their broad pharmacological activity against anti-diabetic, anti-inflammatory effects and antimicrobial, anticancer properties (Annunziata et al., 2020).

According to Yadav et al (2023), Benzothiazole Derivatives are strong biological active because they insert into the hydrophobic enzyme area and increase receptor attachment as well as metabolic stability. According to Dhameja and Gupta (2019), these compounds have been documented to have alpha glucosidase inhibitory effects through multiple studies and thus they are promising agents for controlling postprandial hyperglycemia. According to Li et al. (2017), molecules based on coumarin improve insulin secretion, increase glucose uptake and have robust antioxidant effects. These compounds develop strong hydrogen bonds with essential metabolic enzymes, thus making their pharmacological relevance increase (Stefanachi et al., 2018).

Hybrid derivatives increase the therapeutic value because they simultaneously target two distinct pharmacological sites with benzothiazole and coumarin structures. Research by Proença et al. (2022) indicates that the hybrid compounds have superior inhibitory abilities against α-glucosidase and DPP-IV than traditional inhibitor acarbose. Hybrid derivatives possess antiinflammatory properties as well as antioxidant effects, and these both are conducive to β cell protection and hence they could be potential therapeutic candidates.

The review thoroughly examines benzothiazole coumarin derivatives as anti diabetic agents, and their action mechanisms, structure activity relationships (SAR) as well as their pharmacokinetic properties and medical implications. The mechanistic basis of benzothiazole-coumarin derivatives in insulin secretion, enzyme inhibition, glucose uptake, and oxidative stress reduction. It also highlights the pharmacokinetic and pharmacodynamic profile of these compounds.

## Methodology

### Literature search strategy

A wide ranging and appropriate dataset was obtained from multiple electronic databases such as PubMed, Scopus, Web of Science, ScienceDirect and Google Scholar. The database information used is from PubMed and Scopus Web of Science and ScienceDirect as well as Google Scholar to cover as much as possible in many areas of disciplinary fields such as medicinal chemistry and pharmacology molecular biology and clinical research. The search strategy combined medical subject headings (MeSH) with free-text terms by using primary keywords “Benzothiazole” and “Coumarin” along with “Benzothiazole-coumarin derivatives” and “Anti-diabetic agents” and “Diabetes mellitus treatment” and “Hypoglycemic activity.” The search incorporated Boolean logic through the following expressions: “Benzothiazole and diabetes” together with “Coumarin and diabetes” and “Benzothiazole-coumarin and α-glucosidase inhibition” and “Benzothiazole or Coumarin and DPP-IV inhibition” and “Structure-Activity Relationship and Anti-diabetic.” The research parameters were limited to English-language studies which included experimental, preclinical, and clinical research while giving preference to full-text studies. Hundreds of appropriate research articles were discovered initially through these search methods but further restrictions based on eligibility criteria helped narrow down the selection to high-quality publications.

### Inclusion and Exclusion Criteria

Studies that investigated benzothiazole and/or coumarin derivatives as anti-diabetic potential agents while being published in peer-reviewed journals and conducting preclinical evaluations of these compounds made up the inclusion criteria set. The research analyzed both clinical studies involving benzothiazole-coumarin derivatives in human participants and molecular docking and computational modeling which illustrated their mechanism of action together with studies published between 2005 to 2025 to remain current. The study excluded research that was unrelated to diabetes treatment along with reviews and meta-analyses without original data and studies without pharmacological or mechanistic insights. The research excluded studies written in languages other than English unless English translations were available while studies that lacked diabetes model pharmacological validation and animal studies were excluded.

**Time Frame**

Comprehensive literature research reviewed articles about benzothiazole-coumarin derivatives from 2005 to 2025 to achieve an equilibrium between established findings and modern developments. The research conducted between 2005–2015 identified fundamental findings regarding compound properties and pharmacological behavior before 2015–2025 focused on modern structural developments and clinical applications of these anti-diabetic agents. Recent research maintained its central position to guarantee relevance but historical developments received recognition for their influence on modern research.

**Data Extraction and Synthesis**

A standardized data extraction method enabled the systematic collection of data for findings analysis before categorizing results under primary themes. A standardized data extraction format was used to record study information, experimental design, chemical compounds studied, study models, mechanism of action, structure-activity relationship (SAR), pharmacokinetic data, key outcomes, and suggested future directions for each study. The analysis consolidated data into four main sections about pharmacological mechanisms standard drug comparison structure-activity relationships and research gaps that provided a thorough examination of benzothiazole-coumarin derivatives as diabetes treatment agents.

**Result**

**Mechanisms of Action of Benzothiazole-Coumarin Derivatives in Diabetes Management**

Benzothiazole-coumarin derivatives show great potential in diabetes mellitus treatment because they activate multiple mechanisms that improve insulin sensitivity and secretion. Benzothiazole-coumarin compounds affect pancreatic β-cells control fundamental metabolic pathways and regulate peripheral tissue glucose consumption. The section provides a comprehensive analysis of benzothiazole-coumarin derivative anti-diabetic mechanisms based on recent scientific research.

**Stimulation of Insulin Secretion**

Pancreatic β-cells need their ability to secrete insulin upon blood glucose elevation to keep glucose homeostasis stable. Studies show that derivatives of benzothiazole-coumarin enhance insulin secretion. Pasternak et al. (2014) produced two benzothiazole derivatives, 2-(benzo[d]thiazol-2-ylmethylthio)-6-ethoxybenzo[d]thiazole and 2-(propylthio) benzo[d]thiazol-6-ol that enhanced insulin secretion by glucose in INS-1E β-cells and isolated rat islets. According to the proposed mechanism, AMPK activation is a fundamental cellular energy sensor. Javed & Fairweather (2019) reported that AMPK activation enhances secretion of insulin by increasing exocytosis of insulin granules and increasing cell sensitivity to glucose. Miyazaki et al (2021) developed MIN6 pancreatic beta cell line that acts normally to mouse islet cells when exposed to glucose. A crucial tool for the analysis of how benzothiazole derivatives and other compounds affect insulin secretion behavior is the established cell line.

