IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

CHROMONE-AMINOPHOSPHONATE-TZD HYBRIDS: A TRIPARTITE MOLECULAR STRATEGY FOR DIABETES CONTROL

G.R. Satyanarayana[1*], V.M. Rakesh[2], DKRS Prakasarao[3], P. Esubha[4], S. Saketh Reddy[5], Ch. NagaVamsi[6]

[1,2,3,4,5,6] *Department of Chemistry, Sir C R Reddy College, Eluru, Andhra Pradesh-534007, India.*

***Corresponding author: G.R. Satyanarayana**, Professor, P.G. Department of Chemistry, Sir C R Reddy College, Eluru, Andhra Pradesh-534007, India.
ORCID: https://orcid.org/0000-0002-6984-0003

ABSTRACT:

Background: The worldwide diabetes epidemic currently impacts 537 million adults, a figure anticipated to escalate to 783 million within two decades. Managing post-meal glucose elevation remains a cornerstone therapeutic objective. The enzymes α-amylase and α-glucosidase serve as gatekeepers of carbohydrate breakdown, positioning them as prime candidates for pharmaceutical intervention. Existing medications suffer from drawbacks such as unwanted side effects, suboptimal effectiveness, and narrow mechanistic focus.

Objective: This review critically evaluates the rational design, chemical synthesis, computational binding analysis, and biological assessment of innovative hybrid structures that merge chromone, α-aminophosphonate, and thiazolidine-2,4-dione (TZD) frameworks to create bifunctional inhibitors targeting both α-amylase and α-glucosidase. This tripartite fusion strategy offers a novel pathway toward advanced antidiabetic therapeutics.

Methods: We systematically examined contemporary scientific literature spanning 2015-2026, emphasizing hybrid molecular architecture, eco-friendly synthetic protocols, computational docking investigations, and laboratory-based pharmacological testing. Critical evaluation of structure-function correlations and mechanistic understanding formed the analytical core. Coverage includes computational modeling, nano-catalyst-mediated synthesis under microwave and ultrasonic activation, and detailed enzyme inhibition profiling.

Results: These tripartite hybrid molecules exhibit remarkable dual-enzyme inhibitory potency, with half-maximal inhibitory concentrations spanning 0.51 ± 0.02 to 55.43 ± 0.66 μM against α-amylase and 0.01247 ± 0.01 to 51.28 ± 0.88 μM against α-glucosidase, frequently outperforming acarbose (IC_{50} = 0.68 ± 0.02 μM for α-amylase; 0.316 ± 0.02 to 17.21 μM for α-glucosidase). Computational docking analyses demonstrate binding affinities between -7.26 and -15.4 kcal/mol, featuring essential contacts with active site amino acids Asp321, His591, Asp199, Tyr473, and Ser289. Environmentally conscious synthetic routes employing nano-catalysts (ZnO, Sb_2O_3) with microwave or ultrasound energy deliver excellent efficiency, achieving 63-95% yields with dramatically shortened reaction durations.

Conclusion: Integrating chromone, α-aminophosphonate, and TZD structural elements through molecular hybridization constitutes a forward-looking strategy for creating superior antidiabetic compounds featuring enhanced potency, simultaneous dual-enzyme blockade, optimized pharmacokinetic characteristics, and diminished adverse reactions. These multifunctional molecules simultaneously address several disease mechanisms, potentially surpassing conventional single-target medications

Keywords: chromone scaffolds, α-aminophosphonate derivatives, thiazolidine-2,4-dione, hybrid molecular design, α-amylase inhibition, α-glucosidase inhibition, computational docking, structure-function relationships, diabetes therapeutics, post-meal hyperglycemia

1. INTRODUCTION

1.1 The Global Diabetes Challenge: Epidemiological Landscape

The diabetes pandemic stands as one of humanity's most formidable health crises in the modern era. Current epidemiological data reveal that 537 million adults worldwide live with this metabolic disorder, representing a staggering disease burden that continues to escalate [1]. Forecasting models project an alarming trajectory, with prevalence expected to reach 783 million cases by 2045, underscoring the urgent need for innovative therapeutic interventions [2]. Type 2 diabetes mellitus (T2DM) dominates the clinical landscape, comprising 90-95% of all diabetes diagnoses and manifesting through insulin resistance coupled with progressive pancreatic β-cell deterioration [3].

The economic ramifications of diabetes extend far beyond individual health impacts. Global healthcare expenditures attributable to diabetes management and complications exceed $966 billion annually, placing enormous strain on medical infrastructure worldwide [4]. This financial burden reflects not only direct treatment costs but also productivity losses, disability, and premature mortality. The disease's insidious progression leads to devastating microvascular complications-including retinal damage, kidney dysfunction, and peripheral nerve injury-alongside macrovascular pathologies such as coronary artery disease, cerebrovascular accidents, and peripheral vascular disease [5]. These complications profoundly diminish quality of life and substantially reduce life expectancy, making diabetes prevention and effective management paramount public health priorities [6].

1.2 Targeting Post-Meal Glucose Spikes: Therapeutic Rationale

Elevated blood glucose concentrations following food intake, termed postprandial hyperglycemia (PPG), represents a critical yet often underappreciated therapeutic target in diabetes care [7]. PPG functions as an independent cardiovascular risk determinant and significantly contributes to the pathogenesis of diabetic complications [8]. Unlike fasting hyperglycemia, which reflects basal glucose dysregulation, PPG captures the dynamic challenge of meal-related glucose excursions that stress the cardiovascular system and promote oxidative damage [9].

Therapeutic strategies targeting PPG focus on modulating the kinetics of dietary carbohydrate digestion and subsequent glucose absorption within the gastrointestinal tract [10]. This approach offers distinct advantages over systemic glucose-lowering interventions by addressing the problem at its source-preventing excessive glucose entry into circulation rather than attempting to manage elevated glucose after absorption [11]. By slowing carbohydrate breakdown, these strategies attenuate the rapid glucose spikes that characterize the postprandial state, thereby reducing glycemic variability and associated metabolic stress [12].

The clinical significance of PPG control extends beyond immediate glucose management. Accumulating evidence demonstrates that postprandial glucose excursions correlate more strongly with cardiovascular events than fasting glucose levels in certain patient populations [13]. Furthermore, PPG contributes to the formation of advanced glycation end products (AGEs), which play central roles in diabetic complication development [14]. Consequently, pharmaceutical interventions that effectively blunt postprandial glucose rises offer multifaceted benefits, addressing both immediate glycemic control and long-term complication prevention [15].

1.3 Carbohydrate-Degrading Enzymes: Key Intervention Points

The enzymatic machinery responsible for dietary carbohydrate breakdown presents attractive pharmaceutical targets for diabetes management. Two enzymes occupy central positions in this metabolic pathway: α-amylase and α-glucosidase [16]. These catalytic proteins orchestrate the sequential degradation of complex polysaccharides into absorbable monosaccharides, making them critical gatekeepers of glucose entry into systemic circulation [17].

α-Amylase initiates carbohydrate digestion by cleaving internal α-1,4-glycosidic bonds within starch molecules, generating shorter oligosaccharides and maltose [18]. This enzyme exists in two primary forms: salivary α-amylase, which begins digestion in the oral cavity, and pancreatic α-amylase, which continues the process in the small intestinal lumen [19]. The enzyme's catalytic mechanism involves a sophisticated active site architecture featuring critical aspartate, glutamate, and histidine residues that facilitate substrate binding and catalysis [20].

α-Glucosidase completes the digestive process by hydrolyzing terminal α-1,4-glycosidic linkages in oligosaccharides, releasing free glucose molecules suitable for intestinal absorption [21]. This enzyme family includes multiple isoforms localized to the intestinal brush border membrane, including maltase-glucoamylase, sucrase-isomaltase, and others [22]. The enzyme's active site features a deep pocket that accommodates substrate binding and positions the glycosidic bond for nucleophilic attack [23].

Pharmacological inhibition of these enzymes offers a rational strategy for PPG management. By retarding carbohydrate breakdown, enzyme inhibitors delay glucose liberation and absorption, effectively flattening the postprandial glucose curve [24]. This mechanism-based approach has proven clinically successful, as evidenced by the widespread use of acarbose, voglibose, and miglitol-established α-glucosidase inhibitors that have demonstrated efficacy in diabetes management [25]. However, these first-generation inhibitors suffer from limitations including gastrointestinal side effects, modest efficacy, and single-enzyme targeting, motivating the search for improved alternatives [26].

1.4 Hybrid Molecular Design: Revolutionary Drug Discovery Paradigm

The concept of molecular hybridization has emerged as a transformative strategy in contemporary medicinal chemistry, offering solutions to the limitations of traditional single-target drug design [27]. This approach involves the deliberate fusion of multiple pharmacophoric elements-structural features responsible for biological activity-into a single molecular entity [28]. The resulting hybrid molecules can simultaneously engage multiple biological targets or exhibit enhanced activity against a single target through synergistic interactions [29].

The theoretical foundation of hybrid drug design rests on several key principles. First, combining pharmacophores from different bioactive scaffolds can generate molecules with additive or synergistic effects, potentially achieving superior efficacy compared to individual components [30]. Second, hybrid molecules may exhibit improved pharmacokinetic properties, including enhanced membrane permeability, metabolic stability, and bioavailability [31]. Third, multi-target engagement can address complex diseases more effectively than single-target approaches, particularly for conditions involving multiple pathophysiological mechanisms [32].

In the context of diabetes therapeutics, hybrid molecular design offers compelling advantages. Diabetes involves numerous interconnected metabolic disturbances, including impaired insulin secretion, insulin resistance, excessive hepatic glucose production, and dysregulated incretin signaling [33]. Single-target drugs address only one aspect of this complex pathophysiology, often necessitating combination therapy with multiple medications [34]. Hybrid molecules that simultaneously modulate multiple targets can potentially achieve more comprehensive disease control while simplifying treatment regimens and reducing pill burden [35].

The chromone-aminophosphonate-TZD hybrid strategy exemplifies this innovative approach. By integrating three distinct pharmacophoric elements-each with established biological activity-into unified molecular architectures, researchers aim to create superior antidiabetic agents [36]. Chromone scaffolds contribute antioxidant and anti-inflammatory properties alongside enzyme inhibitory activity [37]. α-Aminophosphonate moieties serve as transition-state analogs that enhance enzyme binding affinity [38]. TZD frameworks provide insulin-sensitizing effects and potential PPAR-γ modulation [39]. The synergistic combination of these elements in hybrid molecules offers the prospect of dual α-amylase/α-glucosidase inhibition with enhanced potency, selectivity, and pharmacological profiles [40].

2. CHROMONE SCAFFOLDS: PRIVILEGED STRUCTURES IN DRUG DISCOVERY

2.1 Core Structural Characteristics and Medicinal Relevance

The chromone nucleus, chemically designated as 4H-chromen-4-one, represents a privileged scaffold in medicinal chemistry-a structural motif capable of binding multiple biological targets with high affinity [41]. This bicyclic system comprises a benzene ring fused to a γ-pyrone moiety, creating a planar aromatic framework with diverse substitution possibilities [42]. The chromone core's electronic properties, including its conjugated π-system and carbonyl functionality, enable multiple modes of molecular recognition and binding interactions [43].

Chromone derivatives occur abundantly in nature, particularly within plant secondary metabolites such as flavonoids, isoflavonoids, and neoflavonoids [44]. This natural prevalence correlates with generally favorable safety profiles and biocompatibility, making chromone-based compounds attractive starting points for drug development [45]. The scaffold's synthetic accessibility further enhances its appeal, as numerous well-established synthetic routes enable efficient preparation of diverse chromone analogs [46].

The medicinal relevance of chromone scaffolds stems from their remarkable biological versatility. Chromone derivatives exhibit a broad spectrum of pharmacological activities, including antioxidant, anti-inflammatory, antimicrobial, anticancer, neuroprotective, and antidiabetic effects [47]. This polypharmacology reflects the scaffold's ability to interact with diverse protein targets through multiple binding modes [48]. The planar aromatic system facilitates π-π stacking interactions with aromatic amino acids, while the carbonyl oxygen serves as a hydrogen bond acceptor, and various substituents can be introduced to modulate physicochemical properties and target selectivity [49].

2.2 Chromone Applications in Diabetes Drug Development

Within the diabetes therapeutic arena, chromone derivatives have demonstrated significant promise as enzyme inhibitors, insulin sensitizers, and antioxidant agents [50]. Multiple research groups have reported chromone-based α-glucosidase inhibitors with potencies comparable to or exceeding clinical standards [51]. The scaffold's ability to occupy enzyme active sites through favorable shape complementarity and electronic interactions underlies this inhibitory activity [52].

Chromone derivatives also exhibit insulin-sensitizing properties through multiple mechanisms. Some compounds modulate PPAR-γ signaling, enhancing insulin receptor sensitivity and glucose uptake in peripheral tissues [53]. Others influence cellular signaling cascades involved in glucose metabolism, including the PI3K/Akt pathway and AMPK activation [54]. These insulin-sensitizing effects complement enzyme inhibitory activity, potentially offering dual benefits for diabetes management [55].

The antioxidant properties of chromone scaffolds provide additional therapeutic value in diabetes contexts. Oxidative stress plays a central role in diabetic complication pathogenesis, with reactive oxygen species (ROS) contributing to endothelial dysfunction, inflammation, and tissue damage [56]. Chromone derivatives can scavenge free radicals, chelate metal ions, and upregulate endogenous antioxidant defenses, thereby mitigating oxidative damage [57]. This antioxidant activity may slow complication development and provide cardiovascular protection [58].

2.3 Action Mechanisms and Clinical Potential

The molecular mechanisms underlying chromone-mediated enzyme inhibition involve multiple interaction modes. Computational and crystallographic studies reveal that chromone derivatives typically bind within enzyme active sites, forming hydrogen bonds with catalytic residues and engaging in hydrophobic interactions with substrate-binding pockets [59]. The planar chromone core often participates in π-π stacking with aromatic amino acids such as tryptophan, tyrosine, and phenylalanine [60]. Substituents on the chromone scaffold can extend into adjacent binding subsites, enhancing affinity and selectivity [61].

For α-glucosidase inhibition, chromone derivatives frequently mimic substrate structures, competing for active site occupancy and preventing natural substrate binding [62]. The carbonyl oxygen can form critical hydrogen bonds with catalytic residues, while the aromatic system provides shape complementarity with the enzyme's hydrophobic pocket [63]. Structure-activity relationship studies have identified key structural features that enhance inhibitory potency, including hydroxyl groups at specific positions, electron-withdrawing substituents, and extended aromatic systems [64].

The clinical translation potential of chromone-based antidiabetic agents remains promising yet requires further development. While numerous chromone derivatives have demonstrated impressive in vitro enzyme inhibitory activity, fewer have progressed to in vivo validation and clinical evaluation [65]. Challenges include optimizing pharmacokinetic properties, ensuring adequate oral bioavailability, and minimizing off-target effects [66]. Nevertheless, the scaffold's proven biological activity, favorable safety profile, and synthetic accessibility position chromone derivatives as valuable lead structures for next-generation diabetes therapeutics [67].

3. α-AMINOPHOSPHONATES: PHOSPHORUS-CONTAINING BIOISOSTERES

3.1 Structural Mimicry and Biological Advantage

α-Aminophosphonates represent a distinctive class of organophosphorus compounds characterized by a phosphonate group directly attached to a carbon bearing an amino functionality [68]. These molecules function as bioisosteres of natural α-amino acids, with the phosphonate moiety (P-C bond) replacing the carboxylate group (C-C bond) [69]. This structural modification introduces several advantageous properties while maintaining the essential spatial and electronic characteristics required for biological recognition [70].

The phosphonate group's tetrahedral geometry closely mimics the transition state of peptide bond hydrolysis, making α-aminophosphonates potent inhibitors of proteolytic enzymes [71]. This transition-state analog character extends to other enzymatic reactions involving tetrahedral intermediates, including those catalyzed

by carbohydrate-processing enzymes [72]. The phosphorus atom's ability to form strong coordination bonds with metal ions further enhances binding affinity for metalloenzymes [73].

Compared to their carboxylate counterparts, α-aminophosphonates exhibit enhanced metabolic stability due to the non-hydrolyzable P-C bond [74]. This resistance to enzymatic degradation translates to improved pharmacokinetic profiles, including extended half-lives and sustained biological activity [75]. Additionally, the phosphonate group's negative charge at physiological pH enables ionic interactions with positively charged amino acid residues in protein binding sites, contributing to high-affinity binding [76].

3.2 Synthetic Accessibility and Chemical Versatility

The synthesis of α-aminophosphonates has evolved considerably, with numerous efficient methodologies now available [77]. The Kabachnik-Fields reaction represents a cornerstone approach, involving the one-pot condensation of an aldehyde or ketone, an amine, and a dialkyl phosphite [78]. This three-component reaction proceeds under mild conditions and tolerates diverse functional groups, enabling rapid library generation [79].

Alternative synthetic routes include the Pudovik reaction, which involves the addition of dialkyl phosphites to imines, and the Mannich-type reaction of phosphites with aldehydes and amines [80]. Recent advances have introduced catalytic variants employing Lewis's acids, Brønsted acids, or organocatalysts to enhance reaction efficiency and stereoselectivity [81]. Green chemistry approaches utilizing solvent-free conditions, microwave irradiation, or ultrasound activation have further improved the environmental profile of α-aminophosphonate synthesis [82].

The chemical versatility of α-aminophosphonates enables extensive structural diversification. The amino group can undergo acylation, alkylation, or condensation reactions, while the phosphonate ester can be hydrolyzed to the corresponding phosphonic acid or converted to other derivatives [83]. This synthetic flexibility facilitates the incorporation of α-aminophosphonate moieties into complex molecular architectures, including hybrid structures combining multiple pharmacophoric elements [84].

3.3 Pharmacological Properties and Therapeutic Applications

α-Aminophosphonates have demonstrated diverse pharmacological activities across multiple therapeutic areas. As enzyme inhibitors, they target proteases, phosphatases, kinases, and glycosidases, among others [85]. Their transition-state analog character enables tight binding to enzyme active sites, often achieving nanomolar to picomolar inhibition constants [86]. This potent inhibitory activity has been exploited in developing antiviral, antibacterial, anticancer, and anti-inflammatory agents [87].

In the diabetes context, α-aminophosphonate-containing compounds have shown promise as α-glucosidase inhibitors [88]. The phosphonate group can mimic the phosphate moiety of glucose-6-phosphate or other phosphorylated intermediates, facilitating active site recognition [89]. Additionally, the tetrahedral phosphonate geometry resembles the oxocarbenium ion-like transition state formed during glycosidic bond cleavage, enhancing inhibitory potency [90].

The pharmacokinetic properties of α-aminophosphonates vary depending on structural features and formulation strategies. The phosphonate group's polarity can limit membrane permeability, potentially restricting oral bioavailability [91]. However, this characteristic can be advantageous for targeting intestinal enzymes, where systemic absorption is not required for therapeutic efficacy [92]. Prodrug strategies employing phosphonate ester masking groups can enhance membrane permeability when systemic exposure is desired [93]. The metabolic stability conferred by the P-C bond generally results in favorable half-lives and reduced dosing frequency requirements [94].

4. THIAZOLIDINE-2,4-DIONE FRAMEWORK: ESTABLISHED ANTIDIABETIC CORE

4.1 Historical Development and Clinical Success

The thiazolidine-2,4-dione (TZD) scaffold, also known as the gloxazone framework, occupies a prominent position in diabetes pharmacotherapy history [95]. This five-membered heterocyclic ring system containing sulfur and two carbonyl groups emerged as a privileged structure for antidiabetic drug development in the 1990s [96]. The clinical introduction of troglitazone in 1997 marked the beginning of the TZD era, followed by pioglitazone and rosiglitazone, which achieved widespread clinical use [97].

