Nigerian Research Journal of Chemical Sciences **(ISSN: 2682-6054)**
Volume 15, Issue 1, 2026

A Review on the Synthesis and Antidiabetic Activities of Benzimidazole Derivatives

*Abdullahi Ahmad, Aliyu Muhammad Musa, Maryam Abdullahi, Asmau Nasir Hamza, Ahmadu Jibril, Ikram Abdulrahman Ezzeldin, and Yusuf Jimoh

Department of Pharmaceutical and Medicinal Chemistry,

Ahmadu Bello University, Zaria, Nigeria

*Corresponding Author: Abdulnaiya57@gmail.com

Accepted: *June 8, 2026*. **Published Online**: *June 11, 2026*

ABSTRACT

Benzimidazole is a key class of nitrogen-containing heterocyclic compounds that have attracted considerable attention in medicinal chemistry due to their diverse biological activities. Structurally, benzimidazole consists of a fused benzene and imidazole ring system that resembles naturally occurring purine, which contributes to its significant pharmacological potential. Numerous synthetic approaches have been reported for the preparation of benzimidazole derivatives, most commonly involving the condensation of O-phenylenediamine with various reagents such as aldehydes, carboxylic acids, alcohols, benzylamines, and other functional substrates under different catalytic conditions. Classical methods such as the Phillips method, as well as modern strategies employing green chemistry approaches, microwave irradiation, and nanoparticle catalysts, have improved reaction efficiency and product yields. In addition to their synthetic versatility, benzimidazole derivatives have demonstrated promising pharmacological activities, including antimicrobial, anticancer, antiviral, antiparasitic, and particularly antidiabetic effects. Several derivatives have shown significant inhibitory activity against enzymes involved in glucose metabolism, such as α-glucosidase and α-amylase, and have demonstrated improved glucose tolerance and reduced blood glucose levels in experimental models. This review highlights the major synthetic strategies for benzimidazole derivatives and summarizes their reported antidiabetic potential, emphasizing their importance as promising scaffolds for the development of novel therapeutic agents for diabetes management.

Keywords: Medicinal chemistry, benzimidazole, heterocyclic compounds, synthesis, and antidiabetic activity.

INTRODUCTION

This review aims to provide a comprehensive overview of the synthesis and antidiabetic potential of benzimidazole derivatives. Specifically, it examines the structural features and pharmacological importance of the benzimidazole scaffold, discusses the major synthetic strategies for preparing its derivatives, evaluates the influence of catalysts and modern green chemistry approaches on synthetic efficiency, and summarizes the reported antidiabetic activities. Furthermore, the review highlights the therapeutic potential of these derivatives as promising candidates for diabetes management and identifies future research directions to develop more potent and selective antidiabetic agents.

Medicinal chemists have developed a strong interest in nitrogenous heterocyclic compounds for the development of new therapies [1]. A significant number of these possible heterocyclic medications are benzimidazole scaffolds [2]. Benzimidazole (Figure 1) derivatives are important as chemotherapeutic agents because of their isostructural pharmacophore of naturally occurring active biomolecules [3]. Benzimidazoles are a class of heterocyclic, aromatic compounds that share a fundamental structural characteristic of a six-membered benzene fused to a five-membered imidazole moiety [4]. It is an aromatic conjugated acid compound with a formula $C_7H_6N_2$ and a molecular weight of 118.14 g/mol that exhibits tautomerization.

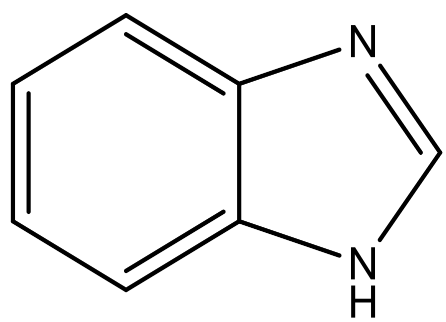


Figure 1: Benzimidazole core structure

The biological application of the benzimidazole nucleus was discovered way back in 1944, when Woolley speculated that benzimidazoles resemble purine-like structures and elicit some biological application [5]. The pharmacological application of benzimidazole analogs has found potent inhibitors of various enzymes and proteins involved in therapeutic uses, including antidiabetic, anticancer, antimicrobial, antiparasitic, analgesics, antiviral, antihistamine, and neurological, endocrinological, and ophthalmological drugs, as shown in Figure 2 [4].