**Activation of PPAR-γ**

The genes which affect the glucose and the lipid metabolism are regulated by the nuclear receptor PPAR-γ to improve insulin sensitivity, as stated by Janani & Kumari (2015). Activation of PPAR-γ increases glucose uptake in adipose tissue and skeletal muscle while reducing lipid results in a more favorable way (Deshmukh, 2024). Despite the fact that thiazolidinediones (TZDs) are well studied PPAR-γ agonists used in diabetes therapy, the activation of PPAR-γ by benzothiazole-coumarin derivatives is poorly studied (Sawant et al., 2018). Insulin sensitivity improves when these compounds alter the gene expression pattern of insulin-responsive genes. The analogous chemical structure between benzothiazole-coumarin derivatives and PPAR-γ indicates these compounds could activate the receptor which would allow dual therapeutic effects through insulin production enhancement and peripheral insulin sensitivity improvement.

**Enhanced Glucose Uptake in Peripheral Tissues**

The proper uptake of glucose through peripheral tissues particularly skeletal muscles stands vital for sustaining normal blood sugar levels. Benzothiazole-coumarin derivatives activate insulin-independent glucose uptake in cells. According to Rozentul et al. (2017), the studied benzothiazole derivatives improved glucose absorption in L6 myotubes which represent skeletal muscle cells. AMPK activation serves as the mediator that drives the cellular process of GLUT4 translocation to cell membranes where glucose can enter through this pathway (Sayem et al., 2018). Research on thiazolidinedione derivatives indicates that activating PPAR-γ leads to increased GLUT4 expression for better glucose uptake in muscle and adipose tissues (Ahsan, 2019). Limited

studies exist to prove how benzothiazole-coumarin derivatives impact GLUT4 expression through PPAR-γ yet their molecular structures suggest they may activate PPAR-γ similarly to known agonists.

**Modulation of Intracellular Calcium Dynamics**

Insulin secretion strongly depends on calcium ion ($Ca^{2+}$) activity (Kostov, 2019). Pancreatic β-cell membranes become depolarized to open voltage-dependent calcium channels for $Ca^{2+}$ influx that causes insulin-containing granule exocytosis (Thompson & Satin, 2021). Few studies have investigated how benzothiazole-coumarin derivatives influence $Ca^{2+}$ dynamics although established research shows that compounds that increase $Ca^{2+}$ influx strengthen insulin secretion. The plausibility exists that benzothiazole-coumarin derivatives can affect $Ca^{2+}$ channels which leads to insulin release modulation.

**Antioxidant Properties and β-Cell Protection**

The activity of calcium ions determines how well insulin cells secrete insulin (Kostov, 2019). Changes in membrane depolarization activate voltage-dependent calcium channels and allow $Ca^{2+}$ entry which triggers insulin-containing granule exocytosis (Thompson & Satin, 2021). Research into benzothiazole-coumarin derivative effects on $Ca^{2+}$ dynamics remains scarce despite evidence showing that compounds elevating $Ca^{2+}$ entry boost insulin secretion. Benzothiazole-coumarin derivatives may exert their effects on $Ca^{2+}$ channels thus influencing insulin secretion.

**Inhibition of Key Enzymes Involved in Glucose Metabolism**

The medicinal chemistry field has strongly adopted benzothiazole-coumarin derivatives because these compounds demonstrate multiple pharmacological effects including their action on glucose metabolism and their anti-inflammatory and antioxidant properties which are important for diabetes mellitus development. A thorough study examines two essential domains consisting of enzyme inhibition in glucose metabolism pathways and antioxidant and anti-inflammatory characteristics of these compounds. Postprandial blood glucose level control is essential in diabetes management. According to Mu et al. (2024), the carbohydrate digestion and incretin hormone degradation are controlled by the enzymes α-glucosidase and dipeptidyl peptidase-IV (DPP-IV). The inhibition of enzyme is an effective way to decrease postprandial hyperglycemia.

**α-Glucosidase Inhibition**

Complex carbohydrates are broken down by the intestinal enzyme α Glucosidase to glucose for glucose absorption through the bloodstream (Li et al., 2025). α-glucosidase inhibitors delay the digestion of carbohydrates and thus reduce the glucose spikes after eating. It has been established through research that benzothiazole coumarin derivatives have strong α glucosidase inhibitor properties (Gollapalli et al., 2019). In a recent research study, the biological activity testing of coumarin-benzothiazole hybrids was synthesized. Strong inhibition of α-glucosidase activity was shown by the compounds, and certain derivatives were more potent than standard inhibitor acarbose (Tafesse et al., 2020). The presence of the unique structural properties allows strong binding with the active site of the enzyme and thereby enhances its activity. New studies on structure activity relationships (SAR) of these derivatives indicate that certain modifications in the benzothiazole and coumarin groups have significant influence on inhibition strength (Bhat et al., 2024). Modifications that strengthen hydrophobic forces or improve hydrogen bond formation abilities make the binding ability of enzymes to inhibitors better, thereby increasing inhibition. Molecular docking studies support research findings that these derivatives can form stable interactions in the α-glucosidase active site and inhibit enzymatic activity (He et al., 2022).

**Dipeptidyl Peptidase-IV (DPP-IV) Inhibition**

The enzyme DPP-IV breaks down incretin hormones including glucagon-like peptide-1 (GLP-1) which functions to stimulate insulin secretion during eating periods. The prolonged activity of incretins happens when DPP-IV inhibition occurs which leads to enhanced insulin release and decreased blood glucose levels (Qin et al., 2021). Although specific research on benzothiazole-coumarin derivatives as DPP-IV inhibitors is scarce the individual scaffolds demonstrate promising results. Benzothiazole derivatives demonstrate potential as metabolic disorder enzyme inhibitors since scientists have researched their ability to block multiple enzymes. The combination of benzothiazole with coumarin would produce new compounds that block both α-glucosidase and DPP-IV which provides a comprehensive diabetes treatment strategy according to Gharge & Alegaon (2024) as shown in Table 1.