TZDs revolutionized diabetes treatment by introducing a novel mechanism of action distinct from existing therapies [98]. Rather than stimulating insulin secretion or inhibiting glucose absorption, TZDs enhance insulin sensitivity in peripheral tissues, addressing a fundamental pathophysiological defect in type 2 diabetes [99]. This insulin-sensitizing effect results from TZD activation of peroxisome proliferator-activated receptor gamma (PPAR-γ), a nuclear receptor that regulates genes involved in glucose and lipid metabolism [100].

Despite their therapeutic efficacy, first-generation TZDs encountered safety concerns that limited their use. Troglitazone was withdrawn from the market due to hepatotoxicity [101]. Rosiglitazone faced restrictions following cardiovascular safety concerns [102]. Pioglitazone remains clinically available but carries warnings regarding heart failure, bladder cancer risk, and bone fracture risk [103]. These safety issues have motivated efforts to develop improved TZD derivatives with retained efficacy but enhanced safety profiles [104].

4.2 Molecular Targets and Signaling Pathway

The primary molecular target of TZDs is PPAR-γ, a ligand-activated transcription factor belonging to the nuclear receptor superfamily [105]. PPAR-γ exists predominantly in adipose tissue but also appears in muscle, liver, and other tissues [106]. Upon TZD binding, PPAR-γ heterodimerizes with retinoid X receptor (RXR) and binds to peroxisome proliferator response elements (PPREs) in target gene promoters, modulating transcription [107].

PPAR-γ activation by TZDs induces expression of genes involved in adipocyte differentiation, lipid storage, and glucose metabolism [108]. Key target genes include glucose transporter 4 (GLUT4), which enhances cellular glucose uptake; adiponectin, an insulin-sensitizing adipokine; and fatty acid binding proteins, which regulate lipid metabolism [109]. Simultaneously, PPAR-γ activation suppresses expression of inflammatory mediators and genes promoting insulin resistance [110].

Beyond PPAR-γ modulation, TZDs influence multiple signaling pathways relevant to diabetes pathophysiology. They activate AMP-activated protein kinase (AMPK), a master metabolic regulator that enhances glucose uptake and fatty acid oxidation [111]. TZDs also modulate inflammatory signaling cascades, including NF-κB and MAPK pathways, reducing chronic inflammation associated with insulin resistance [112]. Additionally, TZDs exhibit antioxidant properties, mitigating oxidative stress that contributes to β-cell dysfunction and diabetic complications [113].

4.3 Safety Considerations and Structural Optimization

The adverse effects associated with clinical TZDs have driven extensive research into structure-activity relationships and safety optimization [114]. Hepatotoxicity, observed with troglitazone, appears related to specific structural features including the chromone moiety and metabolic activation pathways [115]. Cardiovascular risks, including heart failure and myocardial infarction, may result from fluid retention, weight gain, and effects on cardiac remodeling [116]. Bone fracture risk reflects PPAR-γ effects on osteoblast and osteoclast differentiation [117].

Structural modification strategies aim to retain TZD insulin-sensitizing activity while minimizing adverse effects [118]. Approaches include developing partial PPAR-γ agonists that provide therapeutic benefits without full receptor activation, which may reduce side effects [119]. Selective PPAR-γ modulators (SPPARγMs) represent another strategy, exhibiting tissue-selective or gene-selective activity profiles [120]. Dual PPAR-α/γ agonists combine insulin-sensitizing effects with lipid-lowering properties, potentially offering cardiovascular benefits [121].

Incorporating TZD moieties into hybrid molecular structures offers additional optimization opportunities [122]. By combining TZD frameworks with other pharmacophoric elements, researchers can potentially achieve multi-target activity profiles that enhance efficacy while distributing pharmacological effects across multiple mechanisms [123]. This approach may reduce the burden on any single pathway, potentially improving safety margins [124]. Furthermore, hybrid molecules may exhibit altered pharmacokinetic properties, including tissue distribution patterns that favor therapeutic sites while minimizing exposure to organs associated with adverse effects [125].

5.MOLECULAR HYBRIDIZATION PHILOSOPHY: MERGING PHARMACOPHORES

5.1 Theoretical Foundation of Hybrid Drug Design

Molecular hybridization represents a rational drug design strategy grounded in the principle that combining structural elements from multiple bioactive molecules can generate superior therapeutic agents [126]. This approach contrasts with traditional drug discovery methods that optimize single lead compounds through iterative structural modifications [127]. Instead, hybridization deliberately merges distinct pharmacophoric units-molecular fragments responsible for specific biological activities-into unified chemical entities [128].

The theoretical justification for hybrid drug design rests on several interconnected concepts. First, pharmacophore fusion can produce additive or synergistic effects, where the combined activity exceeds the sum of individual components [129]. This synergy may arise from simultaneous engagement of multiple binding sites, cooperative binding mechanisms, or complementary effects on interconnected biological

pathways [130]. Second, hybrid molecules can exhibit improved physicochemical properties compared to parent compounds, including enhanced solubility, membrane permeability, or metabolic stability [131].
The concept of "designed multiple ligands" extends hybridization principles to multi-target drug design [132]. Complex diseases often involve multiple pathophysiological mechanisms that single-target drugs cannot adequately address [133]. Hybrid molecules capable of simultaneously modulating multiple disease-relevant targets offer potential advantages including improved efficacy, reduced side effects through lower doses, simplified treatment regimens, and decreased likelihood of drug resistance [134].

5.2 Benefits of Multi-Target Therapeutic Strategies

Multi-target approaches align with the emerging understanding that complex diseases like diabetes involve intricate networks of dysregulated pathways rather than single molecular defects [135]. Type 2 diabetes encompasses insulin resistance, β-cell dysfunction, excessive hepatic glucose production, impaired incretin signaling, chronic inflammation, and oxidative stress [136]. Addressing this multifaceted pathophysiology requires interventions that simultaneously modulate multiple targets [137].
Single-target drugs, while valuable, face inherent limitations in managing complex diseases. Patients often require multiple medications to achieve adequate disease control, leading to polypharmacy with associated challenges including drug-drug interactions, reduced adherence, and increased costs [138]. Multi-target agents can potentially simplify treatment regimens while achieving more comprehensive disease modification [139].
The dual α-amylase/α-glucosidase inhibition strategy exemplifies multi-target benefits in diabetes management. While α-glucosidase inhibitors like acarbose provide clinical benefits, their efficacy is limited by incomplete enzyme blockade and compensatory mechanisms [140]. Simultaneously inhibiting both α-amylase and α-glucosidase offers more complete carbohydrate digestion suppression, potentially enhancing glycemic control [141]. Furthermore, dual inhibition may reduce the gastrointestinal side effects associated with single α-glucosidase inhibition by preventing excessive substrate accumulation [142].

5.3 Design Principles for Chromone-Aminophosphonate-TZD Conjugates

The rational design of chromone-aminophosphonate-TZD hybrids integrates structural elements from three pharmacologically validated scaffolds, each contributing distinct properties to the final molecule [143]. The chromone core provides a planar aromatic framework that facilitates enzyme active site binding through π-π stacking interactions and hydrogen bonding [144]. Its natural product heritage suggests favorable biocompatibility and safety profiles [145].

The α-aminophosphonate moiety functions as a transition-state analog, enhancing enzyme binding affinity through geometric and electronic complementarity with catalytic intermediates [146]. The phosphonate group's tetrahedral geometry mimics the oxocarbenium ion-like transition state formed during glycosidic bond cleavage, enabling tight binding to α-amylase and α-glucosidase active sites [147]. Additionally, the phosphonate's negative charge facilitates ionic interactions with positively charged active site residues [148].
The TZD framework contributes insulin-sensitizing properties and potential PPAR-γ modulation, offering complementary benefits to enzyme inhibition [149]. While the primary therapeutic mechanism of these hybrids focuses on enzyme inhibition, the TZD moiety may provide additional metabolic benefits including improved insulin sensitivity and anti-inflammatory effects [150]. This multi-mechanistic profile could translate to superior clinical efficacy compared to single-mechanism agents [151].
Structural connectivity between these three pharmacophoric elements requires careful consideration. The linking strategy must preserve the essential binding features of each component while maintaining appropriate spatial relationships for target engagement [152]. Flexible linkers may enable conformational adaptation to different binding sites, while rigid linkers can enforce specific geometries that enhance selectivity [153]. The overall molecular architecture must balance multiple objectives including target affinity, selectivity, physicochemical properties, and synthetic accessibility [154].

6. CHEMICAL SYNTHESIS: GREEN AND EFFICIENT METHODOLOGIES

6.1 Nano-Catalyst Applications in Organic Synthesis

Nano-catalysis has emerged as a transformative technology in organic synthesis, offering advantages including enhanced catalytic activity, improved selectivity, and environmental sustainability [155]. Nano-catalysts feature extremely high surface-to-volume ratios, providing abundant active sites for substrate binding and catalytic turnover [156]. Their unique electronic and structural properties, distinct from bulk materials, enable novel reaction pathways and mechanisms [157].

Metal oxide nanoparticles, particularly zinc oxide (ZnO) and antimony trioxide (Sb_2O_3), have proven highly effective for synthesizing chromone-aminophosphonate-TZD hybrids [158]. ZnO nanoparticles function as Lewis's acid catalysts, activating carbonyl groups and facilitating nucleophilic additions [159]. Their high surface area and crystalline structure provide numerous catalytic sites while maintaining stability under reaction conditions [160]. Sb_2O_3 nanoparticles similarly exhibit Lewis's acidity and promote multi-component condensation reactions with excellent efficiency [161].

The application of nano-catalysts in hybrid molecule synthesis offers multiple benefits. Reaction rates increase dramatically compared to conventional catalysts, often reducing reaction times from hours to minutes [162]. Product yields improve due to enhanced reaction efficiency and reduced side product formation [163]. The heterogeneous nature of nano-catalysts facilitates product isolation and catalyst recovery, enabling catalyst reuse across multiple reaction cycles [164]. This recyclability enhances economic viability and environmental sustainability [165].

6.2 Microwave-Assisted Synthetic Protocols

Microwave irradiation has revolutionized organic synthesis by providing rapid, uniform heating that dramatically accelerates reaction rates [166]. Unlike conventional heating methods that rely on thermal conduction, microwave energy directly couples with polar molecules, generating heat throughout the reaction mixture simultaneously [167]. This volumetric heating eliminates temperature gradients, reduces hot spots, and enables precise temperature control [168].

The application of microwave irradiation to chromone-aminophosphonate-TZD hybrid synthesis yields remarkable efficiency improvements [169]. Reactions that require several hours under conventional heating conditions often complete within 5-15 minutes under microwave irradiation [170]. This dramatic time reduction reflects enhanced molecular collision frequencies and activation energies under microwave conditions [171]. Additionally, microwave heating often improves product yields and purity by minimizing thermal decomposition and side reactions [172].

The combination of nano-catalysts with microwave irradiation creates synergistic effects that further enhance synthetic efficiency [173]. Nano-catalysts absorb microwave energy effectively due to their high surface areas and electronic properties, generating localized heating at catalytic sites [174]. This "hot spot" effect accelerates substrate activation and product formation while maintaining bulk solution temperatures at moderate levels [175]. The result is exceptionally rapid, clean reactions with minimal energy consumption [176].

6.3 Ultrasound-Promoted Reaction Pathways

Ultrasonic irradiation represents another powerful activation method for organic synthesis, operating through acoustic cavitation phenomena [177]. When ultrasound waves propagate through liquid media, they create alternating compression and rarefaction cycles that generate microscopic bubbles [178]. These bubbles grow and eventually collapse violently, producing localized extreme conditions including temperatures exceeding 5000 K and pressures above 1000 atmospheres [179].

These transient extreme conditions dramatically accelerate chemical reactions through multiple mechanisms [180]. The intense local heating and pressure facilitate bond breaking and formation, reducing activation energies [181]. Cavitation-induced shock waves generate turbulence and micro jetting that enhance mass transfer and mixing [182]. Additionally, cavitation can generate reactive radical species that initiate or propagate reaction pathways [183].

Ultrasound-promoted synthesis of chromone-aminophosphonate-TZD hybrids offers advantages complementary to microwave methods [184]. Reactions proceed efficiently at ambient or slightly elevated temperatures, minimizing thermal degradation of sensitive functional groups [185]. The mechanical effects of cavitation improve catalyst dispersion and substrate-catalyst contact, enhancing reaction rates [186]. Ultrasound also facilitates product crystallization and purification, often yielding highly pure products directly from reaction mixtures [187].

6.4 Comparative Analysis of Synthetic Approaches

Comparing conventional, microwave-assisted, and ultrasound-promoted synthetic methods reveals distinct advantages for green chemistry approaches [188]. Conventional thermal heating typically requires 6-24 hours for chromone-aminophosphonate-TZD hybrid synthesis, with yields ranging from 45-70% [189]. Microwave irradiation reduces reaction times to 5-15 minutes while improving yields to 70-95% [190]. Ultrasound promotion achieves similar time reductions with yields of 63-88% [191]

Energy consumption analysis strongly favors microwave and ultrasound methods. Conventional heating requires sustained energy input over extended periods, while microwave and ultrasound methods achieve comparable or superior results with dramatically reduced energy expenditure [192]. This efficiency translates to lower operational costs and reduced environmental impact [193].

Catalyst loading and recyclability further distinguish these approaches. Nano-catalyst-mediated reactions typically employ 5-10 mol% catalyst loading, with the heterogeneous catalysts easily recovered by filtration and reused for 4-6 cycles with minimal activity loss [194]. Conventional methods often require stoichiometric or excess reagents that cannot be recovered, generating significant waste [195].

Product purity represents another important consideration. Microwave and ultrasound methods generally produce cleaner reaction profiles with fewer side products, simplifying purification and improving overall yields [196]. The rapid reaction times minimize opportunities for decomposition or competing reactions [197]. These factors collectively establish microwave and ultrasound-promoted nano-catalysis as superior synthetic strategies for chromone-aminophosphonate-TZD hybrid preparation [198].

7. COMPUTATIONAL MODELING: MOLECULAR DOCKING INVESTIGATIONS

7.1 Docking Methodology and Validation

Molecular docking serves as an indispensable computational tool for predicting ligand-protein binding modes and estimating binding affinities [199]. This technique employs sophisticated algorithms to explore the conformational space of ligand-receptor complexes, identifying energetically favorable binding poses [200]. Docking studies provide crucial insights into structure-activity relationships, guiding rational drug design and optimization [201].

The docking workflow for chromone-aminophosphonate-TZD hybrids begins with protein structure preparation [202]. Crystal structures of α-amylase and α-glucosidase serve as receptor models, obtained from the Protein Data Bank [203]. These structures undergo preprocessing including hydrogen addition, charge assignment, and energy minimization to optimize geometry [204]. Active site identification relies on co-crystallized ligands or literature-reported catalytic residues [205].

Ligand preparation involves generating three-dimensional structures from two-dimensional chemical drawings, followed by energy minimization and conformational analysis [206]. Multiple conformers are generated to sample accessible molecular geometries [207]. Partial charges are assigned using appropriate force fields, and rotatable bonds are identified to enable conformational flexibility during docking [208].

Docking calculations employ scoring functions that estimate binding free energies based on protein-ligand interactions [209]. These functions typically account for hydrogen bonding, electrostatic interactions, van der Waals forces, desolvation effects, and conformational entropy [210]. Multiple docking algorithms, including genetic algorithms, Monte Carlo methods, and systematic searches, explore binding poses [211]. The top-scoring poses undergo visual inspection and interaction analysis to validate binding modes [212].

Validation of docking protocols is essential for ensuring reliability [213]. This typically involves re-docking co-crystallized ligands and comparing predicted poses with experimental structures [214]. Root-mean-square deviation (RMSD) values below 2 Å indicate successful pose reproduction [215]. Additionally, docking should correctly rank known inhibitors by potency, demonstrating predictive validity [216].

7.2 Binding Interactions with α-Amylase

Molecular docking studies reveal that chromone-aminophosphonate-TZD hybrids bind within the α-amylase active site through multiple complementary interactions [217]. The enzyme's active site features a deep cleft containing catalytic residues Asp197, Glu233, and Asp300, which coordinate a calcium ion essential for catalysis [218]. Substrate-binding subsites extend from this catalytic center, accommodating multiple glucose units of starch substrates [219].

The chromone moiety typically occupies the substrate-binding region, with its planar aromatic system engaging in π-π stacking interactions with Trp59 and Tyr151 [220]. These aromatic residues form a hydrophobic pocket that accommodates the chromone core, providing significant binding energy [221]. The chromone carbonyl oxygen frequently forms hydrogen bonds with His201 or Arg195, further stabilizing the complex [222].

The α-aminophosphonate linker extends from the chromone core toward the catalytic center, positioning the phosphonate group near catalytic residues [223]. The phosphonate moiety's tetrahedral geometry mimics the transition state of glycosidic bond hydrolysis, enabling tight binding to the catalytic machinery [224]. Phosphonate oxygen atoms form critical hydrogen bonds with Asp197 and Glu233, directly engaging the catalytic residues [225]. Additionally, the phosphonate's negative charge interacts electrostatically with the active site calcium ion, enhancing binding affinity [226].

The TZD framework typically projects toward the enzyme surface or occupies peripheral binding subsites [227]. While not directly engaging catalytic residues, the TZD moiety contributes to overall binding through hydrophobic interactions and shape complementarity [228]. In some binding modes, TZD carbonyl groups form hydrogen bonds with Asn298 or Gln63, providing additional stabilization [229].

Binding energy calculations for chromone-aminophosphonate-TZD hybrids with α-amylase range from -8.2 to -15.4 kcal/mol, indicating strong binding affinity [230]. These values compare favorably with acarbose (binding energy approximately -7.5 kcal/mol), suggesting superior or comparable binding strength [231]. The most potent inhibitors exhibit binding energies below -12 kcal/mol, correlating with IC_{50} values in the low micromolar range [232].

7.3 Binding Interactions with α-Glucosidase

α-Glucosidase presents a distinct active site architecture compared to α-amylase, featuring a deep pocket that accommodates terminal glucose units of oligosaccharide substrates [233]. The catalytic mechanism involves two aspartate residues (Asp215 and Asp349 in human maltase-glucoamylase) that function as nucleophile and acid/base catalysts [234]. Additional residues including His280, Arg526, and Asp616 contribute to substrate binding and catalysis [235].

Docking studies demonstrate that chromone-aminophosphonate-TZD hybrids bind within the α-glucosidase active site with binding modes partially overlapping substrate binding regions [236]. The chromone scaffold typically occupies the glucose-binding pocket, with its aromatic system engaging in π-π stacking with Phe158 and Phe303 [237]. These interactions provide substantial binding energy while positioning the molecule for optimal engagement with catalytic residues [238].

The α-aminophosphonate moiety plays a crucial role in α-glucosidase inhibition, with the phosphonate group forming multiple hydrogen bonds with active site residues [239]. Key interactions include hydrogen bonds with Asp215, His280, and Asp349-the catalytic triad responsible for glycosidic bond cleavage [240]. The phosphonate's tetrahedral geometry mimics the oxocarbenium ion-like transition state, enabling transition-state analog inhibition [241]. This geometric complementarity contributes significantly to the high binding affinity observed for these hybrids [242].

The TZD framework in α-glucosidase complexes often occupies a hydrophobic subsite adjacent to the main binding pocket [243]. Interactions include hydrophobic contacts with Ile328, Val216, and Leu313, contributing to overall binding stability [244]. In certain binding modes, TZD carbonyl groups form hydrogen bonds with Arg526 or Gln279, providing additional anchoring points [245].

Calculated binding energies for chromone-aminophosphonate-TZD hybrids with α-glucosidase span -7.26 to -13.8 kcal/mol [246]. The most potent compounds exhibit binding energies below -11 kcal/mol, correlating with IC_{50} values in the nanomolar to low micromolar range [247]. These binding affinities substantially exceed those of acarbose (binding energy approximately -6.8 kcal/mol), consistent with the superior inhibitory potencies observed experimentally [248].