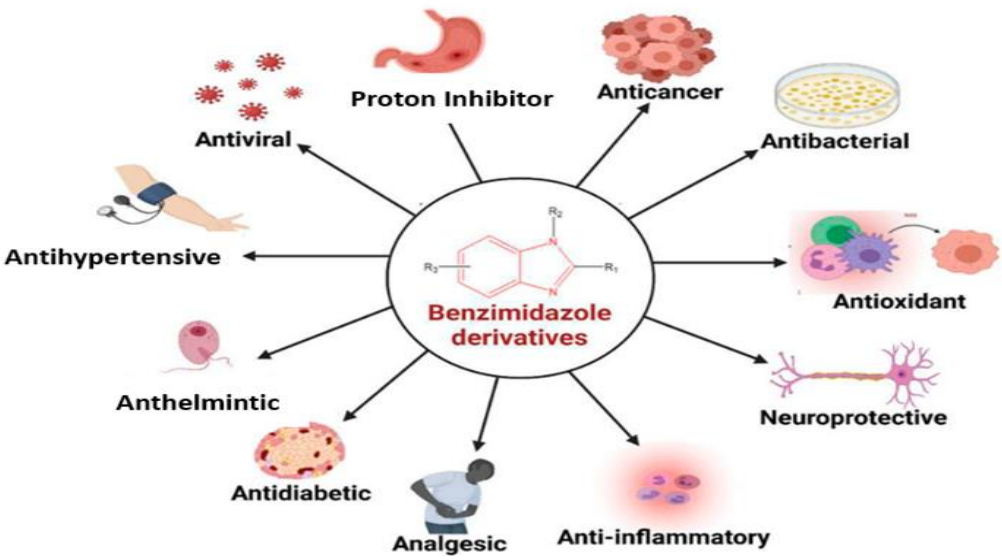


Figure 2: Benzimidazole derivatives with diverse biological activities [3]

Some of the marketed drugs containing benzimidazole are (Omeprazole, Pantoprazole), an antiulcer, Bendamustine, an anticancer, Dabigatran, an anticoagulant, Benomyle, a fungicide, Albendazole as an antiparasitic, whereas lead molecules such as Galeterone and GSK461364 are in different phases of clinical trials for anticancer drugs, as depicted in Figure 3 [4].

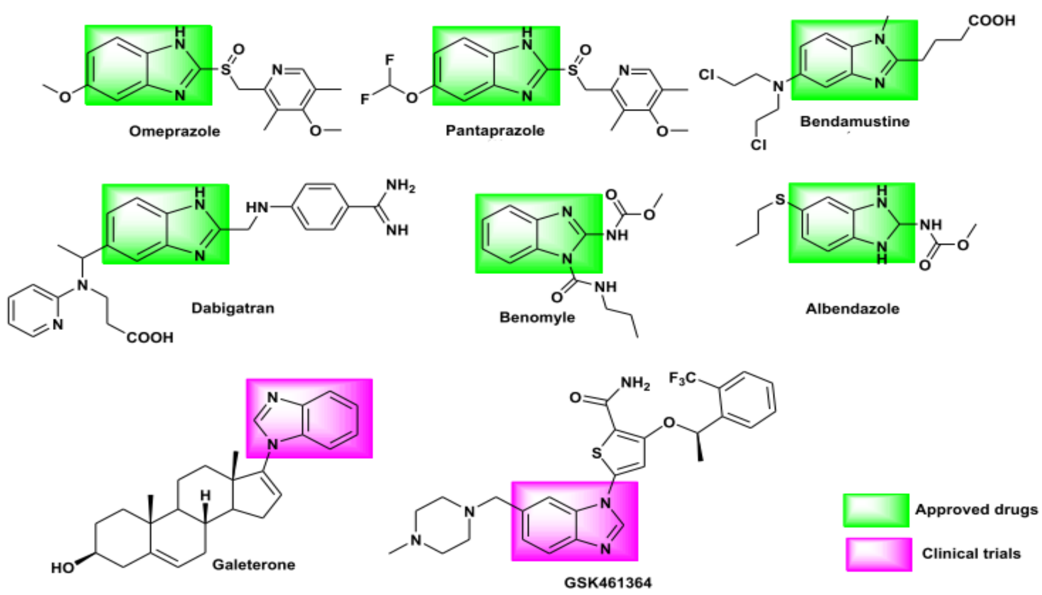


Figure 3: Some of the benzimidazole drugs in the market and in clinical trials [4]

Overview of the synthesis of benzimidazole

The use of benzimidazole began many years ago, starting from 1990 onwards. A vast number of benzimidazole synthetic analogs were reported, which resulted in increased stability, bioavailability, and significant biological activity [6]. Benzimidazole is formed by the fusion of a benzene and an imidazole moiety, and the numbering system according to the IUPAC. Benzimidazoles, which contain a hydrogen atom attached to nitrogen in the 1-position, readily tautomerize, and this may be depicted in Figure 4.

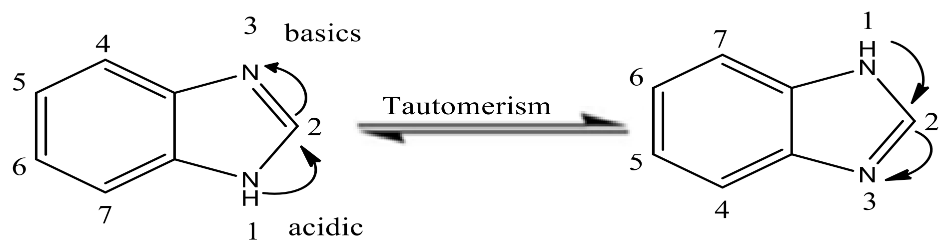
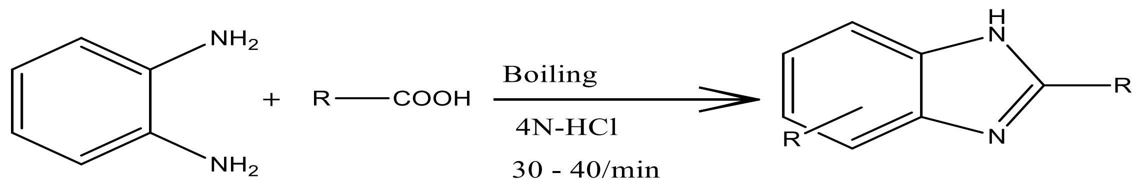