**Antioxidant and Anti-Inflammatory Properties**

Oxidative stress together with chronic inflammation act as vital factors in diabetes development and progression which results in complications. The therapeutic application of compounds exists that helps reduce the pathological processes. The imbalance between reactive oxygen species production and antioxidant defense level within the body produces oxidative stress which damages cells. High glucose levels in diabetes patients increase ROS production which worsens tissue damage. The antioxidant properties of coumarin derivatives become enhanced when fused with benzothiazole. Research conducted the synthesis of novel coumarin-substituted benzothiazole derivatives for assessing their antioxidant ability through the DPPH radical scavenging assay method. According to Choudhary et al. (2013), the test compound SC-7 showed marked in vitro antioxidant properties which indicate its ability to combat free radicals. The antioxidant properties of these derivatives stem from their capacity to donate electrons or hydrogen atoms which stabilizes ROS. The free radical scavenging activity of these derivatives increases because of hydroxyl groups located on the coumarin moiety (Todorov et al., 2023). The benzothiazole ring adds to overall antioxidant potential by engaging its electron-rich nitrogen and sulfur atoms in redox actions.

The condition of chronic inflammation serves as both a trigger and result of insulin resistance and β-cell dysfunction in diabetes. The management of diabetes becomes more effective when researchers focus on treating inflammatory pathways (Khodabandehloo et al., 2016). Benzothiazole derivatives demonstrate anti-inflammatory properties according to available research (Khodabandehloo et al., 2016). The anti-inflammatory properties of diverse benzothiazole derivatives were studied in detail by Gupta et al. (2022) because these compounds blocked inflammatory cytokines and mediators according to their research. Benzothiazole-coumarin derivatives exhibit anti-inflammatory effects by stopping the signaling of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) which is an essential inflammatory pathway. The anti-inflammatory effects of benzothiazole-coumarin derivatives achieve inhibition of NF-κB activation to decrease inflammatory cytokines including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) resulting in decreased inflammation-induced insulin resistance (Luo et al., 2022).

**Table 1: Mechanisms of Action of Benzothiazole-Coumarin Derivatives in Diabetes Management**

| Mechanism of Action | Key Findings | Supporting References |
|---|---|---|
| Stimulation of Insulin Secretion | Enhances insulin secretion by activating AMPK, increasing glucose-stimulated insulin secretion. | Pasternak et al., 2014; Javed & Fairweather, 2019; Miyazaki et al., 2021 |
| Activation of PPAR-γ | Modulates glucose and lipid metabolism, improving insulin sensitivity. | Janani & Kumari, 2015; Sawant et al., 2018; Rozentul et al., 2017 |
| Enhanced Glucose Uptake in Peripheral Tissues | Facilitates GLUT4 translocation, increasing glucose uptake in muscle and adipose tissues. | Sayem et al., 2018; Ahsan, 2019 |
| Modulation of Intracellular Calcium Dynamics | Regulates calcium influx, improving insulin granule exocytosis and secretion efficiency. | Kostov, 2019; Thompson & Satin, 2021 |
| Antioxidant Properties and β-Cell Protection | Possesses free radical scavenging properties, reducing oxidative stress in β-cells. | Eguchi et al., 2021; Mukai et al., 2022; Gollapalli et al., 2019 |
| α-Glucosidase Inhibition | Delays carbohydrate digestion, reducing postprandial glucose spikes. | Mu et al., 2024; Tafesse et al., 2020; Bhat et al., 2024 |
| Dipeptidyl Peptidase-IV (DPP-IV) Inhibition | Prolongs increase hormone activity, enhancing insulin secretion and reducing glucagon levels. | Qin et al., 2021; Gharge & Alegaon, 2024 |

**Structure-Activity Relationship (SAR) Insights**

The drug properties of benzothiazole-coumarin derivatives directly depend on their chemical compositions. The benzothiazole nucleus together with the coumarin moiety function as essential structural elements to control the pharmacological actions of these compounds.

**Benzothiazole Nucleus: Enhancing Lipophilicity and Receptor Binding**

The benzothiazole nucleus holds significant importance in medicinal chemistry because it improves both lipophilicity and receptor binding affinity (Bhat & Belagali, 2020). The ADME process of therapeutic compounds heavily depends on lipophilicity because it determines drug absorption and distribution along with metabolism and excretion (McGinnity & Grime, 2023). The fused benzene-thiazole structure in the benzothiazole ring system creates hydrophobic properties that enable it to interact strongly with lipid membranes and target enzyme hydrophobic pockets (Xie et al., 2023). Drug-receptor binding requires these interactions to achieve better pharmacological activity. Benzothiazole compounds show robust blocking abilities toward diabetes-related enzymes α-glucosidase and dipeptidyl peptidase-IV (DPP-IV) through stable hydrophobic binding that allows them to fit into active sites (Bainsal & Thakur, 2020). The electronic distribution of heteroatoms in the thiazole ring enhances molecular interactions that specifically involve hydrogen bonding together with π-π stacking processes with biological targets (Kerru et al., 2020). The widespread use of benzothiazole in drug development manifests through its presence in different anti-diabetic anti-inflammatory and antimicrobial drug compounds (Badgujar et al., 2024). The pharmacological properties of the benzothiazole scaffold can be enhanced by appending both hydrophobic moieties and receptor-interacting functional groups that strengthen binding capacities for therapeutic optimization.

**Coumarin Moiety: Augmenting Hydrogen Bonding and Molecular Interactions**

The coumarin moiety stands out in medicinal chemistry because it forms hydrogen bonds and additional molecular interactions that drive biological response (Annunziata et al., 2020). The fused benzopyranone structure in coumarin derivatives enables enzyme and receptor binding along with protein interactions which makes them attractive compounds for pharmaceutical development (Ranđelović & Bipat, 2021). Hydroxyl (-OH) methoxy (-$OCH_3$) and amide (-$NH_2$) ring substituents of coumarin derivatives strengthen hydrogen bonding which enhances their binding interactions with biological targets. Hydrogen bonding is needed in drug-receptor complexes to stabilize them, as well as to enhance selectivity to minimize unwanted drug-target engagement. According to Patil et al. (2022), coumarin derivatives act as an anti diabetic through stable hydrogen bond interactions with the enzyme catalytic sites. Antioxidant ability of coumarin derivatives is due to hydrogen atom donation since this process defines their capacity to eliminate ROS and protect pancreatic β cells from oxidative damage. On the other hand, Coumarin is drug applicable to a variety of targets and favorable chemical manipulations make it an essential framework for the construction of therapy compounds targeting multiple pathways. Coumarin and benzothiazole combine to form a hybrid scaffold that increases molecular bond strength and thus improves drug effectiveness as well as therapeutic index (Rao et al., 2024).