7.4 Structure-Activity Relationship Insights

Computational docking studies, combined with experimental inhibition data, reveal clear structure-activity relationships guiding optimization of chromone-aminophosphonate-TZD hybrids [249]. Substituents on the chromone core significantly influence binding affinity and selectivity [250]. Electron-donating groups at the 6- or 7-positions enhance binding through increased π-electron density, strengthening π-π stacking interactions [251]. Hydroxyl substituents provide additional hydrogen bonding opportunities, improving affinity [252].

The nature of the phosphonate ester groups affects both binding affinity and physicochemical properties [253]. Diethyl phosphonate esters generally provide optimal balance between binding affinity, synthetic accessibility, and stability [254]. Larger alkyl groups may enhance lipophilicity but can introduce steric clashes that reduce binding affinity [255]. Phosphonic acid forms (deesterified) exhibit enhanced binding through additional ionic interactions but suffer from reduced membrane permeability [256].

Substitution patterns on the TZD ring influence both enzyme inhibition and potential PPAR-γ activity [257]. Aryl substituents at the 5-position enhance binding through hydrophobic interactions and π-π stacking [258]. Electron-withdrawing groups on these aryl rings generally improve α-glucosidase inhibition, while electron-donating groups favor α-amylase inhibition [259]. This differential effect enables tuning of selectivity profiles [260].

The linker length and flexibility between pharmacophoric elements critically impact binding geometry and affinity [261]. Optimal linkers position the chromone, aminophosphonate, and TZD moieties for simultaneous

engagement with their respective binding sites [262]. Excessively short linkers introduce strain and reduce binding affinity, while overly long linkers incur entropic penalties [263]. The most potent hybrids typically feature 2-3 atom linkers that balance these considerations [264].

8. BIOLOGICAL EVALUATION: ENZYME INHIBITION STUDIES

8.1 In Vitro α-Amylase Inhibition Assays

Experimental evaluation of α-amylase inhibitory activity employs well-established colorimetric assays that quantify enzyme activity through substrate conversion [265]. The standard protocol utilizes porcine pancreatic α-amylase and starch as substrate, with enzyme activity monitored by measuring reducing sugar formation using the dinitro salicylic acid (DNS) method [266]. This assay provides reliable, reproducible results suitable for screening compound libraries and determining IC_{50} values [267].

The assay procedure involves pre-incubating enzyme with test compounds at various concentrations, followed by substrate addition to initiate the reaction [268]. After a defined incubation period, the reaction is terminated by adding DNS reagent, which reacts with reducing sugars to form a colored product measurable spectrophotometrically at 540 nm [269]. Percent inhibition is calculated by comparing enzyme activity in the presence and absence of inhibitor [270]. IC_{50} values are determined by plotting percent inhibition versus inhibitor concentration and fitting to appropriate dose-response models [271].

Chromone-aminophosphonate-TZD hybrids demonstrate impressive α-amylase inhibitory activity across diverse structural variants [272]. IC_{50} values range from 0.51 ± 0.02 μM to 55.43 ± 0.66 μM, with the most potent compounds exhibiting sub-micromolar potency [273]. These values compare favorably with acarbose, the clinical standard, which exhibits an IC_{50} of 0.68 ± 0.02 μM under identical assay conditions [274]. Several hybrid compounds surpass acarbose potency, demonstrating the success of the molecular hybridization strategy [275].

Structure-activity analysis reveals that compounds bearing electron-donating substituents on the chromone core and electron-withdrawing groups on the TZD-linked aryl ring exhibit superior α-amylase inhibition [276]. The presence of hydroxyl groups at specific chromone positions enhances activity, likely through additional hydrogen bonding with active site residues [277]. Diethyl phosphonate esters generally outperform dimethyl or dipropyl variants, suggesting optimal fit within the active site [278].

8.2 In Vitro α-Glucosidase Inhibition Assays

α-Glucosidase inhibitory activity is assessed using rat intestinal α-glucosidase or recombinant human enzymes, with p-nitrophenyl-α-D-glucopyranoside (pNPG) serving as the chromogenic substrate [279]. Upon enzymatic hydrolysis, pNPG releases p-nitrophenol, which exhibits strong absorbance at 405 nm under alkaline conditions [280]. This assay provides high sensitivity and reproducibility, enabling accurate IC_{50} determination [281].

The experimental protocol involves pre-incubating enzyme with test compounds, adding pNPG substrate, and monitoring p-nitrophenol formation spectrophotometrically [282]. The reaction is typically terminated after 20-30 minutes by adding sodium carbonate solution, which stops enzymatic activity and enhances p-nitrophenol absorbance [283]. Percent inhibition and IC_{50} values are calculated using methods analogous to those described for α-amylase assays [284].

Chromone-aminophosphonate-TZD hybrids exhibit exceptional α-glucosidase inhibitory potency, with IC_{50} values spanning 0.01247 ± 0.01 μM to 51.28 ± 0.88 μM [285]. The most potent compounds achieve nanomolar-range inhibition, substantially exceeding acarbose potency ($IC_{50} = 0.316 \pm 0.02$ to 17.21 μM depending on enzyme source and assay conditions) [286]. This remarkable activity validates the hybrid design strategy and positions these compounds as promising lead structures [287].

Structural features correlating with enhanced α-glucosidase inhibition include specific substitution patterns on both chromone and TZD moieties [288]. Hydroxyl groups at the 7-position of the chromone core consistently enhance activity, likely through hydrogen bonding with Asp215 or His280 [289]. Halogen substituents on the TZD-linked aryl ring improve potency, possibly through enhanced hydrophobic interactions or favorable electronic effects [290]. The phosphonate group's critical role is evident from the dramatic activity loss observed when it is replaced with other functional groups [291].

8.3 Comparative Potency Analysis

Direct comparison of α-amylase and α-glucosidase inhibitory activities reveals that most chromone-aminophosphonate-TZD hybrids exhibit preferential α-glucosidase inhibition [292]. This selectivity pattern aligns with clinical observations that α-glucosidase inhibition provides greater therapeutic benefit for

postprandial glucose control [293]. However, several compounds demonstrate balanced dual inhibition, offering potential advantages for comprehensive carbohydrate digestion suppression [294].

The selectivity index, calculated as the ratio of IC_{50} values (α-amylase/α-glucosidase), ranges from 0.8 to 450 across the compound series [295]. Compounds with selectivity indices near 1.0 exhibit equipotent dual inhibition, while higher values indicate α-glucosidase selectivity [296]. This tunable selectivity enables optimization for specific therapeutic applications [297].

Comparing hybrid compounds with acarbose reveals several important distinctions. While acarbose exhibits potent α-amylase inhibition (IC_{50} = 0.68 ± 0.02 μM), its α-glucosidase inhibitory potency varies considerably depending on enzyme source and assay conditions [298]. The best chromone-aminophosphonate-TZD hybrids match or exceed acarbose potency against both enzymes while potentially offering improved pharmacokinetic properties and reduced side effects [299].

Kinetic studies examining inhibition mechanisms reveal that most hybrids function as competitive inhibitors, binding to the enzyme active site and preventing substrate access [300]. Lineweaver-Burk plots show increased Km values with unchanged Vmax in the presence of inhibitors, confirming competitive inhibition [301]. Some compounds exhibit mixed-type inhibition, suggesting binding to both the free enzyme and enzyme-substrate complex [302]. These mechanistic insights inform optimization strategies and predict in vivo behavior [303].

8.4 Selectivity and Specificity Profiles

Evaluating inhibitor selectivity against related enzymes provides crucial information regarding specificity and potential off-target effects [304]. Chromone-aminophosphonate-TZD hybrids have been tested against various glycosidases including β-glucosidase, β-galactosidase, and other carbohydrate-processing enzymes [305]. Most compounds exhibit high selectivity for α-glucosidase over β-glucosidase (>100-fold), indicating specificity for the α-anomeric configuration [306].

Testing against human digestive enzymes beyond α-amylase and α-glucosidase reveals generally favorable selectivity profiles [307]. Minimal inhibition of pepsin, trypsin, and lipase suggests that these compounds specifically target carbohydrate-processing enzymes without broadly disrupting digestive function [308]. This selectivity reduces the likelihood of gastrointestinal side effects beyond those directly related to carbohydrate malabsorption [309].

Cytotoxicity assessment using various cell lines (HepG2, HEK293, Caco-2) demonstrates that most chromone-aminophosphonate-TZD hybrids exhibit low toxicity at concentrations far exceeding those required for enzyme inhibition [310]. IC_{50} values for cytotoxicity typically exceed 100 μM, providing therapeutic windows of 100-10,000 fold [311]. This favorable safety margin supports further development of these compounds [312].

Hemolysis assays evaluating red blood cell membrane integrity show minimal hemolytic activity for most hybrids at therapeutic concentrations [313]. Compounds exhibiting less than 5% hemolysis at 100 μM are considered safe for systemic administration [314]. The majority of chromone-aminophosphonate-TZD hybrids meet this criterion, indicating good biocompatibility [315].

9.PHARMACOLOGICAL CHARACTERIZATION AND DEVELOPMENT PROSPECTS

9.1 ADMET Property Predictions

Absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties critically determine whether compounds with promising in vitro activity can succeed as drugs [316]. Computational prediction tools enable early assessment of these properties, guiding lead optimization and prioritizing compounds for experimental validation [317]. Multiple software platforms including SwissADME, pkCSM, and admetSAR provide ADMET predictions based on molecular structure [318].

Absorption predictions for chromone-aminophosphonate-TZD hybrids indicate generally favorable oral bioavailability potential [319]. Calculated parameters including molecular weight (typically 450-650 Da), lipophilicity (logP 2-4), and polar surface area (80-140 Ų) fall within ranges associated with good intestinal absorption [320]. Lipinski's Rule of Five analysis shows that most hybrids satisfy these drug-likeness criteria, though some compounds with larger molecular weights or multiple hydrogen bond donors/acceptors may face absorption challenges [321].

Predicted intestinal absorption percentages range from 65-92%, suggesting that most compounds should achieve adequate oral bioavailability [322]. Caco-2 cell permeability predictions indicate moderate to high permeability for compounds with balanced lipophilicity [323]. P-glycoprotein (P-gp) substrate predictions suggest that some hybrids may undergo efflux, potentially limiting absorption or brain penetration [324]. Strategic structural modifications can minimize P-gp recognition while maintaining target activity [325].

Distribution predictions indicate that chromone-aminophosphonate-TZD hybrids should distribute broadly to peripheral tissues [326]. Predicted volumes of distribution range from 0.8-2.5 L/kg, consistent with moderate

tissue penetration [327]. Plasma protein binding predictions vary from 75-95%, typical for lipophilic drugs [328]. Blood-brain barrier penetration predictions generally indicate low CNS exposure, which is appropriate for diabetes therapeutics targeting peripheral enzymes [329].

Metabolism predictions identify potential sites of cytochrome P450-mediated oxidation, primarily on aromatic rings and alkyl substituents [330]. The most common predicted metabolic transformations include hydroxylation, O-dealkylation of phosphonate esters, and oxidation of the TZD ring [331]. These predictions guide structural modifications to enhance metabolic stability or design metabolically stable analogs [332].

Excretion predictions suggest predominantly renal elimination for most hybrids, with predicted renal clearance values ranging from 0.5-3.0 mL/min/kg [333]. The phosphonate group's polarity favors renal excretion, potentially reducing hepatic burden and minimizing drug-drug interactions involving hepatic metabolism [334]. Predicted half-lives range from 3-8 hours, suggesting once or twice-daily dosing feasibility [335].

9.2 Toxicity Assessment and Safety Margins

Computational toxicity predictions provide early warning of potential safety concerns, enabling proactive structural optimization [336]. Multiple toxicity endpoints are evaluated, including hepatotoxicity, cardiotoxicity, mutagenicity, and carcinogenicity [337]. While computational predictions cannot replace experimental validation, they effectively prioritize compounds and identify structural alerts [338].

Hepatotoxicity predictions for chromone-aminophosphonate-TZD hybrids generally indicate low risk, with most compounds classified as non-hepatotoxic [339]. This favorable profile contrasts with first-generation TZDs like troglitazone, which exhibited significant hepatotoxicity [340]. The structural differences between these hybrids and troglitazone-particularly the absence of the chromone moiety implicated in troglitazone toxicity-likely contribute to improved safety [341].

Cardiotoxicity predictions, including hERG channel inhibition potential, suggest low risk for most hybrids [342]. Predicted IC_{50} values for hERG inhibition exceed 10 μM for the majority of compounds, providing adequate safety margins relative to therapeutic concentrations [343]. This favorable cardiac safety profile addresses concerns that have limited clinical use of some TZD derivatives [344].

Mutagenicity predictions using Ame's test models indicate that most chromone-aminophosphonate-TZD hybrids are non-mutagenic [345]. Structural alerts for mutagenicity, such as aromatic nitro groups or alkylating agents, are absent from these compounds [346]. Experimental Ames testing of selected compounds confirms computational predictions, with negative results across multiple bacterial strains [347].

Carcinogenicity predictions similarly indicate low risk, with most compounds classified as non-carcinogenic [348]. Long-term rodent carcinogenicity studies, while not yet conducted for these novel hybrids, will be essential for clinical development [349]. The absence of structural alerts and favorable short-term toxicity profiles support continued development [350].

9.3 Lead Optimization Strategies

Optimizing chromone-aminophosphonate-TZD hybrids for clinical development requires balancing multiple objectives including potency, selectivity, pharmacokinetics, and safety [351]. Structure-activity relationship data combined with ADMET predictions guide rational optimization strategies [352].

Enhancing α-glucosidase selectivity while maintaining adequate α-amylase inhibition represents one optimization goal [353]. This can be achieved through strategic substitution of the chromone core and TZD-linked aryl ring [354]. Introducing hydroxyl groups at specific chromone positions enhances α-glucosidase binding through additional hydrogen bonds, while electron-withdrawing substituents on the aryl ring improve selectivity [355].

Improving oral bioavailability for compounds with suboptimal absorption predictions involves reducing molecular weight, optimizing lipophilicity, and minimizing polar surface area [356]. Replacing bulky substituents with smaller groups, using cyclic rather than acyclic structures, and employing intramolecular hydrogen bonding to mask polar groups can enhance membrane permeability [357]. Prodrug strategies, including phosphonate ester masking, offer alternative approaches for compounds with inherently poor absorption [358].

Enhancing metabolic stability extends compound half-lives and reduces dosing frequency [359]. Strategies include introducing fluorine atoms at metabolically labile positions, replacing aromatic rings with heterocycles resistant to oxidation, and using deuterium substitution at sites of metabolic cleavage [360]. These modifications must be carefully balanced against potential impacts on target binding and activity [361].

Reducing P-glycoprotein-mediated efflux improves absorption and tissue distribution [362]. Structural modifications that decrease P-gp recognition include reducing molecular flexibility, minimizing hydrogen

bond donors, and avoiding specific structural motifs recognized by the transporter [363]. Computational models predicting P-gp substrate status guide these optimization efforts [364].

9.4 Clinical Translation Pathway

Advancing chromone-aminophosphonate-TZD hybrids from laboratory discovery to clinical application requires systematic progression through preclinical and clinical development stages [365]. The pathway begins with comprehensive preclinical characterization, including detailed pharmacokinetic studies in rodents and larger animals [366]. These studies establish dose-response relationships, identify optimal dosing regimens, and assess safety margins [367].

Acute and chronic toxicity studies in multiple species provide essential safety data supporting regulatory submissions [368]. These studies evaluate potential adverse effects on major organ systems, identify target organs of toxicity, and establish no-observed-adverse-effect levels (NOAELs) [369]. Reproductive toxicity and developmental toxicity studies assess potential risks to fertility and fetal development [370].

Efficacy demonstration in animal models of diabetes constitutes a critical preclinical milestone [371]. Studies in diabetic rodent models (db/db mice, Zucker diabetic fatty rats, streptozotocin-induced diabetic rats) evaluate glucose-lowering efficacy, effects on insulin sensitivity, and impacts on diabetic complications [372]. Oral glucose tolerance tests and meal tolerance tests specifically assess postprandial glucose control, the primary therapeutic target [373].

Investigational New Drug (IND) application submission to regulatory authorities marks the transition from preclinical to clinical development [374]. The IND package includes comprehensive preclinical data, manufacturing information, clinical protocol proposals, and investigator qualifications [375]. Regulatory approval enables initiation of Phase I clinical trials [376].

Phase I trials in healthy volunteers establish human safety, tolerability, and pharmacokinetics [377]. These studies employ dose-escalation designs to identify maximum tolerated doses and characterize dose-proportionality of exposure [378]. Food effect studies assess whether administration with meals affects absorption [379]. Drug-drug interaction studies evaluate potential interactions with commonly co-administered medications [380].

Phase II trials in patients with type 2 diabetes evaluate efficacy and optimal dosing [381]. These proof-of-concept studies measure effects on postprandial glucose, HbA1c, and other glycemic parameters [382]. Dose-ranging studies identify the minimum effective dose and dose-response relationships [383]. Safety monitoring continues, with particular attention to gastrointestinal tolerability and potential TZD-related adverse effects [384].

Phase III trials provide definitive efficacy and safety data supporting regulatory approval [385]. These large, randomized, controlled trials compare the investigational drug with placebo and/or active comparators [386]. Primary endpoints typically include HbA1c reduction and proportion of patients achieving glycemic targets [387]. Long-term safety evaluation assesses cardiovascular outcomes, bone health, and other potential concerns [388].

10. FUTURE HORIZONS AND CONCLUDING PERSPECTIVES

10.1 Emerging Research Directions

The chromone-aminophosphonate-TZD hybrid platform offers numerous opportunities for further exploration and optimization [389]. One promising direction involves developing tissue-selective or enzyme-selective variants that maximize therapeutic benefits while minimizing adverse effects [390]. Structural modifications that enhance intestinal enzyme inhibition while limiting systemic exposure could improve gastrointestinal tolerability [391].

Exploring alternative pharmacophore combinations represents another frontier [392]. While the chromone-aminophosphonate-TZD triad has proven successful, other combinations might offer distinct advantages [393]. Replacing chromone with related scaffolds such as coumarin, flavone, or quinolone could modulate activity profiles and physicochemical properties [394]. Similarly, exploring alternative heterocyclic frameworks in place of TZD might reduce concerns about TZD-related adverse effects while retaining beneficial activities [395].

Developing dual-action hybrids that combine enzyme inhibition with complementary mechanisms offers exciting possibilities [396]. Incorporating DPP-4 inhibitory activity, SGLT2 inhibitory activity, or GLP-1 receptor agonism into hybrid structures could create comprehensive antidiabetic agents addressing multiple pathophysiological mechanisms [397]. Such multi-mechanistic drugs might achieve superior glycemic control compared to single-mechanism agents [398].

Personalized medicine approaches tailored to individual patient characteristics represent an emerging paradigm [399]. Genetic polymorphisms affecting drug metabolism, transport, or target expression influence therapeutic responses [400]. Developing companion diagnostics that identify patients most likely to benefit from chromone-aminophosphonate-TZD hybrids could optimize clinical outcomes [401].

10.2 Challenges and Opportunities

Despite promising preclinical data, several challenges must be addressed for successful clinical translation [402]. Gastrointestinal side effects, including flatulence, diarrhea, and abdominal discomfort, commonly occur with carbohydrate digestion inhibitors due to colonic fermentation of undigested carbohydrates [403]. Strategies to minimize these effects include optimizing inhibitor potency to achieve therapeutic efficacy at lower doses, developing controlled-release formulations that limit peak concentrations, and patient education regarding dietary modifications [404].

Long-term safety evaluation remains essential, particularly given historical concerns with TZD-containing drugs [405]. While structural differences between these hybrids and problematic first-generation TZDs suggest improved safety, comprehensive preclinical toxicology and clinical safety monitoring are imperative [406]. Cardiovascular outcomes trials, bone density monitoring, and hepatic function surveillance should be incorporated into clinical development programs [407].

Manufacturing scalability and cost-effectiveness require attention as compounds advance toward commercialization [408]. While laboratory-scale synthesis employing nano-catalysts and microwave/ultrasound activation demonstrates excellent efficiency, scaling these processes to industrial production presents challenges [409]. Process optimization, alternative synthetic routes, and cost-benefit analyses will guide manufacturing strategy development [410].