Figure 4: Numbering system and tautomeric forms of benzimidazole

In recent years, various protocols have been reported for the successful preparation of benzimidazole and its derivatives. Most of the methods for preparing the benzimidazole nucleus involve using OPD as a precursor [6]. Ortho-phenylene Diamine was condensed with aldehyde, carboxylic acid, alcohol, benzylamine, N-substituted amide, and arylidene malononitrile. Several catalysts such as H_2SO_4,H_3BO_3 NH_4Cl, H_2O_2/TiO_2, SBA-15-Ph-PrSO_3H, sulfonated cobalt ferrite solid acid catalyst, SO_3H, phosphor sulfonic acid etc. have been employed during the preparation [7]. Some of the reported methods for the synthesis from OPD are as follows

Phillips methods

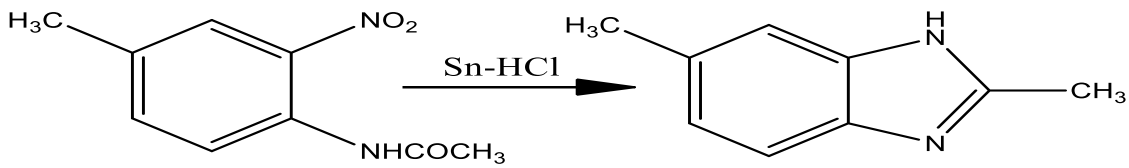
The first method for the synthesis of benzimidazole was discovered by Phillips known as (Phillips methods) The process show that 2-methylbenziminazoles are readily formed by the action of boiling dilute hydrochloric acid on mono- or di-acetyl-o-diamines and by the action of acetic anhydride and hydrochloric acid on o-phenylenediamines, It was suggested that hydrolysis of the diacetyl to the monoacetyl compound constituted a stage in the formation of the ring compound from the former. These reactions have now been extended to the formation of other 2-substituted Benzimidazoles. It has been shown in (Scheme 1) that o-phenylenediamine, on condensation with formic, acetic, propionic, glycolic, lactic, and mandelic acids in the presence of boiling dilute hydrochloric acid, gives good yields of the corresponding cyclic compound [8].



Scheme 1: Synthetic route for the formation of benzimidazoles by Phillips method

Hoe Brecker Synthesis

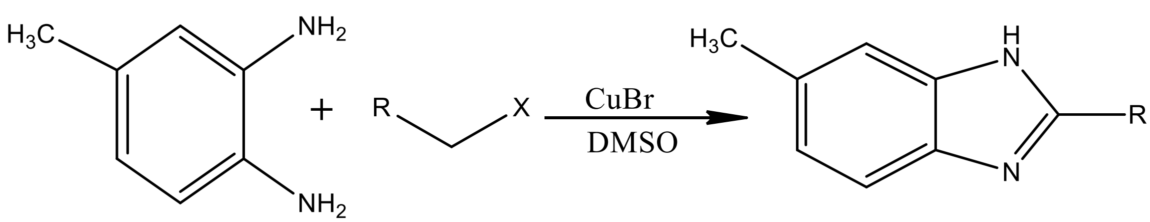
Hoe Brecker in 1872 synthesized benzimidazoles by the reduction of 2-nitro-4-methylacetanilide in the presence of hydrochloric acid (Scheme 2). 2,5 or (2,6)-Dimethylbenzimidazole was obtained in this process [9].



Scheme 2: Synthetic route for the formation of benzimidazoles from reduction of 2-nitro-4-methylacetanilide

Reaction with alkyl halides

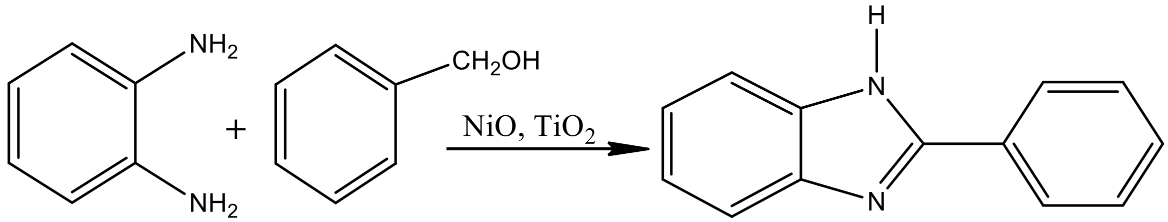
Several 2-arylbenzimidazole derivatives were efficiently synthesized from arylmethyl halides and o-phenylenediamine, using copper bromide (CuBr) as a catalyst under aerobic oxidation conditions (Scheme 3), yielding high quantities of the products [10].



Scheme 3: Synthetic route for the formation of benzimidazole from O-phenylenediamine and alkyl halides

Reaction with alcohols

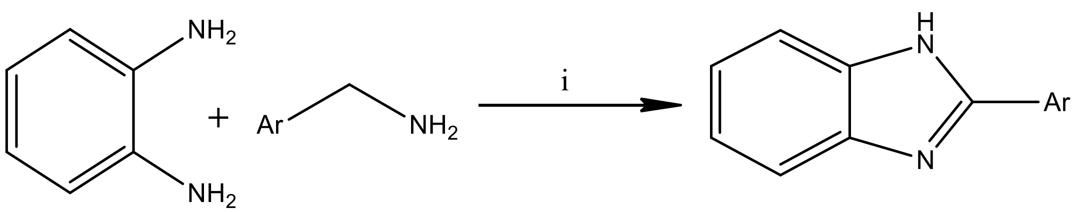
2-Aminobenzimidazoles were obtained with excellent yields from the reaction of benzyl alcohol with o-phenylenediamines under combined ultrasonication photo radiation (5 min) in the presence of NiO anatase/rutile-TiO_2 nanoparticles shown in (Scheme 4) [6].



