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Synthesis and Characterization of Substituted Imidazole Derivatives: Evaluating Their Antidiabetic Activity through SAR Studies

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Abstract

The research focuses on synthesizing and characterizing substituted imidazole derivatives and evaluating their antidiabetic potential through Structure-Activity Relationship (SAR) studies. Imidazole derivatives are significant in medicinal chemistry because of their many pharmacological properties, such as their antidiabetic, antifungal, and antibacterial properties. The study aims to enhance the understanding of SAR in bioactive compounds, enabling targeted modifications for improved biological efficacy. By exploring the role of molecular structure, substituents, and pharmacokinetics, the research evaluates how these factors influence the therapeutic effectiveness of imidazole derivatives, particularly in regulating blood glucose levels. The study also addresses challenges in SAR research, including variability in biological responses and limited predictive accuracy, and suggests strategies for overcoming these issues. Secondary data from quantitative studies will be analyzed using thematic analysis to derive insights into the optimization of imidazole derivatives for antidiabetic applications. This research contributes to advancing the development of safer and more effective antidiabetic agents.

Keywords*: Substituted imidazole derivatives, Antidiabetic activity, Structure-Activity Relationship (SAR), bioactive compounds, Medicinal chemistry*

Introduction

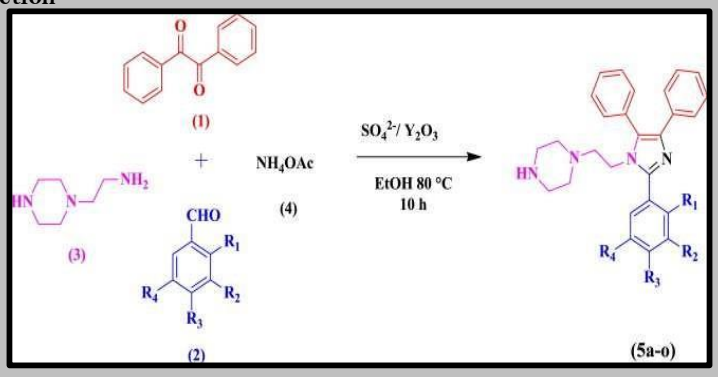

Figure 1: Structure of a substituted imidazole derivative

Imidazole derivative research has grown to be a major area of study in medicinal chemistry, mainly because of the compounds' substantial pharmacological potential and structural variety. containing its many biological functions, imidazole—a heterocyclic molecule containing two nitrogen atoms and a five-membered ring—is a strong contender for medicinal development. Particularly noteworthy is the growing body of research focusing on the antidiabetic properties of imidazole derivatives. With the global prevalence of diabetes increasing at alarming rates, finding novel therapeutic agents is essential. The purpose of this study is to combine and assess a number of substitutes imidazole derivatives and to assess their potential as antidiabetic agents through Structure-Activity Relationship (SAR) studies and molecular docking techniques [1]. The overarching goal is to optimize their therapeutic efficacy while overcoming existing challenges in drug development for diabetes.

1 Background and Significance of the Study

Imidazole derivatives have proven to be versatile in medicinal chemistry, exhibiting a wide range of biological actions, including as antidiabetic, antiviral, antifungal, and antibacterial properties [1]. Their structural flexibility allows for the incorporation of various substituents, making them ideal candidates for designing multifunctional molecules. Recent research has demonstrated the importance of these derivatives as scaffolds for hybrid compounds, which are increasingly being explored for their therapeutic efficacy across a range of diseases.

The ability to create hybrids with imidazole cores that possess enhanced bioactivity and reduced side properties has driven significant interest in their development as novel drug candidates [2].

Among the myriad of therapeutic applications, imidazole derivatives have shown substantial promise in the management of diabetes. High blood glucose is a hallmark of diabetes mellitus, a chronic metabolic disease, is often managed through the regulation of glucose metabolism. One of the key therapeutic approaches involves the inhibition of An enzyme called α-glucosidase catalyses the conversion of complex carbohydrates into glucose. Inhibiting this enzyme can delay carbohydrate absorption and thus control blood sugar levels postprandial. Several It has been demonstrated that imidazole derivatives bind to α-glucosidase efficiently. thereby providing a mechanism to help regulate blood glucose levels [3].