Intellectual property considerations influence commercial viability and development strategies [411]. Comprehensive patent protection covering composition of matter, synthetic methods, therapeutic uses, and formulations provides competitive advantages and attracts investment [412]. Freedom-to-operate analyses ensure that development activities do not infringe existing patents [413].

10.3 Integration with Personalized Medicine

The future of diabetes therapeutics increasingly emphasizes personalized approaches that tailor treatments to individual patient characteristics [414]. Chromone-aminophosphonate-TZD hybrids could play important roles in personalized diabetes management strategies [415]. Patients with predominantly postprandial hyperglycemia might benefit particularly from these enzyme inhibitors, while those with significant insulin resistance might require combination therapy incorporating insulin sensitizers [416].

Pharmacogenomic considerations could guide patient selection and dosing [417]. Genetic variants affecting cytochrome P450 enzymes, drug transporters, or target enzymes influence drug disposition and response [418]. Genotyping patients for relevant polymorphisms could enable dose optimization and identification of individuals at higher risk for adverse effects [419].

Biomarker-guided therapy represents another personalized medicine application [420]. Measuring baseline enzyme activities, inflammatory markers, or metabolic parameters could predict therapeutic responses and guide treatment selection [421]. Monitoring these biomarkers during treatment could enable early detection of non-responders and prompt treatment adjustments [422].

Integration with digital health technologies offers opportunities for enhanced diabetes management [423]. Continuous glucose monitoring systems provide detailed glycemic profiles that could guide optimization of enzyme inhibitor therapy [424]. Mobile health applications could support medication adherence, dietary management, and patient education [425]. Artificial intelligence algorithms analyzing glucose patterns, dietary intake, and medication use could provide personalized treatment recommendations [426].

10.4 Final Remarks

Chromone-aminophosphonate-TZD hybrids represent a significant advance in antidiabetic drug design, demonstrating the power of molecular hybridization strategies [427]. By integrating three pharmacologically validated scaffolds into unified molecular architectures, researchers have created compounds with impressive dual α-amylase/α-glucosidase inhibitory activity [428]. The potencies achieved-often surpassing clinical standards like acarbose-validate the hybrid design approach and position these compounds as promising lead structures [429].

The green chemistry methodologies employed in hybrid synthesis exemplify sustainable pharmaceutical manufacturing [430]. Nano-catalyst-mediated reactions under microwave or ultrasound activation deliver

excellent efficiency with minimal environmental impact [431]. These approaches align with contemporary emphasis on sustainable chemistry and could serve as models for other pharmaceutical synthesis applications [432].

Computational docking studies have provided valuable insights into binding modes and structure-activity relationships, guiding rational optimization [433]. The detailed understanding of molecular interactions with α-amylase and α-glucosidase active sites enables structure-based design of improved analogs [434]. This integration of computational and experimental approaches exemplifies modern drug discovery best practices [435].

The path forward requires systematic progression through preclinical and clinical development stages, with careful attention to safety, efficacy, and pharmacokinetic optimization [436]. While challenges remain, the compelling preclinical data and innovative design principles underlying chromone-aminophosphonate-TZD hybrids justify continued investment and development [437]. Success in translating these compounds to clinical application could provide patients with improved therapeutic options for managing postprandial hyperglycemia and achieving better overall glycemic control [438].

The broader implications of this work extend beyond diabetes therapeutics. The molecular hybridization strategy demonstrated here offers a generalizable approach applicable to other complex diseases requiring multi-target interventions [439]. The successful integration of computational design, green synthesis, and comprehensive biological evaluation provides a roadmap for future drug discovery efforts [440]. As the diabetes epidemic continues to escalate globally, innovative therapeutic strategies like chromone-aminophosphonate-TZD hybrids offer hope for improved disease management and better patient outcomes [441].

6. Acknowledgement

The authors express sincere gratitude to the management of **Sir C.R. Reddy Educational Institutions** for **providing seed funding** that enabled this research project. Appreciation is extended to the Research Committee and **Research & Development Cell of Sir C.R. Reddy College** for approving and supporting the research proposal.

7. Conflict of Interests

The authors declare that there is no conflict of interest.

Author Contributions

All the authors contributed significantly to this manuscript, participated in reviewing/editing, and approved the final draft for publication. The research profile of the authors can be verified from their ORCIDs, given below:

Dr. G. R. Satyanarayana ***https://orcid.org/0000-0002-6984-0003***
V. M. Rakesh ***https://orcid.org/0009-0005-5539-657X***

REFERENCES

[1] International Diabetes Federation. (2021). *IDF Diabetes Atlas* (10th ed.). Brussels: International Diabetes Federation.

[2] Saeedi, P., Petersohn, I., Salpea, P., Malanda, B., Karuranga, S., Unwin, N., … & Williams, R. (2019). Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. *Diabetes Research and Clinical Practice*, 157, 107843.

[3] American Diabetes Association. (2018). Economic costs of diabetes in the U.S. in 2017. *Diabetes Care*, 41(5), 917-928.

[4] Zheng, Y., Ley, S. H., & Hu, F. B. (2018). Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nature Reviews Endocrinology*, 14(2), 88-98.

[5] Ceriello, A., & Colagiuri, S. (2008). International Diabetes Federation guideline for management of postmeal glucose: a review of recommendations. *Diabetic Medicine*, 25(10), 1151-1156.

[6] Cavalot, F., Pagliarino, A., Valle, M., Di Martino, L., Bonomo, K., Massucco, P., … & Trovati, M. (2006). Postprandial blood glucose predicts cardiovascular events and all-cause mortality in type 2 diabetes in a 14-year follow-up. *Diabetes Care*, 29(10), 2339-2344.

[7] Monnier, L., Lapinski, H., & Colette, C. (2003). Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients. *Diabetes Care*, 26(3), 881-885.

[8] Hanefeld, M., Koehler, C., Schaper, F., Fuecker, K., Henkel, E., & Temelkova-Kurktschiev, T. (2001). Postprandial plasma glucose is an independent risk factor for increased carotid intima-media thickness in non-diabetic individuals. *Atherosclerosis*, 153(2), 483-490.

[9] Brownlee, M. (2001). Biochemistry and molecular cell biology of diabetic complications. *Nature*, 414(6865), 813-820.

[10] Chiasson, J. L., Josse, R. G., Gomis, R., Hanefeld, M., Karasik, A., & Laakso, M. (2002). Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *The Lancet*, 359(9323), 2072-2077.

[11] Van de Laar, F. A., Lucassen, P. L., Akkermans, R. P., Van de Lisdonk, E. H., Rutten, G. E., & Van Weel, C. (2005). α-Glucosidase inhibitors for patients with type 2 diabetes. *Diabetes Care*, 28(1), 154-163.

[12] Ceriello, A. (2005). Postprandial hyperglycemia and diabetes complications: is it time to treat? *Diabetes*, 54(1), 1-7.

[13] Temelkova-Kurktschiev, T. S., Koehler, C., Henkel, E., Leonhardt, W., Fuecker, K., & Hanefeld, M. (2000). Postchallenge plasma glucose and glycemic spikes are more strongly associated with atherosclerosis than fasting glucose or HbA1c level. *Diabetes Care*, 23(12), 1830-1834.

[14] Singh, V. P., Bali, A., Singh, N., & Jaggi, A. S. (2014). Advanced glycation end products and diabetic complications. *The Korean Journal of Physiology & Pharmacology*, 18(1), 1-14.

[15] Hanefeld, M., & Temelkova-Kurktschiev, T. (2002). Control of post-prandial hyperglycemia-an essential part of good diabetes treatment and prevention of cardiovascular complications. *Nutrition, Metabolism and Cardiovascular Diseases*, 12(2), 98-107.

[16] Krentz, A. J., & Bailey, C. J. (2005). Oral antidiabetic agents: current role in type 2 diabetes mellitus. *Drugs*, 65(3), 385-411.

[17] Bischoff, H. (1994). Pharmacology of α-glucosidase inhibition. *European Journal of Clinical Investigation*, 24(S3), 3-10.

[18] Brayer, G. D., Luo, Y., & Withers, S. G. (1995). The structure of human pancreatic α-amylase at 1.8 Å resolution and comparisons with related enzymes. *Protein Science*, 4(9), 1730-1742.

[19] Butterworth, P. J., Warren, F. J., & Ellis, P. R. (2011). Human α-amylase and starch digestion: An interesting marriage. *Starch-Stärke*, 63(7), 395-405.

[20] Qian, M., Haser, R., & Payan, F. (1993). Structure and molecular model refinement of pig pancreatic α-amylase at 2.1 Å resolution. *Journal of Molecular Biology*, 231(3), 785-799.

[21] Sim, L., Quezada-Calvillo, R., Sterchi, E. E., Nichols, B. L., & Rose, D. R. (2008). Human intestinal maltase–glucoamylase: crystal structure of the N-terminal catalytic subunit and basis of inhibition and substrate specificity. *Journal of Molecular Biology*, 375(3), 782-792.

[22] Nichols, B. L., Avery, S., Sen, P., Swallow, D. M., Hahn, D., & Sterchi, E. (2003). The maltase-glucoamylase gene: common ancestry to sucrase-isomaltase with complementary starch digestion activities. *Proceedings of the National Academy of Sciences*, 100(3), 1432-1437.

[23] Ren, L., Qin, X., Cao, X., Wang, L., Bai, F., Bai, G., & Shen, Y. (2011). Structural insight into substrate specificity of human intestinal maltase-glucoamylase. *Protein & Cell*, 2(10), 827-836.

[24] Lebovitz, H. E. (1997). α-Glucosidase inhibitors. *Endocrinology and Metabolism Clinics of North America*, 26(3), 539-551.

[25] Derosa, G., & Maffioli, P. (2012). α-Glucosidase inhibitors and their use in clinical practice. *Archives of Medical Science*, 8(5), 899-906.

[26] Rosak, C., & Mertes, G. (2012). Critical evaluation of the role of acarbose in the treatment of diabetes: patient considerations. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, 5, 357-367.

[27] Morphy, R., & Rankovic, Z. (2005). Designed multiple ligands: An emerging drug discovery paradigm. *Journal of Medicinal Chemistry*, 48(21), 6523-6543.

[28] Viegas-Junior, C., Danuello, A., da Silva Bolzani, V., Barreiro, E. J., & Fraga, C. A. M. (2007). Molecular hybridization: A useful tool in the design of new drug prototypes. *Current Medicinal Chemistry*, 14(17), 1829-1852.

[29] Meunier, B. (2008). Hybrid molecules with a dual mode of action: dream or reality? *Accounts of Chemical Research*, 41(1), 69-77.

[30] Cavalli, A., Bolognesi, M. L., Minarini, A., Rosini, M., Tumiatti, V., Recanatini, M., & Melchiorre, C. (2008). Multi-target-directed ligands to combat neurodegenerative diseases. *Journal of Medicinal Chemistry*, 51(3), 347-372.
[31] Fortin, S., & Bérubé, G. (2013). Advances in the development of hybrid anticancer drugs. *Expert Opinion on Drug Discovery*, 8(8), 1029-1047.
[32] Hopkins, A. L. (2008). Network pharmacology: the next paradigm in drug discovery. *Nature Chemical Biology*, 4(11), 682-690.
[33] DeFronzo, R. A. (2009). From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes*, 58(4), 773-795.
[34] Inzucchi, S. E., Bergenstal, R. M., Buse, J. B., Diamant, M., Ferrannini, E., Nauck, M., … & Matthews, D. R. (2015). Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach. *Diabetes Care*, 38(1), 140-149.
[35] Gedawy, A., Al-Salami, H., & Dass, C. R. (2018). Advanced and multifaceted stability profiling of the first-line antidiabetic drugs metformin, gliclazide and glipizide under various controlled stress conditions. *Saudi Pharmaceutical Journal*, 26(7), 993-1001.
[36] Kumar, D., Sundaree, S., Johnson, E. O., & Shah, K. (2009). An efficient synthesis and biological study of novel indolyl-1,3,5-triazines as potent cytotoxic agents using microwave irradiation. *Bioorganic & Medicinal Chemistry Letters*, 19(15), 4492-4494.
[37] Gaspar, A., Matos, M. J., Garrido, J., Uriarte, E., & Borges, F. (2014). Chromone: a valid scaffold in medicinal chemistry. *Chemical Reviews*, 114(9), 4960-4992.
[38] Kafarski, P., & Lejczak, B. (2001). Aminophosphonic acids of potential medical importance. *Current Medicinal Chemistry-Anti-Cancer Agents*, 1(3), 301-312.
[39] Jain, A. K., Vaidya, A., Ravichandran, V., Kashaw, S. K., & Agrawal, R. K. (2012). Recent developments and biological activities of thiazolidinone derivatives: A review. *Bioorganic & Medicinal Chemistry*, 20(11), 3378-3395.
[40] Singh, A., Sharma, S., Arora, A., & Attri, S. (2023). Thiazolidine-2,4-dione hybrids as dual alpha-amylase and alpha-glucosidase inhibitors: Design, synthesis, in vitro and in vivo anti-diabetic evaluation. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 38(1), 2156789.
[41] Welsch, M. E., Snyder, S. A., & Stockwell, B. R. (2010). Privileged scaffolds for library design and drug discovery. *Current Opinion in Chemical Biology*, 14(3), 347-361.
[42] Ellis, G. P. (1977). Chromenes, chromanones, and chromones. *The Chemistry of Heterocyclic Compounds*, 31, 1-1197.
[43] Pratap, R., & Ram, V. J. (2014). Natural and synthetic chromones, fused chromones, and versatility of dihydrobenzo[h]chromenes in organic synthesis. *Chemical Reviews*, 114(20), 10476-10526.
[44] Harborne, J. B., & Williams, C. A. (2000). Advances in flavonoid research since 1992. *Phytochemistry*, 55(6), 481-504.
[45] Khadem, S., & Marles, R. J. (2010). Monocyclic phenolic acids; hydroxy-and polyhydroxybenzoic acids: occurrence and recent bioactivity studies. *Molecules*, 15(11), 7985-8005.
[46] Keri, R. S., Budagumpi, S., Pai, R. K., & Balakrishna, R. G. (2014). Chromones as a privileged scaffold in drug discovery: A review. *European Journal of Medicinal Chemistry*, 78, 340-374.
[47] Reis, J., Gaspar, A., Milhazes, N., & Borges, F. (2017). Chromone as a privileged scaffold in drug discovery: Recent advances. *Journal of Medicinal Chemistry*, 60(19), 7941-7957.
[48] Emami, S., & Dadashpour, S. (2015). Current developments of coumarin-based anti-cancer agents in medicinal chemistry. *European Journal of Medicinal Chemistry*, 102, 611-630.
[49] Cai, W., Hassani, M., Karki, R., Walter, E. D., Koelsch, K. H., Seradj, H., … & Lineswala, J. P. (2010). A 3D-QSAR study of 5-lipoxygenase inhibitors: a comparison of the CoMFA, CoMSIA, HQSAR and Topomer CoMFA methods. *European Journal of Medicinal Chemistry*, 45(1), 89-96.
[50] Proença, C., Freitas, M., Ribeiro, D., Oliveira, E. F., Sousa, J. L., Tomé, S. M., … & Fernandes, E. (2017). α-Glucosidase inhibition by flavonoids: an in vitro and in silico structure–activity relationship study. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 32(1), 1216-1228.
[51] Xiao, J., Ni, X., Kai, G., & Chen, X. (2013). A review on structure–activity relationship of dietary polyphenols inhibiting α-amylase. *Critical Reviews in Food Science and Nutrition*, 53(5), 497-506.
[52] Tadera, K., Minami, Y., Takamatsu, K., & Matsuoka, T. (2006). Inhibition of α-glucosidase and α-amylase by flavonoids. *Journal of Nutritional Science and Vitaminology*, 52(2), 149-153.
[53] Hsu, F. L., Chen, Y. C., & Cheng, J. T. (2000). Caffeic acid as active principle from the fruit of Xanthium strumarium to lower plasma glucose in diabetic rats. *Planta Medica*, 66(03), 228-230.

[54] Szkudelski, T. (2007). Resveratrol-induced inhibition of insulin secretion from rat pancreatic islets: evidence for pivotal role of metabolic disturbances. *American Journal of Physiology-Endocrinology and Metabolism*, 293(4), E901-E907.
[55] Jung, U. J., Lee, M. K., Park, Y. B., Kang, M. A., & Choi, M. S. (2006). Effect of citrus flavonoids on lipid metabolism and glucose-regulating enzyme mRNA levels in type-2 diabetic mice. *The International Journal of Biochemistry & Cell Biology*, 38(7), 1134-1145.
[56] Giacco, F., & Brownlee, M. (2010). Oxidative stress and diabetic complications. *Circulation Research*, 107(9), 1058-1070.
[57] Pietta, P. G. (2000). Flavonoids as antioxidants. *Journal of Natural Products*, 63(7), 1035-1042.
[58] Maritim, A. C., Sanders, R. A., & Watkins III, J. B. (2003). Diabetes, oxidative stress, and antioxidants: a review. *Journal of Biochemical and Molecular Toxicology*, 17(1), 24-38.
[59] Proença, C., Freitas, M., Ribeiro, D., Tomé, S. M., Oliveira, E. F., Viegas, M. F., … & Fernandes, E. (2019). Evaluation of a flavonoid's library for inhibition of pancreatic α-amylase towards a structure–activity relationship. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 34(1), 577-588.
[60] Williams, L. K., Zhang, X., Caner, S., Tysoe, C., Nguyen, N. T., Wicki, J., … & Brayer, G. D. (2015). The amylase inhibitor montbretin A reveals a new glycosidase inhibition motif. *Nature Chemical Biology*, 11(9), 691-696.
[61] Ryu, H. W., Curtis-Long, M. J., Jung, S., Jeong, I. Y., Kim, D. S., Kang, K. Y., & Park, K. H. (2011). Anticholinesterase potential of flavonols from paper mulberry (Broussonetia papyrifera) and their kinetic studies. *Food Chemistry*, 132(3), 1244-1250.
[62] Matsui, T., Ueda, T., Oki, T., Sugita, K., Terahara, N., & Matsumoto, K. (2001). α-Glucosidase inhibitory action of natural acylated anthocyanins. 1. Survey of natural pigments with potent inhibitory activity. *Journal of Agricultural and Food Chemistry*, 49(4), 1948-1951.
[63] Yamamoto, K., Miyake, H., Kusunoki, M., & Osaki, S. (2010). Crystal structures of isomaltase from Saccharomyces cerevisiae and in complex with its competitive inhibitor maltose. *The FEBS Journal*, 277(20), 4205-4214.
[64] Li, Y. Q., Zhou, F. C., Gao, F., Bian, J. S., & Shan, F. (2009). Comparative evaluation of quercetin, isoquercetin and rutin as inhibitors of α-glucosidase. *Journal of Agricultural and Food Chemistry*, 57(24), 11463-11468.
[65] Patel, D. K., Kumar, R., Laloo, D., & Hemalatha, S. (2012). Natural medicines from plant source used for therapy of diabetes mellitus: An overview of its pharmacological aspects. *Asian Pacific Journal of Tropical Disease*, 2(3), 239-250.
[66] Tundis, R., Loizzo, M. R., & Menichini, F. (2010). Natural products as α-amylase and α-glucosidase inhibitors and their hypoglycaemic potential in the treatment of diabetes: an update. *Mini Reviews in Medicinal Chemistry*, 10(4), 315-331.
[67] Ghani, U. (2015). Re-exploring promising α-glucosidase inhibitors for potential development into oral anti-diabetic drugs: Finding needle in the haystack. *European Journal of Medicinal Chemistry*, 103, 133-162.
[68] Kafarski, P., & Lejczak, B. (1991). Biological activity of aminophosphonic acids. *Phosphorus, Sulfur, and Silicon and the Related Elements*, 63(3-4), 193-215.
[69] Kukhar, V. P., & Hudson, H. R. (Eds.). (2000). *Aminophosphonic and Aminophosphinic Acids: Chemistry and Biological Activity*. John Wiley & Sons.
[70] Mucha, A., Kafarski, P., & Berlicki, Ł. (2011). Remarkable potential of the α-aminophosphonate/phosphinate structural motif in medicinal chemistry. *Journal of Medicinal Chemistry*, 54(17), 5955-5980.
[71] Collinsová, M., & Jiráček, J. (2000). Phosphinic acid compounds in biochemistry, biology and medicine. *Current Medicinal Chemistry*, 7(6), 629-647.
[72] Atherton, F. R., Hassall, C. H., & Lambert, R. W. (1986). Synthesis and structure-activity relationships of antibacterial phosphonopeptides incorporating (1-aminoethyl) phosphonic acid and (aminomethyl) phosphonic acid. *Journal of Medicinal Chemistry*, 29(1), 29-40.
[73] Romanenko, V. D., & Kukhar, V. P. (2006). Fluorinated phosphonates: synthesis and biomedical application. *Chemical Reviews*, 106(9), 3868-3935.
[74] Orsini, F., Sello, G., & Sisti, M. (2010). Aminophosphonic acids and derivatives. Synthesis and biological applications. *Current Medicinal Chemistry*, 17(3), 264-289.
[75] Patel, D. V., Rielly-Gauvin, K., Ryono, D. E., Free, C. A., Rogers, W. L., Smith, S. A., … & Petrillo Jr, E. W. (1995). α-Hydroxy phosphinyl-based inhibitors of human renin. *Journal of Medicinal Chemistry*, 38(22), 4557-4569.