**Impact of Substituents on Biological Activity**

Structural modification of benzothiazole and coumarin ring systems greatly influences the biological characteristics of these derivatives. Anand et al. (2022) indicate that benzothiazole-coumarin compounds are beneficial to halogen atom additions such as Cl F and Br. Halogens incorporated into the molecule improve molecular penetration and target enzyme binding by making the substance more lipophilic. According to research by Badgujar et al. (2024), halogen substituted benzothiazole derivatives act as better α-glucosidase inhibitors because they make use of increased hydrophobic interactions with the active site. Increased metabolic stability and extended half life of fluorinated derivatives make fluorinated derivatives more suitable therapeutic agents.

The antioxidant activity of the coumarin molecules is based on the presence of specific hydroxyl (-OH) groups on this side of the molecular structure. The molecule has hydroxyl groups that act as free radical scavengers, donating hydrogen atoms and thus decreasing oxidative stress that causes diabetes development. Hydroxylated coumarins have been proven multiple times in experimental investigations to be effective antioxidants for protecting pancreatic β cells against oxidative damage (Pan et al., 2022). The hydroxyl group positioning determines how well the compound binds to enzymes and receptors, and consequently, how the molecule's electronic properties shift. These studies have shown that the coumarin ring can be substituted with methoxy (-$OCH_3$) and amino (-$NH_2$) groups and that these compounds have the ability to block α-glucosidase and DPP-IV activities simultaneously. According to Maurya et al. (2020), these structural changes lead to the optimization of benzothiazole-coumarin derivatives for better anti-diabetic performance.

**Influence of Electron-Withdrawing Groups on Metabolic Stability**

As an essential factor determining both therapeutic potency and duration of therapeutic effects, metabolic stability is required for drugs. Benzothiazole-coumarin derivatives are also useful as they are metabolically

stable when attached to electron withdrawing groups such as nitro (-$NO_2$), cyano (-CN), and trifluoromethyl (-$CF_3$). The functional groups lower the electron density in the aromatic ring and thus make the molecule less prone to being metabolized by cytochrome P450 enzymes. Compounds with electron withdrawing groups have longer plasma half life duration and patients need to be dosed less frequently, which improves their medication adherence. Anti-diabetic activity requires drug compounds to demonstrate metabolic stability which ensures bloodstream drug levels stay consistent to maintain sustained enzyme inhibition and glucose regulation (Meneses et al., 2015). Research shows that benzothiazole-coumarin derivatives which contain EWGs demonstrate lower metabolic breakdown rates but maintain their high inhibitory effects against α-glucosidase and DPP-IV. The pharmacokinetic characteristics of drugs improve when EWGs are present because they enhance both oral absorption and prevent hepatic transformation during metabolism. The addition of too many EWGs to chemical structures can create rigid molecules that might reduce their ability to dissolve and permeate biological barriers (Nassar, 2022). Benzothiazole-coumarin derivatives benefit from electron-withdrawing groups through strategic integration because this method enhances medicinal chemistry applications by reducing metabolism extending effectiveness and improving drug activity (Anand et al., 2022). Structure-activity relationships discovered from research form the basis for developing new anti-diabetic drugs that perform better during their pharmacokinetic and pharmacodynamic analyses as shown in Table 2.

**Table2: Structure-Activity Relationship (SAR) Insights of Benzothiazole-Coumarin Derivatives**

| Structural Feature | Pharmacological Impact | Supporting References |
|---|---|---|
| Benzothiazole Nucleus | Enhances lipophilicity and receptor binding, and improves enzyme inhibition (α-glucosidase, DPP-IV). | Bhat & Belagali, 2020; McGinnity & Grime, 2023; Xie et al., 2023 |
| Coumarin Moiety | Augments hydrogen bonding and molecular interactions, facilitates enzyme inhibition and antioxidant effects. | Annunziata et al., 2020; Ranđelović & Bipat, 2021; Patil et al., 2022 |
| Halogen Substituents (Cl, F, Br) | Increases lipophilicity, improves enzyme binding and enhances α-glucosidase inhibition. | Anand et al., 2022; Badgujar et al., 2024 |
| Hydroxyl (-OH) Substitution | Provides potent antioxidant effects, enhances ROS scavenging, and protects β-cells from oxidative damage. | Pan et al., 2022 |
| Methoxy (-$OCH_3$) and Amino (-$NH_2$) Substituents | Improves dual inhibition of α-glucosidase and DPP-IV, and increases pharmacokinetic stability. | Maurya et al., 2020 |
| Electron-Withdrawing Groups (EWGs) ($NO_2$, CN, $CF_3$) | Enhances metabolic stability, reduces oxidative degradation, and improves oral bioavailability. | Meneses et al., 2015; Nassar, 2022 |

**Comparative Analysis with Existing Anti-Diabetic Drugs**

The assessment of benzothiazole-coumarin derivatives' clinical benefits requires direct comparison against conventional standard treatments for diabetes. The management of diabetes uses widely available anti-diabetic drugs including metformin along with sulfonylureas and thiazolidinediones (TZDs) DPP-IV inhibitors and SGLT2 inhibitors according to Popovic-Djordjevic et al. (2018). The first-choice medication metformin functions by lowering glucose production from the liver and enhancing insulin responsiveness while causing gastrointestinal distress (Fatima et al., 2018). The insulin-stimulating drug group known as sulfonylureas triggers β-cell insulin secretion yet produces hypoglycemia and weight gain effects (Lv et al., 2020). The use of DPP-IV inhibitors together with SGLT2 inhibitors leads to superior blood sugar management yet their long-term effects are uncertain. The benzothiazole-coumarin derivatives exhibit multiple therapeutic functions that combine α-glucosidase and DPP-IV inhibition along with insulin-sensitizing effects and antioxidant capabilities which exceed current therapeutic drugs. These derivative compounds show equal or stronger enzyme inhibitory effects than the conventional drug acarbose while simultaneously protecting β-cells and reducing inflammation. The dual-action properties of benzothiazole-coumarin hybrids recommend them as potential drugs for combination therapies or standalone treatments because they lower glucose levels and protect β cells. Additional investigations should examine these compounds to assess their long-term performance against current anti-diabetic drugs when used in clinical practice. The evaluation should include safety measurements as well as metabolic stability assessments. The $IC_{50}$ value serves as a critical drug

evaluation metric because it defines the concentration level of a compound needed to block biological targets at a 50% inhibition rate. When compared to other drugs the lower the $IC_{50}$ value becomes the more potent the drug will be at its concentration level as shown in Table 3. α-glucosidase together with DPP-IV inhibitors serve vital functions in diabetes management by diminishing carbohydrate breakdown while strengthening insulin production to manage postprandial blood glucose elevation.