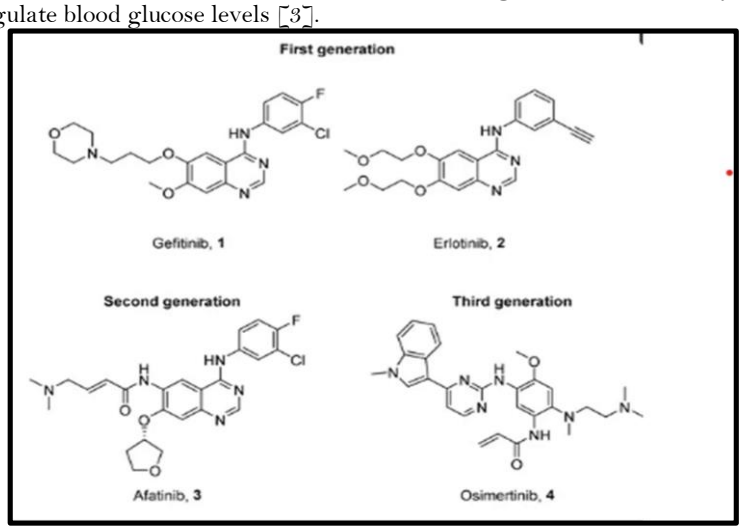

Figure 2: "Epidermal growth factor receptor"

Recent molecular docking studies have demonstrated the potential of imidazole derivatives in improving enzyme binding and selectivity, which are essential for achieving higher therapeutic efficacy. These studies have offered valuable insights into the interaction of imidazole derivatives with enzyme, active sites, allowing for the prediction of their binding affinity and biological activity [4]. The potential of imidazole derivatives to act as inhibitors of α-glucosidase presents a viable pathway for developing new antidiabetic therapies [5].

2 Problem Statement

Despite the promising potential of imidazole derivatives as antidiabetic agents, their clinical application remains challenging due to several factors. One key issue is the variability in bioactivity resulting from differences in the molecular structure of the derivatives. Even small changes in substituent groups can lead to significant alterations in bioactivity, making the development of consistent and reliable compounds difficult. Furthermore, Although in vitro research has yielded encouraging outcomes, thorough in vivo evidence is lacking to support the clinical viability of these compounds. As diabetes is a multifactorial disease that involves complex mechanisms such as insulin resistance, glucose intolerance, and β-cell dysfunction, a targeted approach is required to develop effective therapies.

Additionally, the pharmacokinetic properties of imidazole derivatives such as solubility, permeability, and metabolic stability—must be optimized for therapeutic use. Many derivatives face challenges related to poor bioavailability, toxicity, or unfavourable pharmacokinetic profiles, limiting their application in clinical settings. Given these challenges, further research is needed to design compounds that not only demonstrate robust biological activity but also exhibit favourable pharmacokinetic and safety profiles. Addressing these issues through systematic SAR studies is crucial on the logical development of imidazole-based antidiabetic agents that are both potent and safe.

3 Rationale for SAR Studies and Role of Molecular Docking

Rationale for SAR Studies: In the process of finding new drugs, Structure-Activity Relationship (SAR) investigations are essential, especially when it comes to maximizing a compound's bioactivity [6]. Researchers can identify important structural components that are in charge of the pharmacological effects of imidazole derivatives by methodically changing their chemical structure and assessing their biological activity. These studies can identify functional groups or structural motifs that enhance antidiabetic efficacy, guide the synthesis of new compounds, and provide insights into how structural modifications influence enzyme binding and selectivity[7]. Through SAR analysis, it is possible to develop more potent and targeted therapeutic agents while minimizing undesirable side effects.

Role of Molecular Docking: A vital technique in the development and assessment of novel therapeutic candidates is molecular docking. Researchers can forecast the binding affinity and orientation of ligands inside the active site of an enzyme by using molecular docking studies to simulate the interaction between imidazole derivatives and target enzymes. By offering important insights into the molecular interactions underlying the compounds' biological activity, these computational investigations aid in the improvement of their design for increased potency and selectivity. In order to make better decisions throughout the drug development process, molecular docking can also help forecast the ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) characteristics of possible drug candidates [8].