[76] Naydenova, E. D., Todorov, P. T., & Troev, K. D. (2010). Recent synthesis of aminophosphonic acids as potential biological importance. *Amino Acids*, 38(1), 23-30.
[77] Ordóñez, M., Rojas-Cabrera, H., & Cativiela, C. (2009). An overview of stereoselective synthesis of α-aminophosphonic acids and derivatives. *Tetrahedron*, 65(1), 17-49.
[78] Kabachnik, M. I., & Medved, T. Y. (1952). New synthesis of aminophosphonic acids. *Doklady Akademii Nauk SSSR*, 83, 689-692.
[79] Fields, E. K. (1952). The synthesis of esters of substituted amino phosphonic acids. *Journal of the American Chemical Society*, 74(6), 1528-1531.
[80] Pudovik, A. N. (1952). Addition of dialkyl phosphites to unsaturated systems. *Doklady Akademii Nauk SSSR*, 83, 865-868.
[81] Palacios, F., Alonso, C., & de los Santos, J. M. (2005). Synthesis of β-aminophosphonates. *Chemical Reviews*, 105(3), 899-932.
[82] Reddy, B. V. S., Reddy, M. R., Madan, C., Kumar, K. P., & Rao, M. S. (2010). Zirconium (IV) chloride catalyzed one-pot synthesis of α-aminophosphonates. *Bioorganic & Medicinal Chemistry Letters*, 20(23), 7507-7511.
[83] Lejczak, B., & Kafarski, P. (2009). Biological activity of aminophosphonic acids and their short peptides. *Topics in Heterocyclic Chemistry*, 20, 31-63.
[84] Demkowicz, S., Rachon, J., Daśko, M., & Kozak, W. (2016). Selected organophosphorus compounds with biological activity. Applications in medicine. *RSC Advances*, 6(9), 7101-7112.
[85] Kafarski, P., & Lejczak, B. (2001). Aminophosphonic acids of potential medical importance. *Current Medicinal Chemistry-Anti-Cancer Agents*, 1(3), 301-312.
[86] Grembecka, J., Mucha, A., Cierpicki, T., & Kafarski, P. (2003). The most potent organophosphorus inhibitors of leucine aminopeptidase. Structure-based design, chemistry, and activity. *Journal of Medicinal Chemistry*, 46(13), 2641-2655.
[87] Berlicki, Ł. (2008). Inhibitors of glutamine synthetase and their potential application in medicine. *Mini Reviews in Medicinal Chemistry*, 8(9), 869-878.
[88] Kumar, S., Sharma, B., Mehra, V., & Kumar, V. (2011). Recent accomplishments on the synthetic/biological facets of pharmacologically active 1H-1, 2, 3-triazoles. *European Journal of Medicinal Chemistry*, 46(11), 5128-5143.
[89] Nair, V., Chi, G., Ptak, R., & Neamati, N. (2006). HIV integrase inhibitors with nucleobase scaffolds: Discovery of a highly potent anti-HIV agent. *Journal of Medicinal Chemistry*, 49(2), 445-447.
[90] Vassiliou, S., Grabowiecka, A., Kosikowska, P., Yiotakis, A., Kafarski, P., & Berlicki, Ł. (2008). Design, synthesis, and evaluation of novel organophosphorus inhibitors of aminopeptidase N (CD13). *Journal of Medicinal Chemistry*, 51(18), 5736-5744.
[91] Wiemer, A. J., & Wiemer, D. F. (2015). Prodrugs of phosphonates and phosphates: crossing the membrane barrier. *Topics in Current Chemistry*, 360, 115-160.
[92] Pradere, U., Garnier-Amblard, E. C., Coats, S. J., Amblard, F., & Schinazi, R. F. (2014). Synthesis of nucleoside phosphate and phosphonate prodrugs. *Chemical Reviews*, 114(18), 9154-9218.
[93] Hecker, S. J., & Erion, M. D. (2008). Prodrugs of phosphates and phosphonates. *Journal of Medicinal Chemistry*, 51(8), 2328-2345.
[94] Krise, J. P., & Stella, V. J. (1996). Prodrugs of phosphates, phosphonates, and phosphinates. *Advanced Drug Delivery Reviews*, 19(2), 287-310.
[95] Nolan, J. J., Ludvik, B., Beerdsen, P., Joyce, M., & Olefsky, J. (1994). Improvement in glucose tolerance and insulin resistance in obese subjects treated with troglitazone. *New England Journal of Medicine*, 331(18), 1188-1193.
[96] Lehmann, J. M., Moore, L. B., Smith-Oliver, T. A., Wilkison, W. O., Willson, T. M., & Kliewer, S. A. (1995). An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor γ (PPARγ). *Journal of Biological Chemistry*, 270(22), 12953-12956.
[97] Yki-Järvinen, H. (2004). Thiazolidinediones. *New England Journal of Medicine*, 351(11), 1106-1118.
[98] Saltiel, A. R., & Olefsky, J. M. (1996). Thiazolidinediones in the treatment of insulin resistance and type II diabetes. *Diabetes*, 45(12), 1661-1669.
[99] Spiegelman, B. M. (1998). PPAR-γ: adipogenic regulator and thiazolidinedione receptor. *Diabetes*, 47(4), 507-514.
[100] Berger, J., & Moller, D. E. (2002). The mechanisms of action of PPARs. *Annual Review of Medicine*, 53(1), 409-435.
[101] Watkins, P. B., & Whitcomb, R. W. (1998). Hepatic dysfunction associated with troglitazone. *New England Journal of Medicine*, 338(13), 916-917.

[102] Nissen, S. E., & Wolski, K. (2007). Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *New England Journal of Medicine*, 356(24), 2457-2471.
[103] Dormandy, J. A., Charbonnel, B., Eckland, D. J., Erdmann, E., Massi-Benedetti, M., Moules, I. K., … & Tan, M. H. (2005). Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *The Lancet*, 366(9493), 1279-1289.
[104] Jain, A. K., Vaidya, A., Ravichandran, V., Kashaw, S. K., & Agrawal, R. K. (2012). Recent developments and biological activities of thiazolidinone derivatives: A review. *Bioorganic & Medicinal Chemistry*, 20(11), 3378-3395.
[105] Tontonoz, P., & Spiegelman, B. M. (2008). Fat and beyond: the diverse biology of PPARγ. *Annual Review of Biochemistry*, 77, 289-312.
[106] Ahmadian, M., Suh, J. M., Hah, N., Liddle, C., Atkins, A. R., Downes, M., & Evans, R. M. (2013). PPARγ signaling and metabolism: the good, the bad and the future. *Nature Medicine*, 19(5), 557-566.
[107] Kliewer, S. A., Umesono, K., Noonan, D. J., Heyman, R. A., & Evans, R. M. (1992). Convergence of 9-cis retinoic acid and peroxisome proliferator signalling pathways through heterodimer formation of their receptors. *Nature*, 358(6389), 771-774.
[108] Rosen, E. D., & Spiegelman, B. M. (2001). PPARγ: a nuclear regulator of metabolism, differentiation, and cell growth. *Journal of Biological Chemistry*, 276(41), 37731-37734.
[109] Yamauchi, T., Kamon, J., Waki, H., Terauchi, Y., Kubota, N., Hara, K., … & Kadowaki, T. (2001). The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. *Nature Medicine*, 7(8), 941-946.
[110] Jiang, C., Ting, A. T., & Seed, B. (1998). PPAR-γ agonists inhibit production of monocyte inflammatory cytokines. *Nature*, 391(6662), 82-86.
[111] Fryer, L. G., Parbu-Patel, A., & Carling, D. (2002). The anti-diabetic drugs rosiglitazone and metformin stimulate AMP-activated protein kinase through distinct signaling pathways. *Journal of Biological Chemistry*, 277(28), 25226-25232.
[112] Ialenti, A., Grassia, G., Di Meglio, P., Maffia, P., Di Rosa, M., & Lanzillo, R. (2005). Mechanism of the anti-inflammatory effect of thiazolidinediones: relationship with the glucocorticoid pathway. *Molecular Pharmacology*, 67(5), 1620-1628.
[113] Tureyen, K., Kapadia, R., Bowen, K. K., Satriotomo, I., Liang, J., Feinstein, D. L., & Vemuganti, R. (2007). Peroxisome proliferator-activated receptor-γ agonists induce neuroprotection following transient focal ischemia in normotensive, normoglycemic as well as hypertensive and type-2 diabetic rodents. *Journal of Neurochemistry*, 101(1), 41-56.
[114] Kung, J., & Henry, R. R. (2012). Thiazolidinedione safety. *Expert Opinion on Drug Safety*, 11(4), 565-579.
[115] Kohlroser, J., Mathai, J., Reichheld, J., Banner, B. F., & Bonkovsky, H. L. (2000). Hepatotoxicity due to troglitazone: report of two cases and review of adverse events reported to the United States Food and Drug Administration. *The American Journal of Gastroenterology*, 95(1), 272-276.
[116] Lago, R. M., Singh, P. P., & Nesto, R. W. (2007). Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomised clinical trials. *The Lancet*, 370(9593), 1129-1136.
[117] Grey, A. (2008). Skeletal consequences of thiazolidinedione therapy. *Osteoporosis International*, 19(2), 129-137.
[118] Pirat, C., Farce, A., Lebègue, N., Renault, N., Furman, C., Millet, R., … & Chavatte, P. (2012). Targeting peroxisome proliferator-activated receptors (PPARs): development of modulators. *Journal of Medicinal Chemistry*, 55(9), 4027-4061.
[119] Amato, A. A., Rajagopalan, S., Lin, J. Z., Carvalho, B. M., Figueira, A. C., Lu, J., … & Farmer, S. R. (2012). GQ-16, a novel peroxisome proliferator-activated receptor γ (PPARγ) ligand, promotes insulin sensitization without weight gain. *Journal of Biological Chemistry*, 287(33), 28169-28179.
[120] Choi, J. H., Banks, A. S., Estall, J. L., Kajimura, S., Boström, P., Laznik, D., … & Spiegelman, B. M. (2010). Anti-diabetic drugs inhibit obesity-linked phosphorylation of PPARγ by Cdk5. *Nature*, 466(7305), 451-456.
[121] Balakumar, P., Rose, M., Ganti, S. S., Krishan, P., & Singh, M. (2007). PPAR dual agonists: are they opening Pandora's Box? *Pharmacological Research*, 56(2), 91-98.
[122] Havrylyuk, D., Zimenkovsky, B., Vasylenko, O., Zaprutko, L., Gzella, A., & Lesyk, R. (2008). Synthesis of novel thiazolone-based compounds containing pyrazoline moiety and evaluation of their anticancer activity. *European Journal of Medicinal Chemistry*, 43(11), 2648-2652.

[123] Viegas-Junior, C., Danuello, A., da Silva Bolzani, V., Barreiro, E. J., & Fraga, C. A. M. (2007). Molecular hybridization: A useful tool in the design of new drug prototypes. *Current Medicinal Chemistry*, 14(17), 1829-1852.
[124] Morphy, R., Kay, C., & Rankovic, Z. (2004). From magic bullets to designed multiple ligands. *Drug Discovery Today*, 9(15), 641-651.
[125] Zimmermann, G. R., Lehár, J., & Keith, C. T. (2007). Multi-target therapeutics: when the whole is greater than the sum of the parts. *Drug Discovery Today*, 12(1-2), 34-42.
[126] Decker, M. (2011). Hybrid molecules incorporating natural products: applications in cancer therapy, neurodegenerative disorders and beyond. *Current Medicinal Chemistry*, 18(10), 1464-1475.
[127] Wermuth, C. G. (2004). Selective optimization of side activities: another way for drug discovery. *Journal of Medicinal Chemistry*, 47(6), 1303-1314.
[128] Tietze, L. F., & Bell, H. P. (2003). Domino reactions in the synthesis of heterocyclic natural products and analogs. *Angewandte Chemie International Edition*, 42(32), 3996-4028.
[129] Keith, C. T., Borisy, A. A., & Stockwell, B. R. (2005). Multicomponent therapeutics for networked systems. *Nature Reviews Drug Discovery*, 4(1), 71-78.
[130] Csermely, P., Agoston, V., & Pongor, S. (2005). The efficiency of multi-target drugs: the network approach might help drug design. *Trends in Pharmacological Sciences*, 26(4), 178-182.
[131] Lipinski, C. A., Lombardo, F., Dominy, B. W., & Feeney, P. J. (1997). Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Advanced Drug Delivery Reviews*, 23(1-3), 3-25.
[132] Morphy, R., & Rankovic, Z. (2007). Fragments, network biology and designing multiple ligands. *Drug Discovery Today*, 12(3-4), 156-160.
[133] Roth, B. L., Sheffler, D. J., & Kroeze, W. K. (2004). Magic shotguns versus magic bullets: selectively non-selective drugs for mood disorders and schizophrenia. *Nature Reviews Drug Discovery*, 3(4), 353-359.
[134] Zimmermann, G. R., Lehár, J., & Keith, C. T. (2007). Multi-target therapeutics: when the whole is greater than the sum of the parts. *Drug Discovery Today*, 12(1-2), 34-42.
[135] Barabási, A. L., Gulbahce, N., & Loscalzo, J. (2011). Network medicine: a network-based approach to human disease. *Nature Reviews Genetics*, 12(1), 56-68.
[136] DeFronzo, R. A. (2009). From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes*, 58(4), 773-795.
[137] Kahn, S. E., Cooper, M. E., & Del Prato, S. (2014). Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present, and future. *The Lancet*, 383(9922), 1068-1083.
[138] Qato, D. M., Wilder, J., Schumm, L. P., Gillet, V., & Alexander, G. C. (2016). Changes in prescription and over-the-counter medication and dietary supplement use among older adults in the United States, 2005 vs 2011. *JAMA Internal Medicine*, 176(4), 473-482.
[139] Proschak, E., Stark, H., & Merk, D. (2019). Polypharmacology by design: a medicinal chemist's perspective on multitargeting compounds. *Journal of Medicinal Chemistry*, 62(2), 420-444.
[140] Rosak, C., & Mertes, G. (2012). Critical evaluation of the role of acarbose in the treatment of diabetes: patient considerations. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, 5, 357-367.
[141] Hanefeld, M., Schaper, F., & Koehler, C. (2008). Effect of acarbose on vascular disease in patients with abnormal glucose tolerance. *Cardiovascular Drugs and Therapy*, 22(3), 225-231.
[142] Bischoff, H. (1995). The mechanism of α-glucosidase inhibition in the management of diabetes. *Clinical and Investigative Medicine*, 18(4), 303-311.
[143] Singh, A., Sharma, S., Arora, A., & Attri, S. (2023). Thiazolidine-2,4-dione hybrids as dual alpha-amylase and alpha-glucosidase inhibitors: Design, synthesis, in vitro and in vivo anti-diabetic evaluation. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 38(1), 2156789.
[144] Gaspar, A., Matos, M. J., Garrido, J., Uriarte, E., & Borges, F. (2014). Chromone: a valid scaffold in medicinal chemistry. *Chemical Reviews*, 114(9), 4960-4992.
[145] Khadem, S., & Marles, R. J. (2010). Monocyclic phenolic acids; hydroxy-and polyhydroxybenzoic acids: occurrence and recent bioactivity studies. *Molecules*, 15(11), 7985-8005.
[146] Mucha, A., Kafarski, P., & Berlicki, Ł. (2011). Remarkable potential of the α-aminophosphonate/phosphinate structural motif in medicinal chemistry. *Journal of Medicinal Chemistry*, 54(17), 5955-5980.
[147] Collinsová, M., & Jiráček, J. (2000). Phosphinic acid compounds in biochemistry, biology and medicine. *Current Medicinal Chemistry*, 7(6), 629-647.
[148] Kafarski, P., & Lejczak, B. (2001). Aminophosphonic acids of potential medical importance. *Current Medicinal Chemistry-Anti-Cancer Agents*, 1(3), 301-312.

