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Review Article

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ANTIDIABETIC JOURNEY OF BENZIMIDAZOLE: A REVIEW

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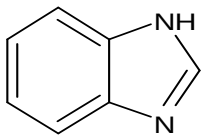
ABSTRACT

Benzimidazole core is an exceptional chemical structure that manifests vast biological and therapeutic activities like antiviral, anti-histaminic, anticancer, antiulcer, antihypertensive, antidiabetic, antifungal, and antimicrobial activity. It is a fused aromatic heterocyclic compound consists of benzene and imidazole. Aimed at the structural modifications for biological potentials, various derivatives of benzimidazole have been synthesized to increase the stability, bioavailability and promising biological profiles. This review confers about the different benzimidazole derivatives as target agents for anti-diabetic activity by inhibiting enzyme α-amylase and α- glucosidase.

KEYWORDS: Benzimidazole, Antidiabetic, α-amylase and α- glucosidase.

INTRODUCTION

Heterocyclic compounds are known to be pharmaceutically active substances, and it has been discovered that they have a substantial impact on drug development and design. Benzimidazole is a heterocyclic aromatic organic compounds having molecular formula $C_7H_6N_2$. It serves as a preferred structural motif in the creation of a large variety of pharmaceuticals with application in many different medical fields.[1] Out of all the benzimidazole derivatives, N-ribosyldimethyl benzimidazole is the most well-known. It functions as an axial ligand for cobalt in vitamin B_{12} and has a variety of other pharmacological actions.[2]



Due to their unique structural features and electron-rich environments, benzimidazole-containing drugs bind to a wide variety of therapeutic targets with a wide range of biological activities. They are also known as benzoglyoxalines. They are also called derivatives of o-phenylenediamine.[3] Both acidic and basic characteristics apply to benzimidazoles. The NH groups found in benzimidazoles are both weakly basic and relatively strongly acidic. The ability of benzimidazoles to form salts is another crucial characteristic. Unsubstituted NH groups in benzimidazoles show rapid prototropic tautomerism, which results in equilibrium mixtures of asymmetrically substituted compounds.[4]

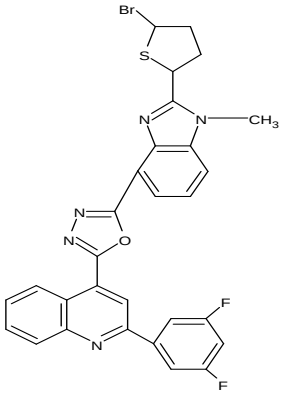
The chronic metabolic disorder known as diabetes mellitus (DM) is characterized by hyperglycemia brought on by defects in insulin secretion and action.[5] The vast majority of cases of DM fall into two broad etiopathogenetic categories: Type 1 and Type 2 DM (T1DM and T2DM, respectively). T1DM, formerly known as insulin-dependent diabetes or juvenile-onset diabetes, is caused by an autoimmune reaction that destroys pancreatic cells on a cellular level; as a result, patients are dependent on exogenous insulin. The majority of cases of DM are caused by T2DM, which is more prevalent among people between the ages of 40 and 60.[6] The World Health Organization (WHO) estimated that more than 220 million people worldwide currently have diabetes, and that by 2030, this number will have doubled.[7]

In order to treat type 2 diabetes, postprandial hyperglycemia must be reduced. This is accomplished by blocking carbohydrate enzymes like α-glucosidase and α-amylase.[8,9] Glucosidases catalyze the breakdown of an oligosaccharide's glycosidic bond, which is the last step in the digestion of carbohydrates. They are responsible for the catalytic cleavage of a glycosidic bond with specificity depending on the position of cleavage site, number of monosaccharides and the configuration of the hydroxyl groups in the substrate.[10] *α*-amylase is basically a calcium metalloenzyme. The main function of α-amylase is to cleave starch's glycosidic linkages at random sites to produce smaller oligosaccharides or disaccharides.[11] The special class of medications known as α-glucosidase inhibitors (AGIs) and α-amylase inhibitors (AAIs) can reduce type 2 diabetes by delaying the action of specific enzymes that break down food and release glucose (sugar) into the

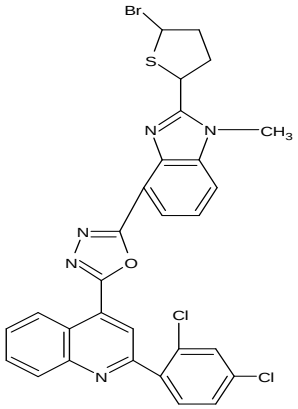
blood.[12] The three drugs for the treatment of diabetes that are commercially available come from natural sources and are called acarbose, miglitol, and voglibose.[13]

LITERATURE REVIEW

Bhardwaj *et. al.,* were synthesized benzimidazole-quinolinyloxadiazole hybrids. A promising anti-diabetic function, namely the inhibition of α -glycosidase, is shown by compounds 30 a and 30 b. Compounds 30a and 30b were the most effective with IC_{50} values of 0.395±0.05 and 0.386±0.02 µm when compared with standard acarbose (IC_{50} = 942.57 ± 157 µm).[14]