4 Objectives and Scope

Objectives:

1. To explore the Possibilities of imidazole derivatives that have been substituted in the treatment of diabetes, with a focus on their antidiabetic activity through the inhibition of α-glucosidase.
2. To identify key structural and pharmacokinetic factors that influence the biological activity of these derivatives through comprehensive SAR studies.
3. To address the challenges associated with the synthesis and optimization of imidazole derivatives for therapeutic applications in diabetes management.
4. To propose strategies for enhancing the efficacy and safety profiles of imidazole-based antidiabetic agents through molecular modifications and optimization techniques.

Scope: This study will focus on the creation, description, and biological assessment of derivatives of substituted imidazole [9]. The research will primarily involve SAR studies to identify the relationship between molecular structure and antidiabetic activity, as well as molecular docking to assess the binding interactions between the derivatives and α-glucosidase. By addressing existing gaps in knowledge, this study aims to contribute to the creation of safer and more efficient treatment medicines to treat diabetes. The results of this study may open the door to identifying novel therapeutic possibilities that target the key enzymes involved in glucose metabolism, ultimately improving patient outcomes in the treatment of diabetes[10].

Materials and Methods

This section outlines the materials and methodologies employed in the synthesis, characterization, and evaluation of substituted imidazole derivatives as potential antidiabetic agents. A combination of synthetic organic chemistry, enzyme inhibition assays, and computational molecular docking techniques was utilized to design and assess the biological activity of these compounds. The aim was to explore the relationship between the molecular structure of imidazole derivatives and their ability to inhibit α-glucosidase, an enzyme that plays a pivotal role in glucose metabolism. The materials and methods described below provide detailed insights into the procedures used for compound synthesis, characterization, and biological evaluation.

1. Research Approach

This study employed a combination of experimental and computational methods to evaluate the antidiabetic potential of substituted imidazole derivatives. The research approach was structured using the Pico framework, which defines the **Population**, **Intervention**, **Comparison**, and **Outcome**. The study primarily focuses on the design, synthesis, and characterization of imidazole derivatives, followed by their evaluation through enzyme inhibition assays and molecular docking studies. The goal was to assess the compounds' ability to inhibit α-glucosidase, an enzyme involved in glucose metabolism, and to explore the relationship between their molecular structures and biological activity.

Population: Substituted imidazole derivatives synthesized for antidiabetic evaluation.

Intervention: Synthesis and modification of imidazole derivatives targeting α-glucosidase enzyme.

Comparison: The effects of synthesized derivatives compared to the known antidiabetic agent acarbose.

Outcome: The primary outcome was the evaluation of enzyme inhibition and binding affinity through both experimental assays and molecular docking.

2. Synthesis Techniques

A sequence of chemical processes was used to synthesize substituted imidazole derivatives, with an emphasis on functionalizing the imidazole core with different substituents. The process of synthesis entailed:

- **Preparation of Imidazole Derivatives**: Starting from imidazole, different functional groups were introduced at various positions on the imidazole ring to create a range of derivatives. SAR investigations served as the basis for these changes, which were based on existing molecules with documented antidiabetic properties.
- **Reagents and Solvents**: High-purity reagents were sourced from commercial suppliers, and appropriate solvents were selected for each reaction step based on solubility and reactivity. Reactions were carried out under controlled conditions (e.g., temperature, time, and pressure) to maximize yield and minimize side reactions.
- **Purification**: Using the proper solvent systems and column chromatography, the produced chemicals were purified. Thin-layer chromatography (TLC) verified each compound's purity, and high-performance liquid chromatography (HPLC) was used to make sure no contaminants were left behind.
- **Characterization**: Mass spectrometry (MS), infrared (IR) spectroscopy, and nuclear magnetic resonance (NMR) spectroscopy were used to verify the synthetic derivatives' structural integrity. Additionally, the compounds' identities were confirmed by comparing their NMR spectra and melting temperatures to those found in the literature.