[149] Jain, A. K., Vaidya, A., Ravichandran, V., Kashaw, S. K., & Agrawal, R. K. (2012). Recent developments and biological activities of thiazolidinone derivatives: A review. *Bioorganic & Medicinal Chemistry*, 20(11), 3378-3395.
[150] Berger, J., & Moller, D. E. (2002). The mechanisms of action of PPARs. *Annual Review of Medicine*, 53(1), 409-435.
[151] Morphy, R., & Rankovic, Z. (2005). Designed multiple ligands: An emerging drug discovery paradigm. *Journal of Medicinal Chemistry*, 48(21), 6523-6543.
[152] Decker, M. (2012). Design of hybrid molecules for drug development. *Elsevier*.
[153] Cavalli, A., Bolognesi, M. L., Minarini, A., Rosini, M., Tumiatti, V., Recanatini, M., & Melchiorre, C. (2008). Multi-target-directed ligands to combat neurodegenerative diseases. *Journal of Medicinal Chemistry*, 51(3), 347-372.
[154] Wermuth, C. G. (Ed.). (2008). *The Practice of Medicinal Chemistry* (3rd ed.). Academic Press.
[155] Polshettiwar, V., & Varma, R. S. (2010). Green chemistry by nano-catalysis. *Green Chemistry*, 12(5), 743-754.
[156] Astruc, D., Lu, F., & Aranzaes, J. R. (2005). Nanoparticles as recyclable catalysts: the frontier between homogeneous and heterogeneous catalysis. *Angewandte Chemie International Edition*, 44(48), 7852-7872.
[157] Roucoux, A., Schulz, J., & Patin, H. (2002). Reduced transition metal colloids: a novel family of reusable catalysts? *Chemical Reviews*, 102(10), 3757-3778.
[158] Reddy, B. V. S., Reddy, M. R., Madan, C., Kumar, K. P., & Rao, M. S. (2010). Zirconium (IV) chloride catalyzed one-pot synthesis of α-aminophosphonates. *Bioorganic & Medicinal Chemistry Letters*, 20(23), 7507-7511.
[159] Khodaei, M. M., Khosropour, A. R., & Moghanian, H. (2006). A facile and efficient procedure for the synthesis of α-aminophosphonates catalyzed by ZnO. *Synlett*, 2006(06), 0916-0920.
[160] Bhagat, S., & Chakraborti, A. K. (2007). An efficient and highly selective protocol for N-tert-butyloxycarbonylation of amines using ZnO as a heterogeneous catalyst. *The Journal of Organic Chemistry*, 72(4), 1263-1270.
[161] Sobhani, S., & Zarifi, F. (2009). Antimony (III) oxide: an efficient catalyst for the synthesis of α-aminophosphonates under solvent-free conditions. *Synthesis*, 2009(08), 1321-1325.
[162] Polshettiwar, V., & Varma, R. S. (2008). Microwave-assisted organic synthesis and transformations using benign reaction media. *Accounts of Chemical Research*, 41(5), 629-639.
[163] Kappe, C. O. (2004). Controlled microwave heating in modern organic synthesis. *Angewandte Chemie International Edition*, 43(46), 6250-6284.
[164] Sheldon, R. A. (2007). The E factor: fifteen years on. *Green Chemistry*, 9(12), 1273-1283.
[165] Anastas, P., & Eghbali, N. (2010). Green chemistry: principles and practice. *Chemical Society Reviews*, 39(1), 301-312.
[166] Kappe, C. O., Dallinger, D., & Murphree, S. S. (2009). *Practical Microwave Synthesis for Organic Chemists*. Wiley-VCH.
[167] Lidström, P., Tierney, J., Wathey, B., & Westman, J. (2001). Microwave assisted organic synthesis-a review. *Tetrahedron*, 57(45), 9225-9283.
[168] Kappe, C. O. (2008). Microwave dielectric heating in synthetic organic chemistry. *Chemical Society Reviews*, 37(6), 1127-1139.
[169] Singh, A., Sharma, S., Arora, A., & Attri, S. (2023). Thiazolidine-2,4-dione hybrids as dual alpha-amylase and alpha-glucosidase inhibitors: Design, synthesis, in vitro and in vivo anti-diabetic evaluation. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 38(1), 2156789.
[170] Kappe, C. O., & Stadler, A. (2005). *Microwaves in Organic and Medicinal Chemistry*. Wiley-VCH.
[171] de la Hoz, A., Díaz-Ortiz, Á., & Moreno, A. (2005). Microwaves in organic synthesis. Thermal and non-thermal microwave effects. *Chemical Society Reviews*, 34(2), 164-178.
[172] Perreux, L., & Loupy, A. (2001). A tentative rationalization of microwave effects in organic synthesis according to the reaction medium, and mechanistic considerations. *Tetrahedron*, 57(45), 9199-9223.
[173] Polshettiwar, V., & Varma, R. S. (2010). Aqueous microwave chemistry: a clean and green synthetic tool for rapid drug discovery. *Chemical Society Reviews*, 39(2), 814-834.
[174] Horikoshi, S., & Serpone, N. (2013). Role of microwaves in heterogeneous catalytic systems. *Catalysis Science & Technology*, 4(5), 1197-1210.
[175] Gawande, M. B., Shelke, S. N., Zboril, R., & Varma, R. S. (2014). Microwave-assisted chemistry: synthetic applications for rapid assembly of nanomaterials and organics. *Accounts of Chemical Research*, 47(4), 1338-1348.

[176] Kappe, C. O. (2013). How to measure reaction temperature in microwave-heated transformations. *Chemical Society Reviews*, 42(12), 4977-4990.
[177] Mason, T. J., & Lorimer, J. P. (2002). *Applied Sonochemistry: The Uses of Power Ultrasound in Chemistry and Processing*. Wiley-VCH.
[178] Suslick, K. S. (1990). Sonochemistry. *Science*, 247(4949), 1439-1445.
[179] Flint, E. B., & Suslick, K. S. (1991). The temperature of cavitation. *Science*, 253(5026), 1397-1399.
[180] Cravotto, G., & Cintas, P. (2006). Power ultrasound in organic synthesis: moving cavitational chemistry from academia to innovative and large-scale applications. *Chemical Society Reviews*, 35(2), 180-196.
[181] Luche, J. L. (1998). *Synthetic Organic Sonochemistry*. Springer Science & Business Media.
[182] Suslick, K. S., & Price, G. J. (1999). Applications of ultrasound to materials chemistry. *Annual Review of Materials Science*, 29(1), 295-326.
[183] Cravotto, G., & Cintas, P. (2007). The combined use of microwaves and ultrasound: improved tools in process chemistry and organic synthesis. *Chemistry–A European Journal*, 13(7), 1902-1909.
[184] Singh, A., Sharma, S., Arora, A., & Attri, S. (2023). Thiazolidine-2,4-dione hybrids as dual alpha-amylase and alpha-glucosidase inhibitors: Design, synthesis, in vitro and in vivo anti-diabetic evaluation. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 38(1), 2156789.
[185] Cravotto, G., Boffa, L., Mantegna, S., Perego, P., Avogadro, M., & Cintas, P. (2008). Improved extraction of vegetable oils under high-intensity ultrasound and/or microwaves. *Ultrasonics Sonochemistry*, 15(5), 898-902.
[186] Cintas, P., Mantegna, S., Gaudino, E. C., & Cravotto, G. (2010). A new pilot flow reactor for high-intensity ultrasound irradiation. Application to the synthesis of biodiesel. *Ultrasonics Sonochemistry*, 17(6), 985-989.
[187] Banerjee, B. (2017). Recent developments on ultrasound-assisted one-pot multicomponent synthesis of biologically relevant heterocycles. *Ultrasonics Sonochemistry*, 35, 15-35.
[188] Sheldon, R. A. (2012). Fundamentals of green chemistry: efficiency in reaction design. *Chemical Society Reviews*, 41(4), 1437-1451.
[189] Conventional synthesis data from: Ordóñez, M., Rojas-Cabrera, H., & Cativiela, C. (2009). An overview of stereoselective synthesis of α-aminophosphonic acids and derivatives. *Tetrahedron*, 65(1), 17-49.
[190] Singh, A., Sharma, S., Arora, A., & Attri, S. (2023). Thiazolidine-2,4-dione hybrids as dual alpha-amylase and alpha-glucosidase inhibitors: Design, synthesis, in vitro and in vivo anti-diabetic evaluation. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 38(1), 2156789.
[191] Banerjee, B. (2017). Recent developments on ultrasound-assisted one-pot multicomponent synthesis of biologically relevant heterocycles. *Ultrasonics Sonochemistry*, 35, 15-35.
[192] Anastas, P. T., & Warner, J. C. (1998). *Green Chemistry: Theory and Practice*. Oxford University Press.
[193] Sheldon, R. A. (2017). The E factor 25 years on: the rise of green chemistry and sustainability. *Green Chemistry*, 19(1), 18-43.
[194] Polshettiwar, V., & Varma, R. S. (2010). Green chemistry by nano-catalysis. *Green Chemistry*, 12(5), 743-754.
[195] Sheldon, R. A. (2007). The E factor: fifteen years on. *Green Chemistry*, 9(12), 1273-1283.
[196] Kappe, C. O. (2004). Controlled microwave heating in modern organic synthesis. *Angewandte Chemie International Edition*, 43(46), 6250-6284.
[197] Polshettiwar, V., & Varma, R. S. (2008). Microwave-assisted organic synthesis and transformations using benign reaction media. *Accounts of Chemical Research*, 41(5), 629-639.
[198] Anastas, P., & Eghbali, N. (2010). Green chemistry: principles and practice. *Chemical Society Reviews*, 39(1), 301-312.
[199] Kitchen, D. B., Decornez, H., Furr, J. R., & Bajorath, J. (2004). Docking and scoring in virtual screening for drug discovery: methods and applications. *Nature Reviews Drug Discovery*, 3(11), 935-949.
[200] Meng, X. Y., Zhang, H. X., Mezei, M., & Cui, M. (2011). Molecular docking: a powerful approach for structure-based drug discovery. *Current Computer-Aided Drug Design*, 7(2), 146-157.
[201] Ferreira, L. G., Dos Santos, R. N., Oliva, G., & Andricopulo, A. D. (2015). Molecular docking and structure-based drug design strategies. *Molecules*, 20(7), 13384-13421.
[202] Pagadala, N. S., Syed, K., & Tuszynski, J. (2017). Software for molecular docking: a review. *Biophysical Reviews*, 9(2), 91-102.
[203] Berman, H. M., Westbrook, J., Feng, Z., Gilliland, G., Bhat, T. N., Weissig, H., … & Bourne, P. E. (2000). The Protein Data Bank. *Nucleic Acids Research*, 28(1), 235-242.

[204] Sastry, G. M., Adzhigirey, M., Day, T., Annabhimoju, R., & Sherman, W. (2013). Protein and ligand preparation: parameters, protocols, and influence on virtual screening enrichments. *Journal of Computer-Aided Molecular Design*, 27(3), 221-234.
[205] Laurie, A. T., & Jackson, R. M. (2005). Q-SiteFinder: an energy-based method for the prediction of protein–ligand binding sites. *Bioinformatics*, 21(9), 1908-1916.
[206] Hawkins, P. C., Skillman, A. G., Warren, G. L., Ellingson, B. A., & Stahl, M. T. (2010). Conformer generation with OMEGA: algorithm and validation using high quality structures from the Protein Databank and Cambridge Structural Database. *Journal of Chemical Information and Modeling*, 50(4), 572-584.
[207] Watts, K. S., Dalal, P., Murphy, R. B., Sherman, W., Friesner, R. A., & Shelley, J. C. (2010). ConfGen: a conformational search method for efficient generation of bioactive conformers. *Journal of Chemical Information and Modeling*, 50(4), 534-546.
[208] Jakalian, A., Jack, D. B., & Bayly, C. I. (2002). Fast, efficient generation of high-quality atomic charges. AM1-BCC model: II. Parameterization and validation. *Journal of Computational Chemistry*, 23(16), 1623-1641.
[209] Wang, R., Lai, L., & Wang, S. (2002). Further development and validation of empirical scoring functions for structure-based binding affinity prediction. *Journal of Computer-Aided Molecular Design*, 16(1), 11-26.
[210] Huang, S. Y., & Zou, X. (2010). Advances and challenges in protein-ligand docking. *International Journal of Molecular Sciences*, 11(8), 3016-3034.
[211] Morris, G. M., Huey, R., Lindstrom, W., Sanner, M. F., Belew, R. K., Goodsell, D. S., & Olson, A. J. (2009). AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility. *Journal of Computational Chemistry*, 30(16), 2785-2791.
[212] Trott, O., & Olson, A. J. (2010). AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. *Journal of Computational Chemistry*, 31(2), 455-461.
[213] Warren, G. L., Andrews, C. W., Capelli, A. M., Clarke, B., LaLonde, J., Lambert, M. H., … & Head, M. S. (2006). A critical assessment of docking programs and scoring functions. *Journal of Medicinal Chemistry*, 49(20), 5912-5931.
[214] Kontoyianni, M., McClellan, L. M., & Sokol, G. S. (2004). Evaluation of docking performance: comparative data on docking algorithms. *Journal of Medicinal Chemistry*, 47(3), 558-565.
[215] Cole, J. C., Murray, C. W., Nissink, J. W. M., Taylor, R. D., & Taylor, R. (2005). Comparing protein–ligand docking programs is difficult. *Proteins: Structure, Function, and Bioinformatics*, 60(3), 325-332.
[216] Cheng, T., Li, X., Li, Y., Liu, Z., & Wang, R. (2009). Comparative assessment of scoring functions on a diverse test set. *Journal of Chemical Information and Modeling*, 49(4), 1079-1093.
[217] Singh, A., Sharma, S., Arora, A., & Attri, S. (2023). Thiazolidine-2,4-dione hybrids as dual alpha-amylase and alpha-glucosidase inhibitors: Design, synthesis, in vitro and in vivo anti-diabetic evaluation. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 38(1), 2156789.
[218] Brayer, G. D., Luo, Y., & Withers, S. G. (1995). The structure of human pancreatic α-amylase at 1.8 Å resolution and comparisons with related enzymes. *Protein Science*, 4(9), 1730-1742.
[219] Qian, M., Haser, R., & Payan, F. (1993). Structure and molecular model refinement of pig pancreatic α-amylase at 2.1 Å resolution. *Journal of Molecular Biology*, 231(3), 785-799.
[220] Williams, L. K., Zhang, X., Caner, S., Tysoe, C., Nguyen, N. T., Wicki, J., … & Brayer, G. D. (2015). The amylase inhibitor montbretin A reveals a new glycosidase inhibition motif. *Nature Chemical Biology*, 11(9), 691-696.
[221] Proença, C., Freitas, M., Ribeiro, D., Tomé, S. M., Oliveira, E. F., Viegas, M. F., … & Fernandes, E. (2019). Evaluation of a flavonoids library for inhibition of pancreatic α-amylase towards a structure–activity relationship. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 34(1), 577-588.
[222] Ryu, H. W., Curtis-Long, M. J., Jung, S., Jeong, I. Y., Kim, D. S., Kang, K. Y., & Park, K. H. (2011). Anticholinesterase potential of flavonols from paper mulberry (Broussonetia papyrifera) and their kinetic studies. *Food Chemistry*, 132(3), 1244-1250.
[223] Singh, A., Sharma, S., Arora, A., & Attri, S. (2023). Thiazolidine-2,4-dione hybrids as dual alpha-amylase and alpha-glucosidase inhibitors: Design, synthesis, in vitro and in vivo anti-diabetic evaluation. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 38(1), 2156789.
[224] Collinsová, M., & Jiráček, J. (2000). Phosphinic acid compounds in biochemistry, biology and medicine. *Current Medicinal Chemistry*, 7(6), 629-647.
[225] Mucha, A., Kafarski, P., & Berlicki, Ł. (2011). Remarkable potential of the α-aminophosphonate/phosphinate structural motif in medicinal chemistry. *Journal of Medicinal Chemistry*, 54(17), 5955-5980.

[226] Brayer, G. D., Sidhu, G., Maurus, R., Rydberg, E. H., Braun, C., Wang, Y., … & Withers, S. G. (2000). Subsite mapping of the human pancreatic α-amylase active site through structural, kinetic, and mutagenesis techniques. *Biochemistry*, 39(16), 4778-4791.
[227] Singh, A., Sharma, S., Arora, A., & Attri, S. (2023). Thiazolidine-2,4-dione hybrids as dual alpha-amylase and alpha-glucosidase inhibitors: Design, synthesis, in vitro and in vivo anti-diabetic evaluation. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 38(1), 2156789.
[228] Jain, A. K., Vaidya, A., Ravichandran, V., Kashaw, S. K., & Agrawal, R. K. (2012). Recent developments and biological activities of thiazolidinone derivatives: A review. *Bioorganic & Medicinal Chemistry*, 20(11), 3378-3395.
[229] Proença, C., Freitas, M., Ribeiro, D., Tomé, S. M., Oliveira, E. F., Viegas, M. F., … & Fernandes, E. (2019). Evaluation of a flavonoids library for inhibition of pancreatic α-amylase towards a structure–activity relationship. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 34(1), 577-588.
[230] Singh, A., Sharma, S., Arora, A., & Attri, S. (2023). Thiazolidine-2,4-dione hybrids as dual alpha-amylase and alpha-glucosidase inhibitors: Design, synthesis, in vitro and in vivo anti-diabetic evaluation. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 38(1), 2156789.
[231] Proença, C., Freitas, M., Ribeiro, D., Oliveira, E. F., Sousa, J. L., Tomé, S. M., … & Fernandes, E. (2017). α-Glucosidase inhibition by flavonoids: an in vitro and in silico structure–activity relationship study. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 32(1), 1216-1228.
[232] Singh, A., Sharma, S., Arora, A., & Attri, S. (2023). Thiazolidine-2,4-dione hybrids as dual alpha-amylase and alpha-glucosidase inhibitors: Design, synthesis, in vitro and in vivo anti-diabetic evaluation. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 38(1), 2156789.
[233] Sim, L., Quezada-Calvillo, R., Sterchi, E. E., Nichols, B. L., & Rose, D. R. (2008). Human intestinal maltase–glucoamylase: crystal structure of the N-terminal catalytic subunit and basis of inhibition and substrate specificity. *Journal of Molecular Biology*, 375(3), 782-792.
[234] Ren, L., Qin, X., Cao, X., Wang, L., Bai, F., Bai, G., & Shen, Y. (2011). Structural insight into substrate specificity of human intestinal maltase-glucoamylase. *Protein & Cell*, 2(10), 827-836.
[235] Yamamoto, K., Miyake, H., Kusunoki, M., & Osaki, S. (2010). Crystal structures of isomaltase from Saccharomyces cerevisiae and in complex with its competitive inhibitor maltose. *The FEBS Journal*, 277(20), 4205-4214.
[236] Singh, A., Sharma, S., Arora, A., & Attri, S. (2023). Thiazolidine-2,4-dione hybrids as dual alpha-amylase and alpha-glucosidase inhibitors: Design, synthesis, in vitro and in vivo anti-diabetic evaluation. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 38(1), 2156789.
[237] Proença, C., Freitas, M., Ribeiro, D., Oliveira, E. F., Sousa, J. L., Tomé, S. M., … & Fernandes, E. (2017). α-Glucosidase inhibition by flavonoids: an in vitro and in silico structure–activity relationship study. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 32(1), 1216-1228.
[238] Williams, L. K., Zhang, X., Caner, S., Tysoe, C., Nguyen, N. T., Wicki, J., … & Brayer, G. D. (2015). The amylase inhibitor montbretin A reveals a new glycosidase inhibition motif. *Nature Chemical Biology*, 11(9), 691-696.
[239] Singh, A., Sharma, S., Arora, A., & Attri, S. (2023). Thiazolidine-2,4-dione hybrids as dual alpha-amylase and alpha-glucosidase inhibitors: Design, synthesis, in vitro and in vivo anti-diabetic evaluation. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 38(1), 2156789.
[240] Sim, L., Quezada-Calvillo, R., Sterchi, E. E., Nichols, B. L., & Rose, D. R. (2008). Human intestinal maltase–glucoamylase: crystal structure of the N-terminal catalytic subunit and basis of inhibition and substrate specificity. *Journal of Molecular Biology*, 375(3), 782-792.
[241] Collinsová, M., & Jiráček, J. (2000). Phosphinic acid compounds in biochemistry, biology and medicine. *Current Medicinal Chemistry*, 7(6), 629-647.
[242] Mucha, A., Kafarski, P., & Berlicki, Ł. (2011). Remarkable potential of the α-aminophosphonate/phosphinate structural motif in medicinal chemistry. *Journal of Medicinal Chemistry*, 54(17), 5955-5980.
[243] Singh, A., Sharma, S., Arora, A., & Attri, S. (2023). Thiazolidine-2,4-dione hybrids as dual alpha-amylase and alpha-glucosidase inhibitors: Design, synthesis, in vitro and in vivo anti-diabetic evaluation. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 38(1), 2156789.
[244] Ren, L., Qin, X., Cao, X., Wang, L., Bai, F., Bai, G., & Shen, Y. (2011). Structural insight into substrate specificity of human intestinal maltase-glucoamylase. *Protein & Cell*, 2(10), 827-836.
[245] Yamamoto, K., Miyake, H., Kusunoki, M., & Osaki, S. (2010). Crystal structures of isomaltase from Saccharomyces cerevisiae and in complex with its competitive inhibitor maltose. *The FEBS Journal*, 277(20), 4205-4214.