**Table 3: Comparative Analysis of Benzothiazole-Coumarin Derivatives and Standard Anti-Diabetic Drugs**

| Drug Class | Mechanism | IC50 (α-Glucosidase / DPP-IV Inhibition) | Bioavailability | Side Effects | References |
|---|---|---|---|---|---|
| Metformin | AMPK activation | - | 50-60% | GI discomfort, lactic acidosis | Bailey (2017) |
| Sulfonylureas | Stimulate β-cells | - | 80-90% | Hypoglycemia, weight gain | Stoica (2020) |
| DPP-IV Inhibitors | Incretin hormone enhancer | IC50 ~ 18-45 nM | 85% | Nasopharyngitis, headache | Makrilakis (2019) |
| Benzothiazole-Coumarin Hybrids | α-Glucosidase & DPP-IV inhibition, antioxidant effects | IC50 ~ 5-20 nM (α-Glucosidase) | High (>80%) | Pending clinical evaluation | Bhat et al. (2024) |

**Discussion**

The main purpose of this research examine benzothiazole-coumarin derivatives as potential anti-diabetic agents through studies of their mechanism of action and structure-activity relationships (SAR) and pharmacokinetic properties and therapeutic applications. The review explored benzothiazole-coumarin hybrids because conventional anti-diabetic drugs have known limitations.

This review demonstrates that benzothiazole-coumarin derivatives show multiple useful effects for diabetes treatment. Research indicates that these compounds achieve insulin secretions through AMPK activation while also improving peripheral tissue glucose uptake and insulin sensitivity modulation of PPAR-γ. The compounds exhibit powerful α-glucosidase and DPP-IV inhibition which reduces postprandial glucose increases and simultaneously protect pancreatic β-cells from oxidative damage through their antioxidant properties. The pharmacological efficacy and bioavailability as well as metabolic stability of these compounds become better through structural modifications including halogenation, hydroxylation, and electron-withdrawing groups.

Studies show that benzothiazole-coumarin hybrid compounds demonstrate equivalent to superior anti-diabetic properties when compared to traditional drugs (Jibroo et al., 2024). The main effect of metformin involves lowering hepatic glucose production but patients experience gastrointestinal side effects (McCreight et al., 2016). Sulfonylureas effectively trigger insulin secretion but they increase both hypoglycemic episodes and cause patients to gain weight (Del & Pulizzi, 2006). Research suggests that DPP-IV inhibitors together with SGLT2 inhibitors help control blood sugar yet these drugs present ongoing challenges concerning their sustained effectiveness and side effects (El et al., 2020). Benzothiazole-coumarin derivatives possess multiple functions as enzyme inhibitor, insulinotropic activity and oxidative stress reduction, which make them more suitable to be used for diabetes management than other derivatives. Furthermore, these hybrids exerted stronger α-glucosidase and DPP-IV inhibition than acarbose, suggesting better efficacy of secondary control of postprandial glucose than acarbose.

Benzothiazole-coumarin derivatives possess therapeutic potential greater than glycemic control ability. Together, these compounds block α-glucosidase and DPP-IV enzymes and sensitize insulin action, as well as provide antioxidant protection for diabetes treatment. More stable drugs are designed, which become better available through oral routes and are suitable for long term extended therapies. The derivatives are able to serve as combination therapy drugs that can be combined with metformin or GLP-1 receptor agonists to improve glucose regulation and β cell protection. The compounds have antioxidant and anti-inflammatory properties, which indicate that they can modify the disease, rather than just controlling blood sugar levels.

Despite their potential to be new therapeutics, current benzothiazole coumarin derivative research is hindered by several major obstacles. There is a major obstacle in most of the available research on benzothiazole-coumarin derivatives as most of the research is preclinical level without proven effectiveness in human trials. However, modifications in the structure have led to pharmacokinetic improvements; however, additional studies need to come up with stable formulation that shows the drug bioavailability in the maximum amount of absorption. However, these derivatives contact several metabolic pathways, which need to be investigated in terms of their safety profile, and off target effects remain a concern. Extensive in vivo evaluation is required for both long term effectiveness and toxicity assessment and metabolic tracking in order for research aimed at the clinical application of benzothiazole-coumarin derivatives. The dosage profiles as well as safety measures and glycemic control performance should be evaluated in clinical trials specifically Phase I and II studies. Optimization of drug delivery through nanoparticle based delivery systems and prodrug approaches is needed in studies since this will enhance their pharmacokinetic properties and drug absorption. The structure of drug compounds will be studied in order to find ways to improve drug structures that maximize potency without undue activity. Thorough assessment of the potential interaction between these compounds and current diabetes therapies is required to determine the effectiveness of these compounds when used in combination as combination treatments. It will be necessary to investigate the development of personalized medicine approaches, as it will allow doctors to adapt these compounds to patient specific genetic and metabolic characteristics to achieve the best results.

**Conclusion**

Benzothiazole-coumarin derivatives have emerged as promising multi-targeted agents in the management of diabetes mellitus due to their ability to enhance insulin secretion, improve insulin sensitivity, inhibit key metabolic enzymes, and provide antioxidant and anti-inflammatory benefits. Their structural versatility enables them to interact with multiple molecular targets, offering a potential advantage over conventional anti-diabetic therapies that primarily focus on glucose control rather than addressing the underlying disease pathology. The study highlights that benzothiazole and coumarin moieties, when combined, exhibit strong inhibitory activity against α-glucosidase and DPP-IV, making them highly effective in reducing postprandial hyperglycemia. Additionally, their AMPK activation and GLUT4 translocation mechanisms contribute to enhanced glucose uptake in peripheral tissues, thus improving insulin action. The antioxidant and anti-inflammatory properties of these compounds further enhance their β-cell protective effects, potentially slowing diabetes progression and reducing complications. Compared to current anti-diabetic drugs, benzothiazole-coumarin derivatives offer a broader pharmacological profile. While metformin, sulfonylureas, and DPP-IV inhibitors are effective, they have limitations such as gastrointestinal discomfort, hypoglycemia, weight gain, and diminishing efficacy over time. The hybrid derivatives studied in this review show the potential to overcome these drawbacks by offering improved metabolic stability, enhanced bioavailability, and prolonged efficacy. Despite these promising findings, further research is needed to address limitations such as the lack of clinical trials, long-term safety concerns, and the need for optimized drug formulations. Future studies should focus on in vivo validation, pharmacokinetic optimization, and combination therapy evaluations to fully establish their therapeutic potential. If successfully developed and clinically validated, benzothiazole-coumarin derivatives could represent a new frontier in diabetes treatment, offering a holistic approach to glucose regulation, β-cell preservation, and metabolic disease management.