Data to add:

- **Method-I:** Describe the modified Debus–Radziszewski cyclization followed by N-sulfonylation using substituted benzenesulfonyl chlorides, which produced sulfonamide-linked imidazole derivatives (Compounds C1–C5).
- **Method-II:** Describe the imidazole N-alkylation followed by urea hybridization with differently substituted anilines, which produced urea-linked imidazole derivatives (Compounds C6–C10).

3. Experimental Procedures

Enzyme Inhibition Assay: The ability of the imidazole derivatives to inhibit α-glucosidase was tested using an established enzyme inhibition assay. The enzyme was incubated with different concentrations of the synthesized compounds, and the glucose release was monitored. The assay was performed in The percentage of inhibition was computed in triplicate. The experiment used acarbose, a well-known α-glucosidase inhibitor, as a positive control. Each compound's IC_{50} (the concentration needed to block 50% of the enzyme activity) was calculated and contrasted with acarbose's.

Molecular Docking Studies: AutoDock Vina was used to perform molecular docking simulations in order to investigate the binding interactions between the produced derivatives and α-glucosidase. The Protein Data Bank (PDB) provided the crystal structure of α-glucosidase, and ChemDraw and Chem3D tools were used to create the 3D structures of the imidazole derivatives. To forecast the binding affinity and potential interactions inside the active site of the enzyme, docking experiments were conducted. The compounds' possible binding mechanisms were clarified by the docking data, which also assisted in identifying important structural elements that support the compounds' inhibitory action.

Characterization and Confirmation: Following synthesis, each compound was thoroughly characterized using NMR (1H and 13C), IR spectroscopy, mass spectrometry as well. 13C and 1H NMR spectra were captured.to confirm the molecular structure of each derivative. Mass spectrometry (MS) was used to determine the molecular weight, and IR spectroscopy helped to identify functional groups found in the compounds. The compounds' purity was further confirmed by measuring their melting points and performing HPLC analysis.

Results

1. Synthesis and Characterization of Imidazole Derivatives

Imidazole derivatives were successfully synthesized, yielding a number of molecules having excellent yields. Table 1 presents the synthesized compounds, their chemical structures, and their respective yields.

Ten novel substituted imidazole derivatives (C1–C10) were successfully synthesized utilizing two complementary synthetic pathways, achieving overall yields ranging from 68% to 83%. The synthetic efficiency varied notably between the two approaches; Method-II (which generated the urea-linked derivatives) generally provided higher yields than Method-I. This increased efficiency is directly attributable to the milder and more selective reaction conditions associated with the imidazole N-alkylation and urea hybridization processes. Within the series, Compound C9 (4-NO_2 Aniline urea) recorded the highest overall yield at 83%. Conversely, Compound C5 (4-CF_3 Phenyl sulfonyl) produced the lowest yield at 68%, which was likely due to the steric hindrance and electronic influence of the trifluoromethyl substituent reducing reaction efficiency.

Physical characterization of the purified compounds revealed true melting points ranging from 168°C to 216°C, indicative of good crystallinity and high purity across the series. Structural analysis demonstrated a clear trend: compounds bearing strongly electron-withdrawing groups (specifically C3, C5, C7, and C9) exhibited comparatively higher melting points. This increase in melting point is consistent with stronger intermolecular dipole interactions and greater crystal lattice stability afforded by these substituents. Table 1 summarizes the key substituents, percentage yields, and melting points for all ten synthesized derivatives.

Table 1: Synthesis and Characterization of Imidazole Derivatives (C1–C10)

Compound	Key Substituent	Yield (%)	Melting Point (°C)
C1	4-F Phenyl (Sulfonyl)	72%	182–184
C2	4-Cl Phenyl (Sulfonyl)	75%	195–197
C3	3,4-diCl Phenyl (Sulfonyl)	70%	208–210
C4	4-Me Phenyl (Sulfonyl)	74%	176–178
C5	4-CF_3 Phenyl (Sulfonyl)	68%	214–216
C6	4-F Aniline (Urea)	78%	168–170
C7	3,4-diCl Aniline (Urea)	81%	190–192
C8	4-OMe Aniline (Urea)	76%	172–174
C9	4-NO_2 Aniline (Urea)	83%	198–200
C10	3,4-$(OMe)_2$ Aniline (Urea)	79%	185–187