Scheme 4: Synthetic route for the formation of benzimidazoles from O-phenylenediamine and Alcohol.

Reaction with Benzylamine

Zinc complexes containing a neutral iminopyrrole-morpholino ligand were synthesized and subsequently used as a catalyst to create a wide variety of benzimidazole derivatives, by aerobic oxidation of different benzylamines with O-phenylenediamine as depicted in (Scheme 5) [11].

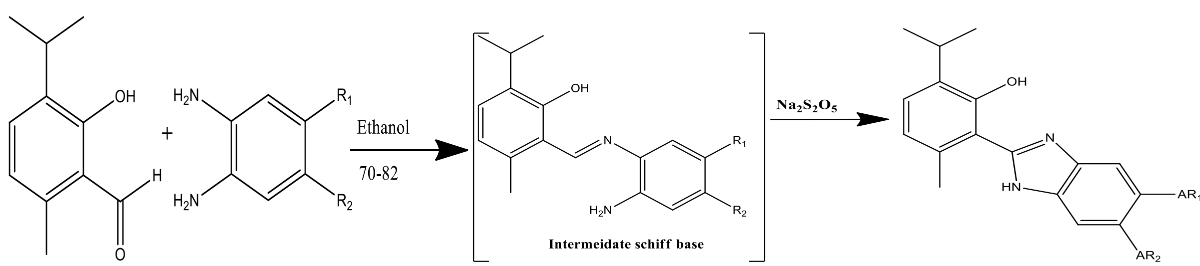


i- zinc complexes supported iminopyrole-morpholine ligand

Scheme 5: Synthetic route for the formation of benzimidazoles from O-phenylenediamine and benzylamine

Reaction with thymol

Scheme 6 shows the synthesis of a new series of benzimidazole thymol derivatives, which have been synthesized by using a general condensation method involving 2-formyl thymol and 1,2-diaminophenyl compounds in the presence of ($Na_2S_2O_5$), with high-yielding products [1].



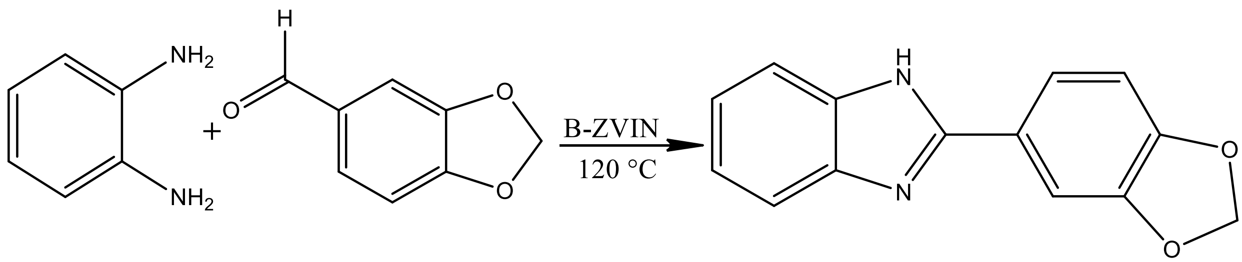
Scheme 6: Synthetic route for the formation of benzimidazoles from O-phenylenediamine and thymol

Reaction with Aldehydes

Benzimidazole was synthesized through the condensation of o-phenylenediamine with various aldehydes in the presence of different catalysts under varying reaction conditions, as shown below.

Solvent Free Synthesis

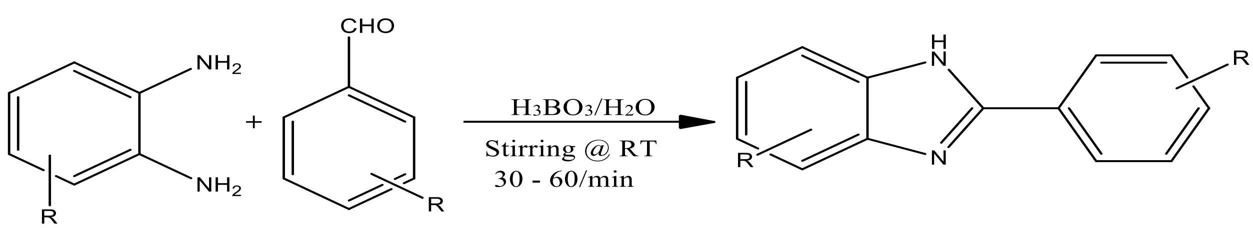
Benzimidazole derivative was prepared by the reaction of *o*-phenylene diamine and piperonal under solvent-free conditions by using bentonite zero valent iron nanoparticle (B-ZVIN) catalyst. The reaction was found to be very fast and the product was obtained in a 95% yield as depicted in (Scheme 7) [4].



Scheme 7: Synthetic route for the formation of benzimidazoles from O-phenylenediamine and Aldehyde

Boric acid as a catalyzed method

Synthesis of benzimidazoles has been developed by the o-phenylenediamine with different aldehydes using boric acid as an efficient catalyst under mild reaction conditions in aqueous media (Scheme 8) [12].