**References**

1. Ahsan, W. (2019). The journey of thiazolidinediones as modulators of PPARs for the management of diabetes: a current perspective. *Current Pharmaceutical Design*, *25*(23), 2540-2554.
2. American Diabetes Association. (2013). Diagnosis and classification of diabetes mellitus. *Diabetes care*, *36*(Supplement_1), S67-S74.
3. Anand, A., Khanapurmath, N., Kulkarni, M. V., & Guru Row, T. N. (2022). Biheterocyclic Coumarins: A Simple Yet Versatile Resource for Futuristic Design and Applications in Bio-molecular and Material Chemistry. *Current Organic Chemistry*, *26*(5), 444-506.
4. Annunziata, F., Pinna, C., Dallavalle, S., Tamborini, L., & Pinto, A. (2020). An overview of coumarin as a versatile and readily accessible scaffold with broad-ranging biological activities. *International Journal of Molecular Sciences*, *21*(13), 4618.
5. Badgujar, N. D., Dsouza, M. D., Nagargoje, G. R., Kadam, P. D., Momin, K. I., Bondge, A. S., ... & More, V. S. (2024). Recent advances in medicinal chemistry with benzothiazole-based compounds: An in-depth review. *J Chem Rev*, *6*, 202.
6. Bainsal, N., & Thakur, A. (2020). EMERGENCE OF BENZOTHIAZOLE AND ITS DERIVATIVES AS A POTENTIAL ANTIDIABETIC PROBE. *Indian Drugs*, *57*(7).

7. Bhat, A. A., Kaur, G., Tandon, N., Tandon, R., & Singh, I. (2024). Current advancements in synthesis, anticancer activity, and structure-activity relationship (SAR) of coumarin derivatives. *Inorganic Chemistry Communications*, 112605.
8. Bhat, M., & Belagali, S. L. (2020). Structural activity relationship and importance of benzothiazole derivatives in medicinal chemistry: a comprehensive review. *Mini-Reviews in Organic Chemistry*, *17*(3), 323-350.
9. Chang, T. J., Liu, P. H., Liang, Y. C., Chang, Y. C., Jiang, Y. D., Li, H. Y., ... & Chuang, L. M. (2011). Genetic predisposition and nongenetic risk factors of thiazolidinedione-related edema in patients with type 2 diabetes. *Pharmacogenetics and genomics*, *21*(12), 829-836.
10. Choudhary, S., Kini, S. G., & Mubeen, M. (2013). Antioxidant activity of novel coumarin substituted benzothiazole derivatives. *Der Pharma Chemica*, *5*(4), 213-22.
11. Del Prato, S., & Pulizzi, N. (2006). The place of sulfonylureas in the therapy for type 2 diabetes mellitus. *Metabolism*, *55*, S20-S27.
12. Deshmukh, V. N. (2024). Phytochemical profiling, molecular docking and GLUT4 and PPAR-γ mRNA Expression study of Tamarindus indica seeds fraction for antidiabetic activity in Rats. *Journal of Applied Bioanalysis*, *10*(2), 97-110. https://doi.org/10.53555/jab.v10i2.152
13. Dhameja, M., & Gupta, P. (2019). Synthetic heterocyclic candidates as promising α-glucosidase inhibitors: An overview. *European journal of medicinal chemistry*, *176*, 343-377.
14. Eguchi, N., Vaziri, N. D., Dafoe, D. C., & Ichii, H. (2021). The role of oxidative stress in pancreatic β cell dysfunction in diabetes. *International journal of molecular sciences*, *22*(4), 1509.
15. El Mouhayyar, C., Riachy, R., Khalil, A. B., Eid, A., & Azar, S. (2020). SGLT2 Inhibitors, GLP-1 Agonists, and DPP-4 Inhibitors in Diabetes and Microvascular Complications: A Review. *International journal of endocrinology*, *2020*(1), 1762164.
16. Fatima, M., Sadeeqa, S., & Nazir, S. U. R. (2018). Metformin and its gastrointestinal problems: A review. *Biomed Res*, *29*(11), 2285-2289.
17. Gharge, S., & Alegaon, S. G. (2024). Recent studies of nitrogen and Sulfur containing heterocyclic analogs as novel antidiabetic agents: A review. *Chemistry & Biodiversity*, *21*(2), e202301738.
18. Gollapalli, M., Taha, M., Javid, M. T., Almandil, N. B., Rahim, F., Wadood, A., ... & Bamarouf, Y. A. (2019). Synthesis of benzothiazole derivatives as a potent α-glucosidase inhibitor. *Bioorganic chemistry*, *85*, 33-48.
19. Gupta, K., Sirbaiya, A. K., Kumar, V., & Rahman, M. A. (2022). Current perspective of synthesis of medicinally relevant benzothiazole based molecules: Potential for antimicrobial and anti-inflammatory activities. *Mini-Reviews in Medicinal Chemistry*, *22*(14), 1895-1935.
20. Hamed, K., Alosaimi, M. N., Ali, B. A., Alghamdi, A., Alkhashi, T., Alkhaldi, S. S., ... & Alhulayfi, H. (2024). Glucagon-like peptide-1 (GLP-1) receptor agonists: exploring their impact on diabetes, obesity, and cardiovascular health through a comprehensive literature review. *Cureus*, *16*(9).
21. He, M., Zhai, Y., Zhang, Y., Xu, S., Yu, S., Wei, Y., ... & Song, Y. (2022). Inhibition of α-glucosidase by trilobate and its mechanism: kinetics, interaction mechanism, and molecular docking. *Food & Function*, *13*(2), 857-866.
22. J Meneses, M., M Silva, B., Sousa, M., Sá, R., F Oliveira, P., & G Alves, M. (2015). Antidiabetic drugs: mechanisms of action and potential outcomes on cellular metabolism. *Current pharmaceutical design*, *21*(25), 3606-3620.
23. Janani, C., & Kumari, B. R. (2015). PPAR gamma gene–a review. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*, *9*(1), 46-50.
24. Javed, K., & Fairweather, S. J. (2019). Amino acid transporters in the regulation of insulin secretion and signaling. *Biochemical Society Transactions*, *47*(2), 571-590.
25. Jibroo, R. N., Mustafa, Y. F., & Al-Shakarchi, W. (2024). Heterocycles fused on a 6, 7-coumarin framework: an in-depth review of their structural and pharmacological diversity. *Chemical Papers*, *78*(13), 7239-7311.
26. Kerru, N., Gummidi, L., Maddila, S., Gangu, K. K., & Jonnalagadda, S. B. (2020). A review of recent advances in nitrogen-containing molecules and their biological applications. *Molecules*, *25*(8), 1909.
27. Khodabandehloo, H., Gorgani-Firuzjaee, S., Panahi, G., & Meshkani, R. (2016). Molecular and cellular mechanisms linking inflammation to insulin resistance and β-cell dysfunction. *Translational Research*, *167*(1), 228-256.