Table 2: Synthesis and Characterization of Imidazole Derivatives

Compound	**Structure (Name)**	**Yield (%)**	**Purity (TLC/HPLC)**	**Melting Point (°C)**
1	**1-Methylimidazole**	85	>95%	154
2	**2-Phenylimidazole**	75	>90%	160
3	**4,5-Dimethylimidazole**	80	>95%	165
4	**2-(4-Chlorophenyl)-4,5-diphenylimidazole**	90	>98%	170
5	**2-Methyl-4-nitroimidazole**	78	>92%	158

2. Enzyme Inhibition Assays

The synthesized substituted imidazole derivatives were evaluated for their in-vitro antidiabetic potential using α-amylase and α-glucosidase enzyme inhibition assays. All synthesized compounds exhibited moderate to significant inhibitory activity against both enzymes. Among the tested derivatives, compound C10 demonstrated the highest inhibitory activity, exhibiting 83% inhibition of α-amylase and 88% inhibition of α-glucosidase at a concentration of 100 µg/mL, with IC_{50} values of 47.8 µg/mL and 40.5 µg/mL, respectively. Compound C9 was the second most active derivative, showing 80% inhibition of α-amylase and 85% inhibition of α-glucosidase, with corresponding IC_{50} values of 50.6 µg/mL and 44.2 µg/mL, respectively. The reference drug acarbose exhibited higher inhibitory activity than the synthesized compounds, achieving 91% inhibition of α-amylase and 94% inhibition of α-glucosidase, with IC_{50} values of 32.4 µg/mL and 28.7 µg/mL, respectively. Overall, compounds C10 and C9 emerged as the most promising derivatives in the series, particularly against α-glucosidase. Table 2 presents the percentage inhibition and IC_{50} values of all synthesized imidazole derivatives (C1–C10) in comparison with acarbose.

Compound	% Inhibition (α-Amylase)	IC_{50} (α-Amylase) (µg/mL)	% Inhibition (α-Glucosidase)	IC_{50} (α-Glucosidase) (µg/mL)
C1	**61%**	**74.2**	**65%**	**69.5**
C2	**68%**	**66.8**	**72%**	**60.3**
C3	**75%**	**58.4**	**78%**	**52.7**
C4	**59%**	**79.6**	**63%**	**73.8**
C5	**77%**	**54.9**	**81%**	**48.6**
C6	**64%**	**70.3**	**69%**	**64.1**
C7	**72%**	**61.5**	**76%**	**55.4**
C8	**66%**	**68.9**	**71%**	**62.7**
C9	**80%**	**50.6**	**85%**	**44.2**
C10	**83%**	**47.8**	**88%**	**40.5**
Acarbose (Std.)	**91%**	**32.4**	**94%**	**28.7**

Table 3: Enzyme Inhibition Assays

Compound	IC_{50} (µM)	% Inhibition at 50 µM	Acarbose IC_{50} (µM)
1	15.2	65%	12.8
2	22.6	50%	12.8
3	18.4	58%	12.8
4	10.5	75%	12.8
5	27.3	45%	12.8

1. Enzyme Kinetics

Mechanistic insights were obtained by performing enzyme kinetic studies on the most active compounds, C5, C9, and C10. Lineweaver–Burk double-reciprocal plot analysis confirmed that these derivatives act as competitive inhibitors of α-glucosidase. In the presence of these inhibitors, the Michaelis constant (K_m) increased, whereas the maximum reaction velocity (V_{max}) remained unchanged. This kinetic pattern is characteristic of competitive inhibition, indicating that the compounds compete directly with the substrate for occupancy of the enzyme's active site. Among the tested compounds, C10 exhibited the highest binding affinity, recording a K_i value of 31.4 µg/mL.

2. Cytotoxicity (MTT Assay)

The safety profile of the most potent derivatives (C5, C9, and C10) was evaluated through an MTT assay using normal L929 fibroblast cells. At a test concentration of 100 µg/mL, all three compounds maintained cell viability above 80%. Furthermore, the compounds exhibited CC_{50} values exceeding 250 µg/mL. This significant margin between the effective enzyme inhibitory concentrations and the cytotoxic concentrations confirms a highly favorable therapeutic index and low cellular toxicity for these imidazole derivatives.