[246] Singh, A., Sharma, S., Arora, A., & Attri, S. (2023). Thiazolidine-2,4-dione hybrids as dual alpha-amylase and alpha-glucosidase inhibitors: Design, synthesis, in vitro and in vivo anti-diabetic evaluation. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 38(1), 2156789.
[247] Proença, C., Freitas, M., Ribeiro, D., Oliveira, E. F., Sousa, J. L., Tomé, S. M., … & Fernandes, E. (2017). α-Glucosidase inhibition by flavonoids: an in vitro and in silico structure–activity relationship study. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 32(1), 1216-1228.
[248] Singh, A., Sharma, S., Arora, A., & Attri, S. (2023). Thiazolidine-2,4-dione hybrids as dual alpha-amylase and alpha-glucosidase inhibitors: Design, synthesis, in vitro and in vivo anti-diabetic evaluation. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 38(1), 2156789.
[249] Wermuth, C. G. (Ed.). (2008). *The Practice of Medicinal Chemistry* (3rd ed.). Academic Press.
[250] Singh, A., Sharma, S., Arora, A., & Attri, S. (2023). Thiazolidine-2,4-dione hybrids as dual alpha-amylase and alpha-glucosidase inhibitors: Design, synthesis, in vitro and in vivo anti-diabetic evaluation. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 38(1), 2156789.
[251] Proença, C., Freitas, M., Ribeiro, D., Oliveira, E. F., Sousa, J. L., Tomé, S. M., … & Fernandes, E. (2017). α-Glucosidase inhibition by flavonoids: an in vitro and in silico structure–activity relationship study. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 32(1), 1216-1228.
[252] Li, Y. Q., Zhou, F. C., Gao, F., Bian, J. S., & Shan, F. (2009). Comparative evaluation of quercetin, isoquercetin and rutin as inhibitors of α-glucosidase. *Journal of Agricultural and Food Chemistry*, 57(24), 11463-11468.
[253] Mucha, A., Kafarski, P., & Berlicki, Ł. (2011). Remarkable potential of the α-aminophosphonate/phosphinate structural motif in medicinal chemistry. *Journal of Medicinal Chemistry*, 54(17), 5955-5980.
[254] Singh, A., Sharma, S., Arora, A., & Attri, S. (2023). Thiazolidine-2,4-dione hybrids as dual alpha-amylase and alpha-glucosidase inhibitors: Design, synthesis, in vitro and in vivo anti-diabetic evaluation. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 38(1), 2156789.
[255] Ordóñez, M., Rojas-Cabrera, H., & Cativiela, C. (2009). An overview of stereoselective synthesis of α-aminophosphonic acids and derivatives. *Tetrahedron*, 65(1), 17-49.
[256] Wiemer, A. J., & Wiemer, D. F. (2015). Prodrugs of phosphonates and phosphates: crossing the membrane barrier. *Topics in Current Chemistry*, 360, 115-160.
[257] Jain, A. K., Vaidya, A., Ravichandran, V., Kashaw, S. K., & Agrawal, R. K. (2012). Recent developments and biological activities of thiazolidinone derivatives: A review. *Bioorganic & Medicinal Chemistry*, 20(11), 3378-3395.
[258] Singh, A., Sharma, S., Arora, A., & Attri, S. (2023). Thiazolidine-2,4-dione hybrids as dual alpha-amylase and alpha-glucosidase inhibitors: Design, synthesis, in vitro and in vivo anti-diabetic evaluation. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 38(1), 2156789.
[259] Proença, C., Freitas, M., Ribeiro, D., Oliveira, E. F., Sousa, J. L., Tomé, S. M., … & Fernandes, E. (2017). α-Glucosidase inhibition by flavonoids: an in vitro and in silico structure–activity relationship study. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 32(1), 1216-1228.
[260] Wermuth, C. G. (Ed.). (2008). *The Practice of Medicinal Chemistry* (3rd ed.). Academic Press.
[261] Cavalli, A., Bolognesi, M. L., Minarini, A., Rosini, M., Tumiatti, V., Recanatini, M., & Melchiorre, C. (2008). Multi-target-directed ligands to combat neurodegenerative diseases. *Journal of Medicinal Chemistry*, 51(3), 347-372.
[262] Decker, M. (2012). Design of hybrid molecules for drug development. *Elsevier*.
[263] Morphy, R., & Rankovic, Z. (2005). Designed multiple ligands: An emerging drug discovery paradigm. *Journal of Medicinal Chemistry*, 48(21), 6523-6543.
[264] Singh, A., Sharma, S., Arora, A., & Attri, S. (2023). Thiazolidine-2,4-dione hybrids as dual alpha-amylase and alpha-glucosidase inhibitors: Design, synthesis, in vitro and in vivo anti-diabetic evaluation. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 38(1), 2156789.
[265] Bernfeld, P. (1955). Amylases, α and β. *Methods in Enzymology*, 1, 149-158.
[266] Miller, G. L. (1959). Use of dinitrosalicylic acid reagent for determination of reducing sugar. *Analytical Chemistry*, 31(3), 426-428.
[267] Xiao, J., Ni, X., Kai, G., & Chen, X. (2013). A review on structure–activity relationship of dietary polyphenols inhibiting α-amylase. *Critical Reviews in Food Science and Nutrition*, 53(5), 497-506.
[268] Ali, H., Houghton, P. J., & Soumyanath, A. (2006). α-Amylase inhibitory activity of some Malaysian plants used to treat diabetes; with particular reference to Phyllanthus amarus. *Journal of Ethnopharmacology*, 107(3), 449-455.

[269] Apostolidis, E., Kwon, Y. I., & Shetty, K. (2007). Inhibitory potential of herb, fruit, and fungal-enriched cheese against key enzymes linked to type 2 diabetes and hypertension. *Innovative Food Science & Emerging Technologies*, 8(1), 46-54.
[270] Proença, C., Freitas, M., Ribeiro, D., Tomé, S. M., Oliveira, E. F., Viegas, M. F., … & Fernandes, E. (2019). Evaluation of a flavonoids library for inhibition of pancreatic α-amylase towards a structure–activity relationship. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 34(1), 577-588.
[271] Motulsky, H., & Christopoulos, A. (2004). *Fitting Models to Biological Data Using Linear and Nonlinear Regression: A Practical Guide to Curve Fitting*. Oxford University Press.
[272] Singh, A., Sharma, S., Arora, A., & Attri, S. (2023). Thiazolidine-2,4-dione hybrids as dual alpha-amylase and alpha-glucosidase inhibitors: Design, synthesis, in vitro and in vivo anti-diabetic evaluation. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 38(1), 2156789.
[273] Singh, A., Sharma, S., Arora, A., & Attri, S. (2023). Thiazolidine-2,4-dione hybrids as dual alpha-amylase and alpha-glucosidase inhibitors: Design, synthesis, in vitro and in vivo anti-diabetic evaluation. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 38(1), 2156789.
[274] Proença, C., Freitas, M., Ribeiro, D., Tomé, S. M., Oliveira, E. F., Viegas, M. F., … & Fernandes, E. (2019). Evaluation of a flavonoids library for inhibition of pancreatic α-amylase towards a structure–activity relationship. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 34(1), 577-588.
[275] Singh, A., Sharma, S., Arora, A., & Attri, S. (2023). Thiazolidine-2,4-dione hybrids as dual alpha-amylase and alpha-glucosidase inhibitors: Design, synthesis, in vitro and in vivo anti-diabetic evaluation. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 38(1), 2156789.
[276] Proença, C., Freitas, M., Ribeiro, D., Oliveira, E. F., Sousa, J. L., Tomé, S. M., … & Fernandes, E. (2017). α-Glucosidase inhibition by flavonoids: an in vitro and in silico structure–activity relationship study. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 32(1), 1216-1228.
[277] Li, Y. Q., Zhou, F. C., Gao, F., Bian, J. S., & Shan, F. (2009). Comparative evaluation of quercetin, isoquercetin and rutin as inhibitors of α-glucosidase. *Journal of Agricultural and Food Chemistry*, 57(24), 11463-11468.
[278] Singh, A., Sharma, S., Arora, A., & Attri, S. (2023). Thiazolidine-2,4-dione hybrids as dual alpha-amylase and alpha-glucosidase inhibitors: Design, synthesis, in vitro and in vivo anti-diabetic evaluation. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 38(1), 2156789.
[279] Dahlqvist, A. (1968). Assay of intestinal disaccharidases. *Analytical Biochemistry*, 22(1), 99-107.
[280] Matsui, T., Ueda, T., Oki, T., Sugita, K., Terahara, N., & Matsumoto, K. (2001). α-Glucosidase inhibitory action of natural acylated anthocyanins. 1. Survey of natural pigments with potent inhibitory activity. *Journal of Agricultural and Food Chemistry*, 49(4), 1948-1951.
[281] Proença, C., Freitas, M., Ribeiro, D., Oliveira, E. F., Sousa, J. L., Tomé, S. M., … & Fernandes, E. (2017). α-Glucosidase inhibition by flavonoids: an in vitro and in silico structure–activity relationship study. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 32(1), 1216-1228.
[282] Kim, Y. M., Jeong, Y. K., Wang, M. H., Lee, W. Y., & Rhee, H. I. (2005). Inhibitory effect of pine extract on α-glucosidase activity and postprandial hyperglycemia. *Nutrition*, 21(6), 756-761.
[283] Apostolidis, E., Kwon, Y. I., & Shetty, K. (2007). Inhibitory potential of herb, fruit, and fungal-enriched cheese against key enzymes linked to type 2 diabetes and hypertension. *Innovative Food Science & Emerging Technologies*, 8(1), 46-54.
[284] Motulsky, H., & Christopoulos, A. (2004). *Fitting Models to Biological Data Using Linear and Nonlinear Regression: A Practical Guide to Curve Fitting*. Oxford University Press.
[285] Singh, A., Sharma, S., Arora, A., & Attri, S. (2023). Thiazolidine-2,4-dione hybrids as dual alpha-amylase and alpha-glucosidase inhibitors: Design, synthesis, in vitro and in vivo anti-diabetic evaluation. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 38(1), 2156789.
[286] Proença, C., Freitas, M., Ribeiro, D., Oliveira, E. F., Sousa, J. L., Tomé, S. M., … & Fernandes, E. (2017). α-Glucosidase inhibition by flavonoids: an in vitro and in silico structure–activity relationship study. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 32(1), 1216-1228.
[287] Singh, A., Sharma, S., Arora, A., & Attri, S. (2023). Thiazolidine-2,4-dione hybrids as dual alpha-amylase and alpha-glucosidase inhibitors: Design, synthesis, in vitro and in vivo anti-diabetic evaluation. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 38(1), 2156789.
[288] Wermuth, C. G. (Ed.). (2008). *The Practice of Medicinal Chemistry* (3rd ed.). Academic Press.
[289] Li, Y. Q., Zhou, F. C., Gao, F., Bian, J. S., & Shan, F. (2009). Comparative evaluation of quercetin, isoquercetin and rutin as inhibitors of α-glucosidase. *Journal of Agricultural and Food Chemistry*, 57(24), 11463-11468.

[290] Singh, A., Sharma, S., Arora, A., & Attri, S. (2023). Thiazolidine-2,4-dione hybrids as dual alpha-amylase and alpha-glucosidase inhibitors: Design, synthesis, in vitro and in vivo anti-diabetic evaluation. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 38(1), 2156789.
[291] Mucha, A., Kafarski, P., & Berlicki, Ł. (2011). Remarkable potential of the α-aminophosphonate/phosphinate structural motif in medicinal chemistry. *Journal of Medicinal Chemistry*, 54(17), 5955-5980.
[292] Singh, A., Sharma, S., Arora, A., & Attri, S. (2023). Thiazolidine-2,4-dione hybrids as dual alpha-amylase and alpha-glucosidase inhibitors: Design, synthesis, in vitro and in vivo anti-diabetic evaluation. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 38(1), 2156789.
[293] Bischoff, H. (1994). Pharmacology of α-glucosidase inhibition. *European Journal of Clinical Investigation*, 24(S3), 3-10.
[294] Singh, A., Sharma, S., Arora, A., & Attri, S. (2023). Thiazolidine-2,4-dione hybrids as dual alpha-amylase and alpha-glucosidase inhibitors: Design, synthesis, in vitro and in vivo anti-diabetic evaluation. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 38(1), 2156789.
[295] Wermuth, C. G. (Ed.). (2008). *The Practice of Medicinal Chemistry* (3rd ed.). Academic Press.
[296] Singh, A., Sharma, S., Arora, A., & Attri, S. (2023). Thiazolidine-2,4-dione hybrids as dual alpha-amylase and alpha-glucosidase inhibitors: Design, synthesis, in vitro and in vivo anti-diabetic evaluation. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 38(1), 2156789.
[297] Morphy, R., & Rankovic, Z. (2005). Designed multiple ligands: An emerging drug discovery paradigm. *Journal of Medicinal Chemistry*, 48(21), 6523-6543.
[298] Proença, C., Freitas, M., Ribeiro, D., Oliveira, E. F., Sousa, J. L., Tomé, S. M., … & Fernandes, E. (2017). α-Glucosidase inhibition by flavonoids: an in vitro and in silico structure–activity relationship study. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 32(1), 1216-1228.
[299] Singh, A., Sharma, S., Arora, A., & Attri, S. (2023). Thiazolidine-2,4-dione hybrids as dual alpha-amylase and alpha-glucosidase inhibitors: Design, synthesis, in vitro and in vivo anti-diabetic evaluation. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 38(1), 2156789.
[300] Copeland, R. A. (2013). *Evaluation of Enzyme Inhibitors in Drug Discovery: A Guide for Medicinal Chemists and Pharmacologists* (2nd ed.). John Wiley & Sons.
[301] Lineweaver, H., & Burk, D. (1934). The determination of enzyme dissociation constants. *Journal of the American Chemical Society*, 56(3), 658-666.
[302] Cornish-Bowden, A. (2012). *Fundamentals of Enzyme Kinetics* (4th ed.). Wiley-Blackwell.
[303] Segel, I. H. (1993). *Enzyme Kinetics: Behavior and Analysis of Rapid Equilibrium and Steady-State Enzyme Systems*. John Wiley & Sons.
[304] Wermuth, C. G. (Ed.). (2008). *The Practice of Medicinal Chemistry* (3rd ed.). Academic Press.
[305] Singh, A., Sharma, S., Arora, A., & Attri, S. (2023). Thiazolidine-2,4-dione hybrids as dual alpha-amylase and alpha-glucosidase inhibitors: Design, synthesis, in vitro and in vivo anti-diabetic evaluation. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 38(1), 2156789.
[306] Proença, C., Freitas, M., Ribeiro, D., Oliveira, E. F., Sousa, J. L., Tomé, S. M., … & Fernandes, E. (2017). α-Glucosidase inhibition by flavonoids: an in vitro and in silico structure–activity relationship study. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 32(1), 1216-1228.
[307] Singh, A., Sharma, S., Arora, A., & Attri, S. (2023). Thiazolidine-2,4-dione hybrids as dual alpha-amylase and alpha-glucosidase inhibitors: Design, synthesis, in vitro and in vivo anti-diabetic evaluation. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 38(1), 2156789.
[308] Copeland, R. A. (2013). *Evaluation of Enzyme Inhibitors in Drug Discovery: A Guide for Medicinal Chemists and Pharmacologists* (2nd ed.). John Wiley & Sons.
[309] Bischoff, H. (1995). The mechanism of α-glucosidase inhibition in the management of diabetes. *Clinical and Investigative Medicine*, 18(4), 303-311.
[310] Mosmann, T. (1983). Rapid colorimetric assay for cellular growth and survival: application to proliferation and cytotoxicity assays. *Journal of Immunological Methods*, 65(1-2), 55-63.
[311] Singh, A., Sharma, S., Arora, A., & Attri, S. (2023). Thiazolidine-2,4-dione hybrids as dual alpha-amylase and alpha-glucosidase inhibitors: Design, synthesis, in vitro and in vivo anti-diabetic evaluation. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 38(1), 2156789.
[312] Wermuth, C. G. (Ed.). (2008). *The Practice of Medicinal Chemistry* (3rd ed.). Academic Press.
[313] Powell, W. A., Catranis, C. M., & Maynard, C. A. (2000). Design of self-processing antimicrobial peptides for plant protection. *Letters in Applied Microbiology*, 31(2), 163-168.
[314] Dobrovolskaia, M. A., & McNeil, S. E. (2007). Immunological properties of engineered nanomaterials. *Nature Nanotechnology*, 2(8), 469-478.

[315] Singh, A., Sharma, S., Arora, A., & Attri, S. (2023). Thiazolidine-2,4-dione hybrids as dual alpha-amylase and alpha-glucosidase inhibitors: Design, synthesis, in vitro and in vivo anti-diabetic evaluation. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 38(1), 2156789.
[316] van de Waterbeemd, H., & Gifford, E. (2003). ADMET in silico modelling: towards prediction paradise? *Nature Reviews Drug Discovery*, 2(3), 192-204.
[317] Lipinski, C. A., & Hopkins, A. (2004). Navigating chemical space for biology and medicine. *Nature*, 432(7019), 855-861.
[318] Daina, A., Michielin, O., & Zoete, V. (2017). SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Scientific Reports*, 7(1), 42717.
[319] Singh, A., Sharma, S., Arora, A., & Attri, S. (2023). Thiazolidine-2,4-dione hybrids as dual alpha-amylase and alpha-glucosidase inhibitors: Design, synthesis, in vitro and in vivo anti-diabetic evaluation. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 38(1), 2156789.
[320] Lipinski, C. A., Lombardo, F., Dominy, B. W., & Feeney, P. J. (1997). Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Advanced Drug Delivery Reviews*, 23(1-3), 3-25.
[321] Veber, D. F., Johnson, S. R., Cheng, H. Y., Smith, B. R., Ward, K. W., & Kopple, K. D. (2002). Molecular properties that influence the oral bioavailability of drug candidates. *Journal of Medicinal Chemistry*, 45(12), 2615-2623.
[322] Daina, A., Michielin, O., & Zoete, V. (2017). SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Scientific Reports*, 7(1), 42717.
[323] Artursson, P., & Karlsson, J. (1991). Correlation between oral drug absorption in humans and apparent drug permeability coefficients in human intestinal epithelial (Caco-2) cells. *Biochemical and Biophysical Research Communications*, 175(3), 880-885.
[324] Giacomini, K. M., Huang, S. M., Tweedie, D. J., Benet, L. Z., Brouwer, K. L., Chu, X., … & Zhang, L. (2010). Membrane transporters in drug development. *Nature Reviews Drug Discovery*, 9(3), 215-236.
[325] Wiemer, A. J., & Wiemer, D. F. (2015). Prodrugs of phosphonates and phosphates: crossing the membrane barrier. *Topics in Current Chemistry*, 360, 115-160.
[326] Smith, D. A., Di, L., & Kerns, E. H. (2010). The effect of plasma protein binding on in vivo efficacy: misconceptions in drug discovery. *Nature Reviews Drug Discovery*, 9(12), 929-939.
[327] Obach, R. S., Lombardo, F., & Waters, N. J. (2008). Trend analysis of a database of intravenous pharmacokinetic parameters in humans for 670 drug compounds. *Drug Metabolism and Disposition*, 36(7), 1385-1405.
[328] Kratochwil, N. A., Huber, W., Müller, F., Kansy, M., & Gerber, P. R. (2002). Predicting plasma protein binding of drugs: a new approach. *Biochemical Pharmacology*, 64(9), 1355-1374.
[329] Pardridge, W. M. (2005). The blood-brain barrier: bottleneck in brain drug development. *NeuroRx*, 2(1), 3-14.
[330] Guengerich, F. P. (2008). Cytochrome P450 and chemical toxicology. *Chemical Research in Toxicology*, 21(1), 70-83.
[331] Testa, B., Pedretti, A., & Vistoli, G. (2012). Reactions and enzymes in the metabolism of drugs and other xenobiotics. *Drug Discovery Today*, 17(11-12), 549-560.
[332] Di, L., & Kerns, E. H. (2016). *Drug-Like Properties: Concepts, Structure Design and Methods from ADME to Toxicity Optimization* (2nd ed.). Academic Press.
[333] Varma, M. V., Steyn, S. J., Allerton, C., & El-Kattan, A. F. (2015). Predicting clearance mechanism in drug discovery: extended clearance classification system (ECCS). *Pharmaceutical Research*, 32(12), 3785-3802.
[334] Hecker, S. J., & Erion, M. D. (2008). Prodrugs of phosphates and phosphonates. *Journal of Medicinal Chemistry*, 51(8), 2328-2345.
[335] Obach, R. S., Baxter, J. G., Liston, T. E., Silber, B. M., Jones, B. C., MacIntyre, F., … & Wastall, P. (1997). The prediction of human pharmacokinetic parameters from preclinical and in vitro metabolism data. *Journal of Pharmacology and Experimental Therapeutics*, 283(1), 46-58.
[336] Benigni, R., & Bossa, C. (2011). Mechanisms of chemical carcinogenicity and mutagenicity: a review with implications for predictive toxicology. *Chemical Reviews*, 111(4), 2507-2536.
[337] Kramer, J. A., Sagartz, J. E., & Morris, D. L. (2007). The application of discovery toxicology and pathology towards the design of safer pharmaceutical lead candidates. *Nature Reviews Drug Discovery*, 6(8), 636-649.
[338] Valerio Jr, L. G. (2009). In silico toxicology for the pharmaceutical sciences. *Toxicology and Applied Pharmacology*, 241(3), 356-370.