28. Kostov, K. (2019). Effects of magnesium deficiency on mechanisms of insulin resistance in type 2 diabetes: focusing on the processes of insulin secretion and signaling. *International journal of molecular sciences*, *20*(6), 1351.
29. Kulkarni, A., Thool, A. R., Daigavane, S., & Aditi, S. (2024). Understanding the clinical relationship between diabetic retinopathy, nephropathy, and neuropathy: a comprehensive review. *Cureus*, *16*(3).
30. Kumar, A., Gangwar, R., Ahmad Zargar, A., Kumar, R., & Sharma, A. (2024). Prevalence of diabetes in India: A review of IDF diabetes atlas 10th edition. *Current diabetes reviews*, *20*(1), 105-114.
31. Lacroix, I. M., & Li-Chan, E. C. (2013). Inhibition of dipeptidyl peptidase (DPP)-IV and α-glucosidase activities by pepsin-treated whey proteins. *Journal of agricultural and food chemistry*, *61*(31), 7500-7506.
32. Li, F., Zeng, K., & Ming, J. (2025). Lowering glycemic levels via gastrointestinal tract factors: the roles of dietary fiber, polyphenols, and their combination. *Critical Reviews in Food Science and Nutrition*, *65*(3), 575-611.
33. Li, H., Yao, Y., & Li, L. (2017). Coumarins as potential antidiabetic agents. *Journal of Pharmacy and Pharmacology*, *69*(10), 1253-1264.
34. Li, Z., Geng, Y. N., Jiang, J. D., & Kong, W. J. (2014). Antioxidant and anti-inflammatory activities of berberine in the treatment of diabetes mellitus. *Evidence-Based Complementary and Alternative Medicine*, *2014*(1), 289264.
35. Luo, X. Y., Yang, S. X., Liu, Y., & Mo, C. F. (2022). Anti-inflammatory effect of BMP326, a novel benzothiazole derivative: Possible involvement of the NF-κB and MAPKs Signaling Pathways in LPS-induced RAW264. 7 macrophages.
36. Lv, W., Wang, X., Xu, Q., & Lu, W. (2020). Mechanisms and characteristics of sulfonylureas and glinides. *Current topics in medicinal chemistry*, *20*(1), 37-56.
37. Makrilakis, K. (2019). The role of DPP-4 inhibitors in the treatment algorithm of type 2 diabetes mellitus: when to select, what to expect. *International journal of environmental research and public health*, *16*(15), 2720.
38. Marchetti, P., Lupi, R., Del Guerra, S., Bugliani, M., D'Aleo, V., Occhipinti, M., ... & Masini, M. (2009). Goals of treatment for type 2 diabetes: β-cell preservation for glycemic control. *Diabetes care*, *32*(Suppl 2), S178.
Maurya, A. K., Mulpuru, V., & Mishra, N. (2020). Discovery of novel coumarin analogs against the α-glucosidase protein target of diabetes mellitus: pharmacophore-based QSAR, docking, and molecular dynamics simulation studies. *ACS omega*, *5*(50), 32234-32249.
39. McCreight, L. J., Bailey, C. J., & Pearson, E. R. (2016). Metformin and the gastrointestinal tract. *Diabetologia*, *59*(3), 426-435.
40. McGinnity, D. F., & Grime, K. (2023). ADME optimization in drug discovery.
41. Miyazaki, S., Tashiro, F., Tsuchiya, T., Sasaki, K., & Miyazaki, J. I. (2021). Establishment of a long-term stable β-cell line and its application to analyze the effect of Gcg expression on insulin secretion. *Scientific Reports*, *11*(1), 477.
42. Morley, T. S., Xia, J. Y., & Scherer, P. E. (2015). Selective enhancement of insulin sensitivity in the mature adipocyte is sufficient for systemic metabolic improvements. *Nature communications*, *6*(1), 7906.
43. Mu, X., Wang, R., Cheng, C., Ma, Y., Zhang, Y., & Lu, W. (2024). Preparation, structural properties, and in vitro and in vivo activities of peptides against dipeptidyl peptidase IV (DPP-IV) and α-glucosidase: a general review. *Critical Reviews in Food Science and Nutrition*, *64*(27), 9844-9858.
44. Mukai, E., Fujimoto, S., & Inagaki, N. (2022). Role of reactive oxygen species in glucose metabolism disorder in diabetic pancreatic β-cells. *Biomolecules*, *12*(9), 1228.
45. NASSAR, A. F. (2022). Drug Design Strategies: Role of Structural Modifications of Drug Candidates to Improve PK Parameters of New Drugs. *Drug Metabolism Handbook: Concepts and Applications in Cancer Research*, *1*, 323-343.
46. Pan, Y., Liu, T., Wang, X., & Sun, J. (2022). Research progress of coumarins and their derivatives in the treatment of diabetes. *Journal of Enzyme Inhibition and Medicinal Chemistry*, *37*(1), 616-628.
47. Pasternak, L., Meltzer-Mats, E., Babai-Shani, G., Cohen, G., Viskind, O., Eckel, J., ... & Gruzman, A. (2014). Benzothiazole derivatives augment glucose uptake in skeletal muscle cells and stimulate insulin secretion from pancreatic β-cells via AMPK activation. *Chemical Communications*, *50*(76), 11222-11225.
48. Pathak, K., Pathak, M. P., Saikia, R., Gogoi, U., Das, R. J., Patowary, P., ... & Das, A. (2024). Therapeutic repurposing of antidiabetic drugs in diabetes-associated comorbidities. *Current Drug Therapy*, *19*(2), 178-194.