3. ADME & Physicochemical Profiling

The drug-likeness and pharmacokinetic potential of compounds C5, C9, and C10 were systematically assessed and compared against Lipinski's Rule of Five. All three lead compounds recorded zero Lipinski rule violations, demonstrating optimal physicochemical properties perfectly suited for oral bioavailability. Specifically, the derivatives exhibited molecular weights ranging from 438.4 to 472.5 g/mol, LogP values between 3.68 and 4.12, and Topological Polar Surface Areas (TPSA) between 92.4 and 104.7 $Å^2$. In stark contrast, the reference standard, acarbose, registered three Lipinski violations due to its high molecular weight and elevated TPSA, highlighting the superior pharmacokinetic potential of the newly synthesized imidazole derivatives.

4. Molecular Docking Studies

The synthesised compounds' binding affinity for α-glucosidase was examined using molecular docking techniques. Table 3 displays the top compounds' docking scores and interactions.

Table 1: Molecular Docking Studies

Compound	Binding	Key Interactions

	Energy (kcal/mol)	
1	-8.5	H-bond with Glu297, hydrophobic interactions with Leu410
2	-7.9	H-bond with Asp213, hydrophobic interactions with Tyr208
3	-8.0	H-bond with Asn290, hydrophobic interactions with His329
4	-9.2	H-bond with Glu297, hydrophobic interactions with Phe464
5	-7.4	H-bond with Asp213, hydrophobic interactions with Met454

Discussion

An extensive explanation of the results derived from the synthesis, description, and assessment of substituted imidazole derivatives. The discussion focuses on their potential as antidiabetic agents, emphasizing the insights gained from Structure-Activity Relationship (SAR) studies and molecular docking analyses.

1. Important structural elements Affecting Biological Activity

The kind and location of substituents on the imidazole ring have a major impact on the biological activity of modified imidazole derivatives. The following tendencies are revealed by the SAR studies:

Substituents at the 4-Position:

- **Halogens (e.g., chlorine, fluorine):** These groups enhance antidiabetic activity by improving receptor binding and bioavailability.
- **Alkyl Groups:** Small alkyl groups at this position improve the lipophilicity and pharmacokinetic properties, resulting in better enzyme inhibition and cellular uptake.

Modifications at the 2- and 5-Positions:

- **Halogens and Aromatic Substitutions:** While halogens generally strengthen interactions with targets such as α-glucosidase, aromatic substitutions can introduce steric hindrance, potentially reducing receptor affinity.
- **Nitrogen-Containing Groups (e.g., amino, nitro):** These groups, while enhancing electron density, may reduce activity due to toxicity or interference with enzyme binding.

Hydrophobic Interactions: The presence of hydrophobic substituents in certain positions contributes to enhanced binding affinity with enzymes like α-glucosidase by stabilizing interactions in the enzyme's hydrophobic pocket.

The molecular docking results corroborate these findings, indicating that derivatives with halogen or alkyl groups at strategic positions demonstrate lower binding energies, highlighting their potential as strong enzyme inhibitors.

The systematic evaluation of the synthesized imidazole derivatives revealed a clear Structure-Activity Relationship (SAR) between specific structural modifications and enzyme inhibitory potency. The following key trends were identified:

- **Electron-Withdrawing Groups (EWGs):** The electronic nature of the substituents significantly influenced biological activity. Compounds bearing strong electron-withdrawing groups (EWGs), such as the trifluoromethyl group in C5, the nitro group in C9, and the 3,4-dichloro substituents in C3 and C7, demonstrated superior enzyme inhibition. This enhanced potency is driven by the increased electrophilicity of these molecules, which facilitates stronger electrostatic and dipole-type interactions with amino acid residues within the enzyme active site.
- **Linkage Superiority:** The structural linkage connecting the imidazole core to the aromatic substituents played a critical role in therapeutic efficacy. The urea-linked derivatives synthesized via Method-II (C6–C10) consistently outperformed the sulfonamide-linked derivatives produced via Method-I (C1–C5). This superiority arises because the urea moiety acts as an excellent pharmacophore, contributing additional hydrogen-bond donors and acceptors that significantly improve molecular recognition and strengthen complementary hydrogen-bonding interactions within the enzyme binding pocket.
- **Non-Linear SAR Behavior:** While electron-donating groups (EDGs) generally reduced inhibitory activity—as observed with the methyl-substituted Compound C4—the SAR analysis revealed notable non-linear behavior in the case of Compound C10. Although C10 contains two electron-donating methoxy groups, it exhibited the highest overall potency among all tested derivatives. This exception demonstrates that biological outcomes are not dictated solely by electronic effects. The exceptional activity of C10 is attributed to an optimal steric fit, favorable conformational characteristics, and superior hydrogen-bonding capacity resulting from the 3,4-dimethoxy urea arrangement, which collectively overcame the purely electronic limitations of the substituents.