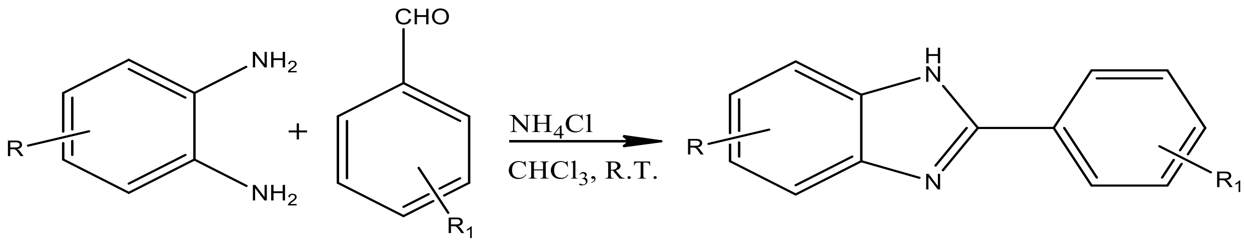


Scheme 8: Synthetic route for the formation of benzimidazoles from O-phenylenediamine and Aldehyde

Ammonium Chloride as a Catalyst

Condensation of different substituted *o*-phenylenediamine with different carbonyl compounds in the presence of ammonium chloride as a catalyst gave benzimidazole derivatives in a 75-94% yield

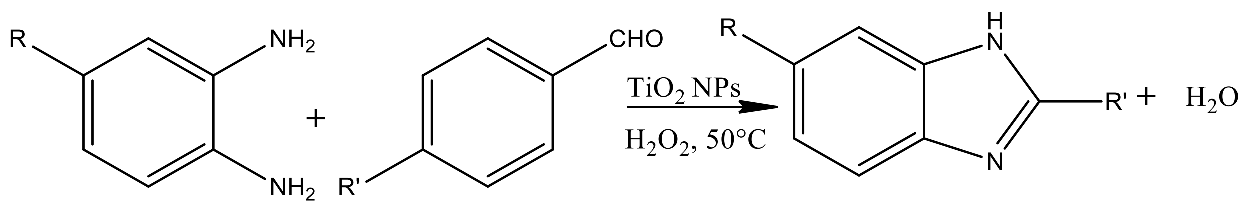
(Scheme 9). This method is simple and inexpensive, and uses ammonium, which is a commercial and environmentally benign catalyst [13].



Scheme 9: Synthetic route for the formation of benzimidazoles from O-phenylenediamine and Aldehyde

Nanoparticles as Catalyst

Oxidative coupling of substituted *o*-phenylenediamine with benzaldehyde using H_2O_2/TiO_2 nanoparticles as catalyst at 50 °C provided benzimidazole derivatives with 55-70% yield (Scheme 10) shows the reaction [10].



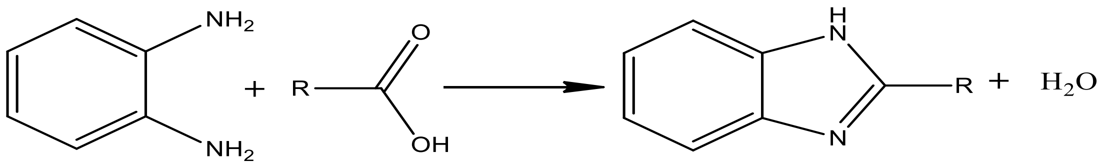
Scheme 10: Synthetic route for the formation of benzimidazoles from O-phenylenediamine and Aldehyde

Reaction with Carboxylic Acid

Benzimidazole was synthesized through the condensation of o-phenylenediamine with various carboxylic acids in the presence of different catalysts under varying reaction conditions, as shown below.

Reaction without Catalyst

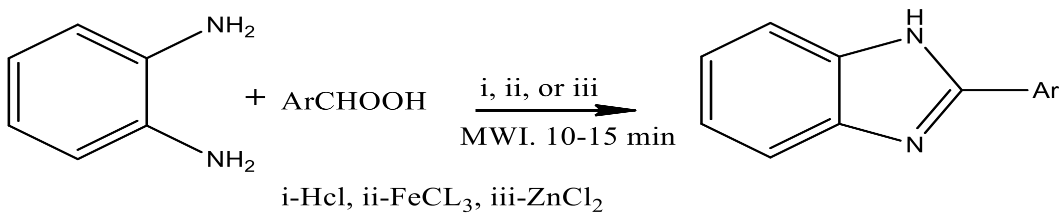
In Scheme 11, 2-Substituted benzimidazoles can be readily synthesized by condensing *o*-phenylenediamine with carboxylic acids under reflux, at elevated temperatures, or by heating in a sealed tube. However, the reaction typically requires a prolonged duration and affords only moderate yields [4].



Scheme 11: Synthetic route for the formation of benzimidazoles from O-phenylenediamine and carboxylic acid.

Reaction with the catalyst

2-Arylbenzimidazoles were synthesized via microwave irradiation (MWI) and without using a solvent under ambient temperature with catalytic amounts of acids. Benzimidazoles and their structural analogs can be easily synthesized using this simple and practical green synthetic procedure as shown in (Scheme 12) [14].