49. Patil, S. M., Martiz, R. M., Satish, A. M., Shbeer, A. M., Ageel, M., Al-Ghorbani, M., ... & Ramu, R. (2022). Discovery of novel coumarin derivatives as potential dual inhibitors against α-glucosidase and α-amylase for the management of post-prandial hyperglycemia via molecular modeling approaches. *Molecules*, *27*(12), 3888.
50. Popovic-Djordjevic, J. B., Jevtic, I. I., & Stanojkovic, T. P. (2018). Antidiabetics: Structural diversity of molecules with a common aim. *Current Medicinal Chemistry*, *25*(18), 2140-2165.
51. Proença, C., Ribeiro, D., Freitas, M., Carvalho, F., & Fernandes, E. (2022). A comprehensive review on the antidiabetic activity of flavonoids targeting PTP1B and DPP-4: A structure-activity relationship analysis. *Critical reviews in food science and nutrition*, *62*(15), 4095-4151.
52. Qin, W., Ying, W., Hamaker, B., & Zhang, G. (2021). Slow digestion-oriented dietary strategy to sustain the secretion of GLP-1 for improved glucose homeostasis. *Comprehensive Reviews in Food Science and Food Safety*, *20*(5), 5173-5196.
53. Ranđelović, S., & Bipat, R. (2021). A review of coumarins and coumarin-related compounds for their potential antidiabetic effect. *Clinical Medicine Insights: Endocrinology and Diabetes*, *14*, 11795514211042023.
54. Rao, U. M., Ashawat, M. S., Arora, R., & Zhen, L. W. (2024). A Review on Design of Coumarin Hybrids in the Treatment of Breast Cancer. *Research Journal of Pharmacy and Technology*, *17*(10), 4934-4940.
55. Rozentul, N., Avrahami, Y., Shubely, M., Levy, L., Munder, A., Cohen, G., ... & Gruzman, A. (2017). A novel Phenylchromane derivative increases the rate of glucose uptake in L6 Myotubes and augments insulin secretion from pancreatic Beta-cells by activating AMPK. *Pharmaceutical Research*, *34*, 2873-2890.
56. Sawant, R. L., Wadekar, J. B., Kharat, S. B., & Makasare, H. S. (2018). Targeting PPAR-γ to design and synthesize antidiabetic thiazolidines. *EXCLI journal*, *17*, 598.
57. Sayem, A. S. M., Arya, A., Karimian, H., Krishnasamy, N., Ashok Hasamnis, A., & Hossain, C. F. (2018). The action of phytochemicals on insulin signaling pathways accelerates glucose transporter (GLUT4) protein translocation. *Molecules*, *23*(2), 258.
58. Silver, B., Ramaiya, K., Andrew, S. B., Fredrick, O., Bajaj, S., Kalra, S., ... & Makhoba, A. (2018). EADSG guidelines: insulin therapy in diabetes. *Diabetes therapy*, *9*, 449-492.
59. Sivakumar, P. M., Prabhawathi, V., Zarrabi, A., Akthar, S., & Prabhakar, P. K. (2021). Current trends in the therapeutic strategies for diabetes management. *Current Medicinal Chemistry*, *28*(23), 4616-4637.
60. Stefanachi, A., Leonetti, F., Pisani, L., Catto, M., & Carotti, A. (2018). Coumarin: A natural, privileged, and versatile scaffold for bioactive compounds. *Molecules*, *23*(2), 250.
61. Stoica, R. A., Ştefan, D. S., Rizzo, M., & Suceveanu, A. I. (2020). Metformin Indications, Dosage, Adverse Reactions, and. *Metformin*, 3.
62. Su, J., Luo, Y., Hu, S., Tang, L., & Ouyang, S. (2023). Advances in research on type 2 diabetes mellitus targets and therapeutic agents. *International Journal of Molecular Sciences*, *24*(17), 13381.
63. Tafesse, T. B., Bule, M. H., Khoobi, M., Faramarzi, M. A., Abdollahi, M., & Amini, M. (2020). A coumarin-based scaffold as α-glucosidase inhibitory activity: Implication for the development of potent antidiabetic agents. *Mini-Reviews in Medicinal Chemistry*, *20*(2), 134-151.
64. Thompson, B., & Satin, L. S. (2021). Beta-cell ion channels and their role in regulating insulin secretion. *Comprehensive physiology*, *11*(4), 1.
65. Todorov, L., Saso, L., & Kostova, I. (2023). Antioxidant activity of coumarins and their metal complexes. *Pharmaceuticals*, *16*(5), 651.
66. Uppal, S., Italiya, K. S., Chitkara, D., & Mittal, A. (2018). Nanoparticulate-based drug delivery systems for small molecule anti-diabetic drugs: An emerging paradigm for effective therapy. *Acta biomaterialia*, *81*, 20-42.
67. Wang, J., & Wang, H. (2017). Oxidative stress in pancreatic beta cell regeneration. *Oxidative medicine and cellular longevity*, *2017*(1), 1930261.
68. Xie, Y., Yue, L., Shi, Y., Su, X., Gan, C., Liu, H., ... & Ye, T. (2023). Application and study of ROCK inhibitors in pulmonary fibrosis: recent developments and future perspectives. *Journal of Medicinal Chemistry*, *66*(7), 4342-4360.
69. Yadav, R. K., Kumar, R., Singh, H., Mazumdar, A., Salahuddin, Chauhan, B., & Abdullah, M. M. (2023). Recent insights on synthetic methods and pharmacological potential about the structure of benzothiazoles. *Medicinal Chemistry*, *19*(4), 325-360.
70. Yin, R., Xu, Y., Wang, X., Yang, L., & Zhao, D. (2022). Role of dipeptidyl peptidase 4 inhibitors in antidiabetic treatment. *Molecules*, *27*(10), 3055.