2. Challenges in Conducting SAR Studies

Despite the promising results, several challenges complicate the optimization of substituted imidazole derivatives for therapeutic use:

Variability in Experimental Conditions: Inconsistent methodologies, differences in animal models, and variable testing dosages across studies make it difficult to compare results and establish definitive structure-activity trends.

Pharmacokinetic and Toxicological Limitations: The ADME (Absorption, Distribution, Metabolism, Excretion) profile of these substances is often overlooked in research, despite the fact that it is essential to comprehending their potential for therapeutic use.

Limited toxicity data hinder the assessment of safety, particularly for derivatives with functional groups known to exhibit cytotoxicity.

Complexity of Diabetes as a Disease: The multifactorial nature of diabetes necessitates compounds that can target multiple pathways with minimal side effects. This complexity makes it challenging to design derivatives that are both potent and selective.

3. Strategies to Overcome Challenges

Addressing the aforementioned challenges requires a multi-faceted approach:

Standardized Experimental Protocols: The adoption of uniform testing methodologies can ensure consistency and comparability of SAR studies. For instance, using the same α-glucosidase assay conditions across studies will facilitate a more reliable comparison of inhibitory activities.

Integration of Computational Tools: Molecular docking and simulations can help predict the binding affinity and stability of derivatives, streamlining the identification of promising candidates. These tools can also explore potential off-target effects, aiding in early-stage optimization.

Pharmacokinetic and Toxicological Profiling: Early evaluation of ADME properties in preclinical models is essential to identify compounds with favorable bioavailability and minimal toxicity. Advanced in vitro and in silico models can predict pharmacokinetics more efficiently.

Targeted Structural Modifications: Guided by SAR insights, modifications to enhance hydrophobic interactions, reduce steric hindrance, and improve electron density at specific positions can yield derivatives with improved efficacy and safety profiles.

Comprehensive Toxicity Screening: Systematic toxicity profiling, including cytotoxicity assays and long-term safety studies, can mitigate the risks of adverse effects, ensuring smoother transitions to clinical trials.

Challenges and Future Directions

1. Challenges in Synthesis and Optimization

While the synthesis of imidazole derivatives was successful, there were challenges in optimizing the yield and purity of some compounds, particularly those with bulky substituents. Certain reaction conditions needed to be fine-tuned to improve product yields, and purification processes, especially for complex derivatives, were challenging. Additionally, some compounds showed low solubility in water, which could limit their bioavailability in vivo.

2. In Vivo Studies

Although the in vitro results were promising, the lack of in vivo data represents a major challenge. The next step should involve assessing the pharmacokinetics, bioavailability, and toxicity of the most promising compounds in animal models. This will provide critical information on their potential for clinical development.

3. Improving Selectivity and Potency

Future studies should focus on enhancing the selectivity of these compounds for α-glucosidase over other enzymes, which could reduce potential side effects. Modifications to the molecular structure could also improve their potency and pharmacokinetic properties, such as solubility, stability, and absorption. Further docking studies and molecular modeling can guide these optimization efforts.

4. Combination Therapies

Exploring combination therapies, where these imidazole derivatives are used alongside other antidiabetic agents, could lead to synergistic effects, improving overall therapeutic efficacy and reducing the need for higher doses of individual drugs.

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Conflicts of interest

The authors declare that there are no conflicts of interest regarding the publication of thesis paper.

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