Scheme 12: Synthetic route for the formation of benzimidazoles from O-phenylenediamine and aromatic carboxylic acid

Benzimidazole as an Antidiabetic

A survey of the literature indicates that numerous benzimidazole derivatives have been synthesized and extensively investigated for a wide range of pharmacological activities, including antidiabetic, antimicrobial, anticancer, antiprotozoal, anti-inflammatory, analgesic, antihistaminic, antimalarial, antitubercular, anti-HIV, and antiviral effects [4]. The synthesized 5-substituted benzylidene benzimidazole-thiazolidinedione derivatives were evaluated for their antidiabetic activity using the Oral Glucose Tolerance Test (OGTT) in experimental rats. The results demonstrated that several compounds exhibited significant glucose-lowering effects when compared to both the control and the standard drug, pioglitazone. Notably, compounds I, II, III, and IV in Figure 5 showed the most potent antihyperglycaemic activity, indicating their effectiveness in improving glucose tolerance and reducing postprandial blood glucose levels [15].

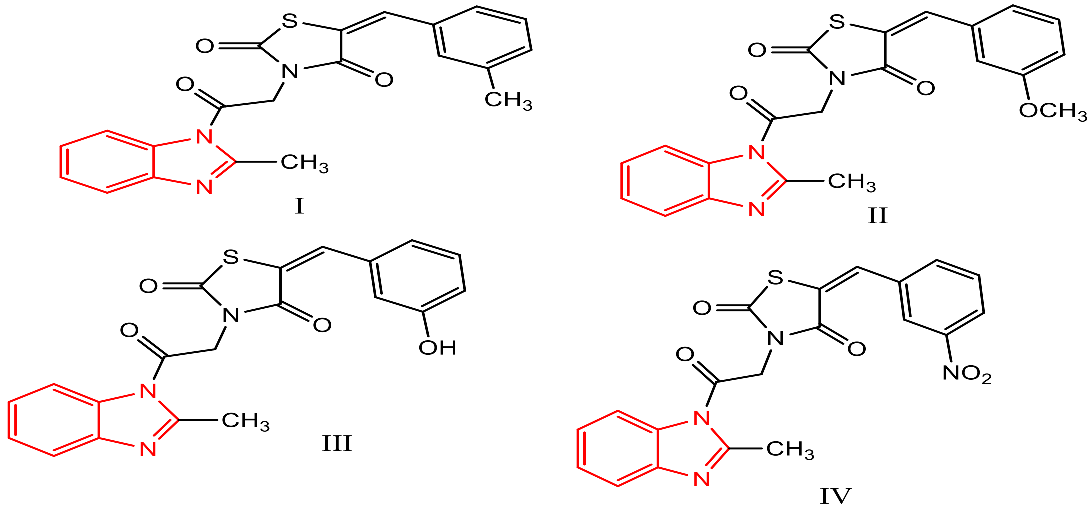


Figure 5. Derivatives of synthesized 5-substituted benzylidene benzimidazole-thiazolidinedione

Benzimidazole derivatives, albendazole (V) and lansoprazole (VI), were investigated for antidiabetic activity using *in-vitro* enzyme inhibition assays and *in-vivo* Type-2 diabetic rat models [16]. The results in Figure 6 demonstrated significant reductions in fasting blood glucose and improved glucose tolerance, serum insulin, and lipid profiles in treated animals compared with diabetic controls, and decreased oxidative stress and improved pancreatic and hepatic histology. These findings highlight the potential of benzimidazole-based compounds as antidiabetic agents and provide a robust comparison for in vitro studies of similar scaffolds [16].

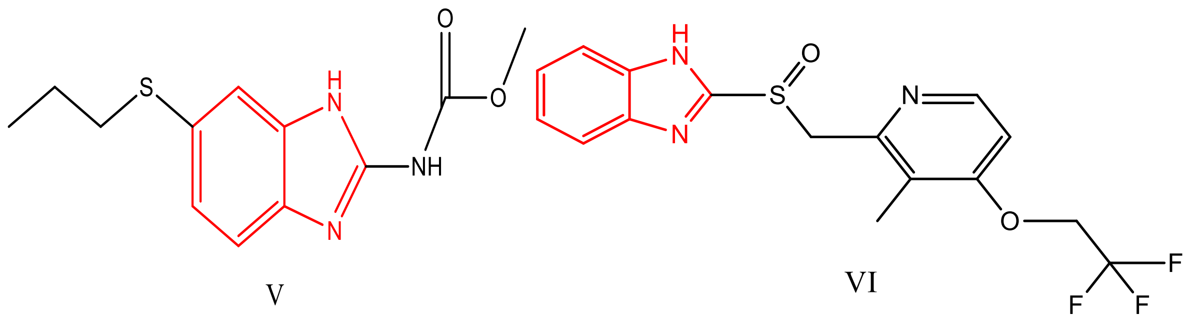


Figure 6. Structures of benzimidazole-based compounds albendazole (V) and lansoprazole (VI), with reported antidiabetic effects

A series of benzimidazole based bis-Schiff base derivatives was synthesized and evaluated for their antidiabetic potential using in vitro α-amylase and α-glucosidase inhibition assays. Among seven compounds tested, three derivatives (III -V) in Figure 7 exhibited pronounced inhibitory activity, with IC_{50} values of 6.94 ± 0.07 µM, 3.16 ± 0.05 µM, and 2.84 ± 0.12 µM, respectively. Notably, these compounds demonstrated inhibitory effects that were comparable to or exceeded those of the reference drug, acarbose [17].