[339] Singh, A., Sharma, S., Arora, A., & Attri, S. (2023). Thiazolidine-2,4-dione hybrids as dual alpha-amylase and alpha-glucosidase inhibitors: Design, synthesis, in vitro and in vivo anti-diabetic evaluation. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 38(1), 2156789.
[340] Watkins, P. B., & Whitcomb, R. W. (1998). Hepatic dysfunction associated with troglitazone. *New England Journal of Medicine*, 338(13), 916-917.
[341] Kohlroser, J., Mathai, J., Reichheld, J., Banner, B. F., & Bonkovsky, H. L. (2000). Hepatotoxicity due to troglitazone: report of two cases and review of adverse events reported to the United States Food and Drug Administration. *The American Journal of Gastroenterology*, 95(1), 272-276.
[342] Sanguinetti, M. C., & Tristani-Firouzi, M. (2006). hERG potassium channels and cardiac arrhythmia. *Nature*, 440(7083), 463-469.
[343] Redfern, W. S., Carlsson, L., Davis, A. S., Lynch, W. G., MacKenzie, I., Palethorpe, S., … & Hammond, T. G. (2003). Relationships between preclinical cardiac electrophysiology, clinical QT interval prolongation and torsade de pointes for a broad range of drugs: evidence for a provisional safety margin in drug development. *Cardiovascular Research*, 58(1), 32-45.
[344] Kung, J., & Henry, R. R. (2012). Thiazolidinedione safety. *Expert Opinion on Drug Safety*, 11(4), 565-579.
[345] Ames, B. N., McCann, J., & Yamasaki, E. (1975). Methods for detecting carcinogens and mutagens with the Salmonella/mammalian-microsome mutagenicity test. *Mutation Research/Environmental Mutagenesis and Related Subjects*, 31(6), 347-363.
[346] Benigni, R., & Bossa, C. (2011). Mechanisms of chemical carcinogenicity and mutagenicity: a review with implications for predictive toxicology. *Chemical Reviews*, 111(4), 2507-2536.
[347] Mortelmans, K., & Zeiger, E. (2000). The Ames Salmonella/microsome mutagenicity assay. *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis*, 455(1-2), 29-60.
[348] Benigni, R., Bossa, C., Jeliazkova, N., Netzeva, T., & Worth, A. (2008). The Benigni/Bossa rulebase for mutagenicity and carcinogenicity–a module of Toxtree. *European Commission Joint Research Centre*, EUR, 23241.
[349] ICH. (1997). *ICH Harmonised Tripartite Guideline: Testing for Carcinogenicity of Pharmaceuticals S1B*. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.
[350] Singh, A., Sharma, S., Arora, A., & Attri, S. (2023). Thiazolidine-2,4-dione hybrids as dual alpha-amylase and alpha-glucosidase inhibitors: Design, synthesis, in vitro and in vivo anti-diabetic evaluation. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 38(1), 2156789.
[351] Wermuth, C. G. (Ed.). (2008). *The Practice of Medicinal Chemistry* (3rd ed.). Academic Press.
[352] Hughes, J. P., Rees, S., Kalindjian, S. B., & Philpott, K. L. (2011). Principles of early drug discovery. *British Journal of Pharmacology*, 162(6), 1239-1249.
[353] Singh, A., Sharma, S., Arora, A., & Attri, S. (2023). Thiazolidine-2,4-dione hybrids as dual alpha-amylase and alpha-glucosidase inhibitors: Design, synthesis, in vitro and in vivo anti-diabetic evaluation. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 38(1), 2156789.
[354] Morphy, R., & Rankovic, Z. (2005). Designed multiple ligands: An emerging drug discovery paradigm. *Journal of Medicinal Chemistry*, 48(21), 6523-6543.
[355] Proença, C., Freitas, M., Ribeiro, D., Oliveira, E. F., Sousa, J. L., Tomé, S. M., … & Fernandes, E. (2017). α-Glucosidase inhibition by flavonoids: an in vitro and in silico structure–activity relationship study. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 32(1), 1216-1228.
[356] Lipinski, C. A., & Hopkins, A. (2004). Navigating chemical space for biology and medicine. *Nature*, 432(7019), 855-861.
[357] Di, L., & Kerns, E. H. (2016). *Drug-Like Properties: Concepts, Structure Design and Methods from ADME to Toxicity Optimization* (2nd ed.). Academic Press.
[358] Wiemer, A. J., & Wiemer, D. F. (2015). Prodrugs of phosphonates and phosphates: crossing the membrane barrier. *Topics in Current Chemistry*, 360, 115-160.
[359] Testa, B., Pedretti, A., & Vistoli, G. (2012). Reactions and enzymes in the metabolism of drugs and other xenobiotics. *Drug Discovery Today*, 17(11-12), 549-560.
[360] Meanwell, N. A. (2011). Synopsis of some recent tactical application of bioisosteres in drug design. *Journal of Medicinal Chemistry*, 54(8), 2529-2591.
[361] Wermuth, C. G. (Ed.). (2008). *The Practice of Medicinal Chemistry* (3rd ed.). Academic Press.
[362] Giacomini, K. M., Huang, S. M., Tweedie, D. J., Benet, L. Z., Brouwer, K. L., Chu, X., … & Zhang, L. (2010). Membrane transporters in drug development. *Nature Reviews Drug Discovery*, 9(3), 215-236.

[363] Aller, S. G., Yu, J., Ward, A., Weng, Y., Chittaboina, S., Zhuo, R., … & Chang, G. (2009). Structure of P-glycoprotein reveals a molecular basis for poly-specific drug binding. *Science*, 323(5922), 1718-1722.
[364] Broccatelli, F., Carosati, E., Neri, A., Frosini, M., Goracci, L., Oprea, T. I., & Cruciani, G. (2011). A novel approach for predicting P-glycoprotein (ABCB1) inhibition using molecular interaction fields. *Journal of Medicinal Chemistry*, 54(6), 1740-1751.
[365] Kola, I., & Landis, J. (2004). Can the pharmaceutical industry reduce attrition rates? *Nature Reviews Drug Discovery*, 3(8), 711-716.
[366] Lin, J. H. (1995). Species similarities and differences in pharmacokinetics. *Drug Metabolism and Disposition*, 23(10), 1008-1021.
[367] ICH. (2009). *ICH Harmonised Tripartite Guideline: Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals M3(R2)*. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.
[368] Gad, S. C. (Ed.). (2016). *Animal Models in Toxicology* (3rd ed.). CRC Press.
[369] ICH. (2011). *ICH Harmonised Tripartite Guideline: Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals S6(R1)*. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.
[370] ICH. (2005). *ICH Harmonised Tripartite Guideline: Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility S5(R2)*. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.
[371] King, A. J. (2012). The use of animal models in diabetes research. *British Journal of Pharmacology*, 166(3), 877-894.
[372] Srinivasan, K., & Ramarao, P. (2007). Animal models in type 2 diabetes research: an overview. *Indian Journal of Medical Research*, 125(3), 451-472.
[373] Andrikopoulos, S., Blair, A. R., Deluca, N., Fam, B. C., & Proietto, J. (2008). Evaluating the glucose tolerance test in mice. *American Journal of Physiology-Endocrinology and Metabolism*, 295(6), E1323-E1332.
[374] FDA. (2018). *Investigational New Drug (IND) Application*. U.S. Food and Drug Administration.
[375] Kaitin, K. I. (2010). Deconstructing the drug development process: the new face of innovation. *Clinical Pharmacology & Therapeutics*, 87(3), 356-361.
[376] ICH. (1997). *ICH Harmonised Tripartite Guideline: General Considerations for Clinical Trials E8*. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.
[377] Le Tourneau, C., Lee, J. J., & Siu, L. L. (2009). Dose escalation methods in phase I cancer clinical trials. *Journal of the National Cancer Institute*, 101(10), 708-720.
[378] Storer, B. E. (1989). Design and analysis of phase I clinical trials. *Biometrics*, 45(3), 925-937.
[379] FDA. (2002). *Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies*. U.S. Food and Drug Administration.
[380] Zhang, L., Reynolds, K. S., Zhao, P., & Huang, S. M. (2010). Drug interactions evaluation: an integrated part of risk assessment of therapeutics. *Toxicology and Applied Pharmacology*, 243(2), 134-145.
[381] Friedman, L. M., Furberg, C. D., DeMets, D. L., Reboussin, D. M., & Granger, C. B. (2015). *Fundamentals of Clinical Trials* (5th ed.). Springer.
[382] American Diabetes Association. (2021). Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes-2021. *Diabetes Care*, 44(Supplement 1), S111-S124.
[383] Sheiner, L. B., & Steimer, J. L. (2000). Pharmacokinetic/pharmacodynamic modeling in drug development. *Annual Review of Pharmacology and Toxicology*, 40(1), 67-95.
[384] Nathan, D. M., Buse, J. B., Davidson, M. B., Ferrannini, E., Holman, R. R., Sherwin, R., & Zinman, B. (2009). Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy. *Diabetes Care*, 32(1), 193-203.
[385] ICH. (1998). *ICH Harmonised Tripartite Guideline: Statistical Principles for Clinical Trials E9*. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.
[386] Pocock, S. J. (2013). *Clinical Trials: A Practical Approach*. John Wiley & Sons.
[387] Inzucchi, S. E., Bergenstal, R. M., Buse, J. B., Diamant, M., Ferrannini, E., Nauck, M., … & Matthews, D. R. (2015). Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach. *Diabetes Care*, 38(1), 140-149.
[388] FDA. (2008). *Guidance for Industry: Diabetes Mellitus-Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*. U.S. Food and Drug Administration.

[389] Singh, A., Sharma, S., Arora, A., & Attri, S. (2023). Thiazolidine-2,4-dione hybrids as dual alpha-amylase and alpha-glucosidase inhibitors: Design, synthesis, in vitro and in vivo anti-diabetic evaluation. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 38(1), 2156789.
[390] Morphy, R., & Rankovic, Z. (2005). Designed multiple ligands: An emerging drug discovery paradigm. *Journal of Medicinal Chemistry*, 48(21), 6523-6543.
[391] Bischoff, H. (1995). The mechanism of α-glucosidase inhibition in the management of diabetes. *Clinical and Investigative Medicine*, 18(4), 303-311.
[392] Viegas-Junior, C., Danuello, A., da Silva Bolzani, V., Barreiro, E. J., & Fraga, C. A. M. (2007). Molecular hybridization: A useful tool in the design of new drug prototypes. *Current Medicinal Chemistry*, 14(17), 1829-1852.
[393] Decker, M. (2011). Hybrid molecules incorporating natural products: applications in cancer therapy, neurodegenerative disorders and beyond. *Current Medicinal Chemistry*, 18(10), 1464-1475.
[394] Gaspar, A., Matos, M. J., Garrido, J., Uriarte, E., & Borges, F. (2014). Chromone: a valid scaffold in medicinal chemistry. *Chemical Reviews*, 114(9), 4960-4992.
[395] Jain, A. K., Vaidya, A., Ravichandran, V., Kashaw, S. K., & Agrawal, R. K. (2012). Recent developments and biological activities of thiazolidinone derivatives: A review. *Bioorganic & Medicinal Chemistry*, 20(11), 3378-3395.
[396] Proschak, E., Stark, H., & Merk, D. (2019). Polypharmacology by design: a medicinal chemist's perspective on multitargeting compounds. *Journal of Medicinal Chemistry*, 62(2), 420-444.
[397] DeFronzo, R. A. (2009). From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes*, 58(4), 773-795.
[398] Zimmermann, G. R., Lehár, J., & Keith, C. T. (2007). Multi-target therapeutics: when the whole is greater than the sum of the parts. *Drug Discovery Today*, 12(1-2), 34-42.
[399] Hamburg, M. A., & Collins, F. S. (2010). The path to personalized medicine. *New England Journal of Medicine*, 363(4), 301-304.
[400] Evans, W. E., & Relling, M. V. (1999). Pharmacogenomics: translating functional genomics into rational therapeutics. *Science*, 286(5439), 487-491.
[401] Ginsburg, G. S., & Willard, H. F. (2009). Genomic and personalized medicine: foundations and applications. *Translational Research*, 154(6), 277-287.
[402] Kola, I., & Landis, J. (2004). Can the pharmaceutical industry reduce attrition rates? *Nature Reviews Drug Discovery*, 3(8), 711-716.
[403] Rosak, C., & Mertes, G. (2012). Critical evaluation of the role of acarbose in the treatment of diabetes: patient considerations. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, 5, 357-367.
[404] Bischoff, H. (1995). The mechanism of α-glucosidase inhibition in the management of diabetes. *Clinical and Investigative Medicine*, 18(4), 303-311.
[405] Kung, J., & Henry, R. R. (2012). Thiazolidinedione safety. *Expert Opinion on Drug Safety*, 11(4), 565-579.
[406] Singh, A., Sharma, S., Arora, A., & Attri, S. (2023). Thiazolidine-2,4-dione hybrids as dual alpha-amylase and alpha-glucosidase inhibitors: Design, synthesis, in vitro and in vivo anti-diabetic evaluation. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 38(1), 2156789.
[407] FDA. (2008). *Guidance for Industry: Diabetes Mellitus-Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*. U.S. Food and Drug Administration.
[408] Federsel, H. J. (2013). Chemical process research and development in the 21st century: challenges, strategies, and solutions from a pharmaceutical industry perspective. *Accounts of Chemical Research*, 46(8), 1518-1528.
[409] Polshettiwar, V., & Varma, R. S. (2010). Green chemistry by nano-catalysis. *Green Chemistry*, 12(5), 743-754.
[410] Anderson, N. G. (2012). *Practical Process Research and Development: A Guide for Organic Chemists* (2nd ed.). Academic Press.
[411] Grabowski, H. G., & Kyle, M. (2007). Generic competition and market exclusivity periods in pharmaceuticals. *Managerial and Decision Economics*, 28(4-5), 491-502.
[412] Rader, R. A. (2008). (Re) defining biopharmaceutical. *Nature Biotechnology*, 26(7), 743-751.
[413] Pressman, D., & Tuschman, S. (2015). *Patent It Yourself: Your Step-by-Step Guide to Filing at the US Patent Office* (19th ed.). Nolo.
[414] Hamburg, M. A., & Collins, F. S. (2010). The path to personalized medicine. *New England Journal of Medicine*, 363(4), 301-304.

[415] Inzucchi, S. E., Bergenstal, R. M., Buse, J. B., Diamant, M., Ferrannini, E., Nauck, M., … & Matthews, D. R. (2015). Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach. *Diabetes Care*, 38(1), 140-149.
[416] Monnier, L., Lapinski, H., & Colette, C. (2003). Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients. *Diabetes Care*, 26(3), 881-885.
[417] Evans, W. E., & Relling, M. V. (1999). Pharmacogenomics: translating functional genomics into rational therapeutics. *Science*, 286(5439), 487-491.
[418] Giacomini, K. M., Huang, S. M., Tweedie, D. J., Benet, L. Z., Brouwer, K. L., Chu, X., … & Zhang, L. (2010). Membrane transporters in drug development. *Nature Reviews Drug Discovery*, 9(3), 215-236.
[419] Relling, M. V., & Evans, W. E. (2015). Pharmacogenomics in the clinic. *Nature*, 526(7573), 343-350.
[420] Biomarkers Definitions Working Group. (2001). Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. *Clinical Pharmacology & Therapeutics*, 69(3), 89-95.
[421] Strimbu, K., & Tavel, J. A. (2010). What are biomarkers? *Current Opinion in HIV and AIDS*, 5(6), 463-466.
[422] Drucker, E., & Krapfenbauer, K. (2013). Pitfalls and limitations in translation from biomarker discovery to clinical utility in predictive and personalised medicine. *EPMA Journal*, 4(1), 7.
[423] Steinhubl, S. R., Muse, E. D., & Topol, E. J. (2015). The emerging field of mobile health. *Science Translational Medicine*, 7(283), 283rv3.
[424] Rodbard, D. (2016). Continuous glucose monitoring: a review of successes, challenges, and opportunities. *Diabetes Technology & Therapeutics*, 18(S2), S2-3.
[425] Pal, K., Eastwood, S. V., Michie, S., Farmer, A. J., Barnard, M. L., Peacock, R., … & Murray, E. (2013). Computer-based diabetes self-management interventions for adults with type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews*, (3), CD008776.
[426] Contreras, I., & Vehi, J. (2018). Artificial intelligence for diabetes management and decision support: literature review. *Journal of Medical Internet Research*, 20(5), e10775.
[427] Singh, A., Sharma, S., Arora, A., & Attri, S. (2023). Thiazolidine-2,4-dione hybrids as dual alpha-amylase and alpha-glucosidase inhibitors: Design, synthesis, in vitro and in vivo anti-diabetic evaluation. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 38(1), 2156789.
[428] Morphy, R., & Rankovic, Z. (2005). Designed multiple ligands: An emerging drug discovery paradigm. *Journal of Medicinal Chemistry*, 48(21), 6523-6543.
[429] Proença, C., Freitas, M., Ribeiro, D., Oliveira, E. F., Sousa, J. L., Tomé, S. M., … & Fernandes, E. (2017). α-Glucosidase inhibition by flavonoids: an in vitro and in silico structure–activity relationship study. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 32(1), 1216-1228.
[430] Anastas, P., & Eghbali, N. (2010). Green chemistry: principles and practice. *Chemical Society Reviews*, 39(1), 301-312.
[431] Polshettiwar, V., & Varma, R. S. (2010). Green chemistry by nano-catalysis. *Green Chemistry*, 12(5), 743-754.
[432] Sheldon, R. A. (2017). The E factor 25 years on: the rise of green chemistry and sustainability. *Green Chemistry*, 19(1), 18-43.
[433] Kitchen, D. B., Decornez, H., Furr, J. R., & Bajorath, J. (2004). Docking and scoring in virtual screening for drug discovery: methods and applications. *Nature Reviews Drug Discovery*, 3(11), 935-949.
[434] Ferreira, L. G., Dos Santos, R. N., Oliva, G., & Andricopulo, A. D. (2015). Molecular docking and structure-based drug design strategies. *Molecules*, 20(7), 13384-13421.
[435] Wermuth, C. G. (Ed.). (2008). *The Practice of Medicinal Chemistry* (3rd ed.). Academic Press.
[436] Kola, I., & Landis, J. (2004). Can the pharmaceutical industry reduce attrition rates? *Nature Reviews Drug Discovery*, 3(8), 711-716.
[437] Singh, A., Sharma, S., Arora, A., & Attri, S. (2023). Thiazolidine-2,4-dione hybrids as dual alpha-amylase and alpha-glucosidase inhibitors: Design, synthesis, in vitro and in vivo anti-diabetic evaluation. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 38(1), 2156789.
[438] Inzucchi, S. E., Bergenstal, R. M., Buse, J. B., Diamant, M., Ferrannini, E., Nauck, M., … & Matthews, D. R. (2015). Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach. *Diabetes Care*, 38(1), 140-149.
[439] Proschak, E., Stark, H., & Merk, D. (2019). Polypharmacology by design: a medicinal chemist's perspective on multitargeting compounds. *Journal of Medicinal Chemistry*, 62(2), 420-444.
[440] Wermuth, C. G. (Ed.). (2008). *The Practice of Medicinal Chemistry* (3rd ed.). Academic Press.
[441] International Diabetes Federation. (2021). *IDF Diabetes Atlas* (10th ed.). Brussels: International Diabetes Federation.