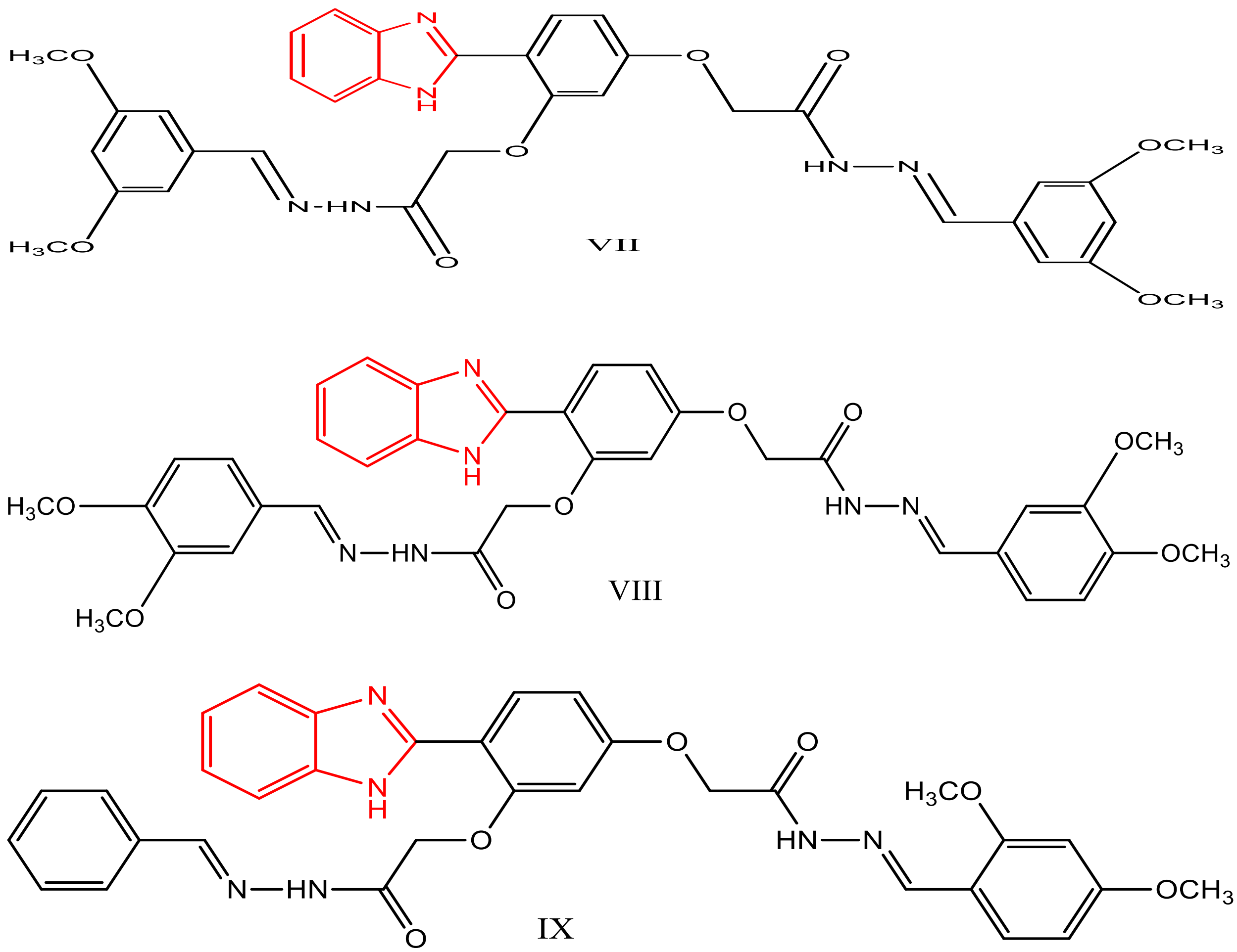


Figure 7. Structures of benzimidazole bis-Schiff base derivatives (VII-IX) with reported antidiabetic effects

CONCLUSION

Benzimidazole derivatives have emerged as an important class of heterocyclic compounds with diverse pharmacological properties. Various synthetic methods have been developed for the preparation of benzimidazole derivatives, most of which involve the condensation of O-phenylenediamine with different substitution such as aldehydes, carboxylic acids, alcohols, and benzylamines under a variety of catalytic conditions. Advances in synthetic strategies, including solvent-free reactions, microwave irradiation, and the use of environmentally friendly catalysts, have significantly improved the efficiency of benzimidazole synthesis. In addition to their synthetic versatility, numerous benzimidazole derivatives have demonstrated promising antidiabetic activity through mechanisms such as inhibition of AMP-activated protein kinase, α-glucosidase and α-amylase enzymes and improvement of glucose metabolism. These findings highlight the potential of benzimidazole scaffolds as valuable candidates for the development of new antidiabetic drugs. Further studies focusing on structure-activity relationships, molecular mechanisms, and clinical evaluation may contribute to the development of more potent and selective benzimidazole-based therapeutic agents for the management of diabetes mellitus.

Acknowledgments: The authors are grateful to the synthesis and drug discovery group members of the Department of Pharmaceutical and Medicinal Chemistry, Ahmadu Bello University, Zaria, Kaduna, Nigeria, for the computational resources.

REFERENCES

[1] Bhoi, R. T., Bhoi, C.N., Nikume, S.R. & Bendre, R.S. (2023). Results in Chemistry Design, synthesis, and in silico studies of benzimidazoles of thymol as potent antiplasmodial and antimicrobial agents. *Results Chem.*, 6, 01112. doi: 10.1016/j.rechem.2023.101112.

[2] Gidado, I., Idris, A. Y., Hamza, A. N., Abdullahi, M., Jibril, A., Hassan, L. A., Jimoh, Y., Yakubu, S., Yakubu, A. & Zukhruf. (2024). Oxidative Stress and Insulin Resistance: Correlation, In-silico Design, and Alpha- Glucosidase Inhibition of Benzimidazole Derivatives. *Niger. Res. J. Chem. Sci.*, 12(2), 261–277.[Online]. Available: https://www.unn.edu.ng/wp-content/uploads/2024/10/Oxidative-Stress-and-Insulin-Resistance-Correlation-In-Silico-Design-and-Alpha-Glucosidase-Inhibition-of-Benzimidazole-Derivatives.pdf

[3] Brishty, S.R., Hossain, M.J., Khandaker, M.U., Faruque, M.R.I., Osman, H. & Rahman, S.M.A (2021). A Comprehensive Account on Recent Progress in Pharmacological Activities of Benzimidazole Derivatives, 12. doi: 10.3389/fphar.2021.762807.

[4] Mohammad, Z., Alzhrani, M., Alam, M.M. & Nazreen, S. (2022). Recent Advancements on Benzimidazole: A Versatile Scaffold in Medicinal Chemistry, Mini Reviews in Medicinary 22 (2), 365-386. doi: 10.2174/1389557521666210331163810.

[5] Woolley, D.W. (1944). Some biological effects produced by benzimidazole and their reversal by purines. *J. Biol. Chem.*, 152, 225–232.

[6] Kamanna, K. (2019). Synthesis and Pharmacological Profile of Benzimidazoles. *Chem. Appl. Benzimidazole its Deriv.* doi: 10.5772/intechopen.85229.

[7] Padhy, G.K., Panda, J., Patro, C.S., Raul, S.K. & Behera, A.K. (2023). Synthetic Approaches of Benzimidazole Derivatives : A Review. *Rasayan J. Chem.*, 16(4), 2009–2018. doi: 10.31788/RJC.2023.1648542.

[8] Alexandra, M. & It, P. (CCCXVI1)-The Formation of 2-substituted benzimidazole. 172, 2393–2399. Journal of Chemical Society. https://doi.org/10.1039/JR9280002393

[9] Das Jony Mallik, J., Feroz Alam, Md., Syed Mainul Hossain, Mahfujur Rahaman, Ferdousi Begum (2018). Chemistry of Benzimidazole and its derivatives: Mini review. *Int. J. Mordern Pharm. Res.*, 7(1), 29–37.

[10] Bahrami, K., Khodaei, M.M. & Naali, F. (2016). TiO2 nanoparticles catalysed synthesis of 2-arylbenzimidazoles and 2-arylbenzothiazoles using hydrogen peroxide under ambient light. *J. Exp. Nanosci.*, 11(2) 148–160. doi: 10.1080/17458080.2015.1038659.

[11] Bano, K., Kisan, D. & Panda, T. (2022). Facile synthesis of benzimidazole and benzothiazole compounds mediated by a zinc precatalyst supported by iminopyrrole-morpholine ligand. *Eur. J. Inorg. Chem.*, 10, doi: 10.1002/ejic.202200023.

[12] Poor Heravi, M.R. & Ashori, M. (2013). Boric acid catalyzed convenient synthesis of benzimidazoles in aqueous media. *J. Chem.*, vol. 2013, doi: 10.1155/2013/496413.

[13] Saha, P., Brishty, S.R. & Rahman, S.M.A. (2020). Synthesis and Evaluation of Disubstituted Benzimidazole Derivatives as Potential Analgesic and Antidiarrheal Agents," *Indian J. Pharm. Sci.*, 82(2), 222–229. doi: 10.36468/PHARMACEUTICAL-SCIENCES.642.

[14] Wang, R., Lu, X., Yu, X., Sun, Y. & Shi, L. (2007). Acid-catalyzed solvent-free synthesis of 2-arylbenzimidazoles under microwave irradiation. *J. Mol. Catal. AChemical*, 266(1–2), 198–201.doi: 10.1016/j.molcata.2006.04.071.

[15] Prajapati, B.K. & Sen, D.J. (2013). Design, Synthesis and Oral Glucose Tolerance Screening of Some 5-substituted Derivatives on Rats. *American Journal of Advanced Drug Delivery AJADD 1(1), 084-092*

[16] Dik, B., Coşkun, D., Bahçivan, E. & Üney, K. (2021). Potential antidiabetic activity of benzimidazole derivative albendazole and lansoprazole drugs in different doses in experimental type 2 diabetic rats. *Turkish J. Med. Sci.*, 51(3), 1578. doi: 10.3906/SAG-2004-38.

[17] Ullah, H., Alam, A., Elhenawy, A.A., Ahmad, I. & Latif, A. (2025). Exploring the anti-diabetic potential of bis - Schiff base derivatives of benzimidazole: In-Vitro α-amylase, α - glucosidase inhibition, molecular docking, ADMET and DFT studies. *Journal of Computational Biology and Chemistry,* 118, 1–9. https://doi.org/10.1016/j.compbiolchem.2025.108497