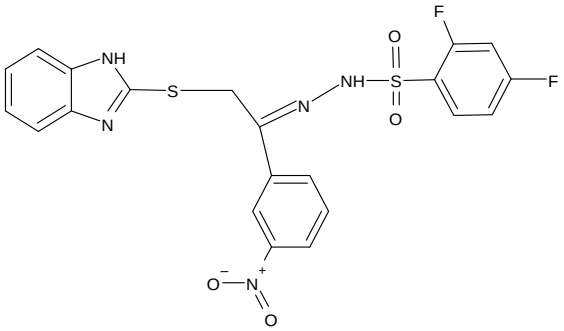


30 a

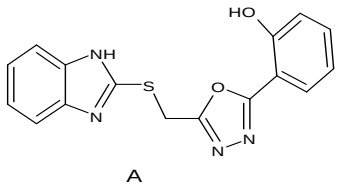


30 b

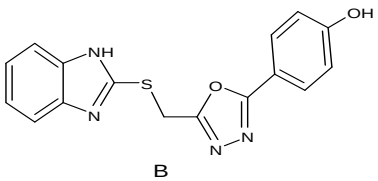
Shafqat Hussain *et. al.,* synthesized 2-mercaptobenzimidazole analogues which having α-amylase inhibition potential. When compared to standard acarbose, which has an IC_{50} value of 1.70±0.10 µm, the compound has an IC_{50} value of 0.90±0.05 µm. Due to the presence of more electronegative NO_2 groups on the phenyl ring and the addition of 2,4 difluoro substituents, these compounds are more potent than standard drugs.[5]



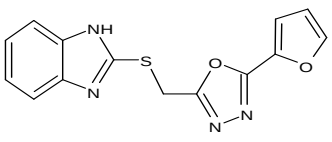
Ramya V. Shingalapur *et. al.,* synthesized 2- mercapto benzimidazole derivative and tested for antidiabetic activity. When compared to glibenclamide, the compounds a-d exhibit a greater drop in blood glucose levels on 9th day.[15]



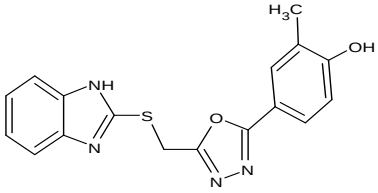
A



B

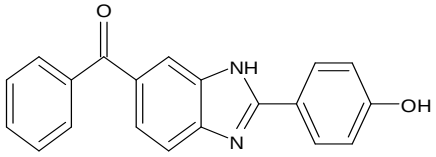


C

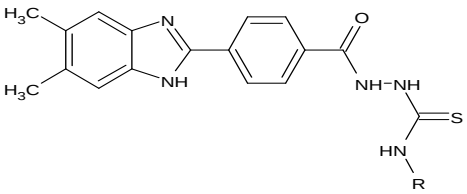


D

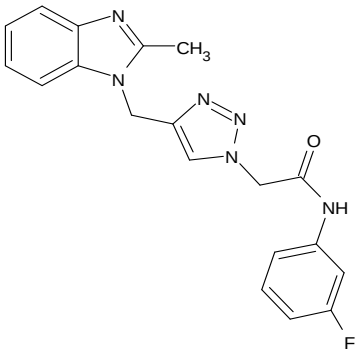
Lofti Aroua *et. al.,* carried out Synthesis of series of novel benzoaryl benzimidazole via condensation of 3,4-diamino- benzophenone and aryl aldehyde in mild condition using NH_4Cl or mixture of NH_4Cl and sodium metabisulfite as catalyst. When compared to acarbose, the standard reference drug, the given compound exhibits the highest levels of activity, inhibiting both α-amylase and α-glycosidase with IC_{50} values of 12.9±0.38 µm and 11.02±0.04 µm respectively.[16]

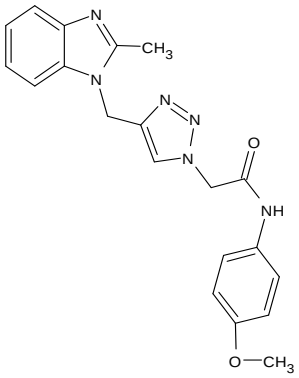


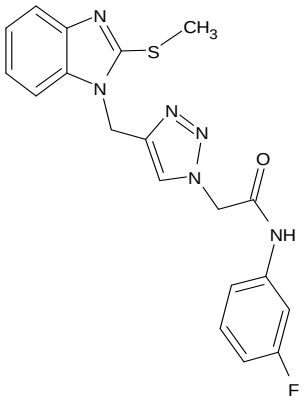
Nik Khairunissa Nik Abdullah Zawawi *et. al.,* synthesized Thiourea derivatives having benzimidazole as α-Glucosidase Inhibitors. Among these compound 10 and 14 showed significant inhibitory effects with IC_{50} value 50.57±0.81 and 35.83±0.66 µM.[17]



R- 4 bromo phenyl, 4 nitro phenyl

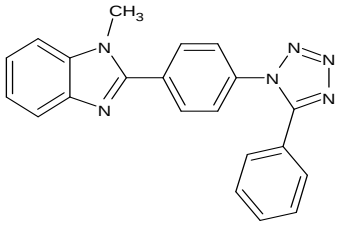




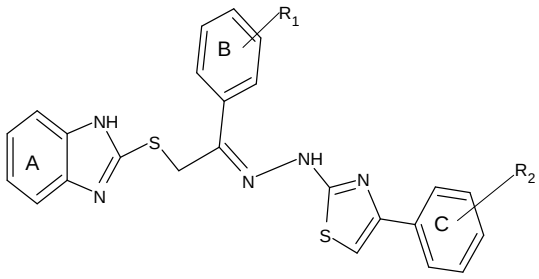


Rafaqat Hussain *et. al.,* synthesized hybrid analogs of benzimidazole containing a thiazole moiety and tested for α-amylase and α-glucosidase inhibition. Analogs bearing substituents of smaller size was found to be a better competitor of both targeted α-amylase and α-glucosidase, compared to analogs that bear substituents of larger size. Moreover, it was also noted that inhibition properties for both α-amylase and α-glucosidase enzymes were greatly influenced by varying the numbers, positions and natures (electron-donating or electron-withdrawing groups) of substituents around both rings B and C, respectively.[20]

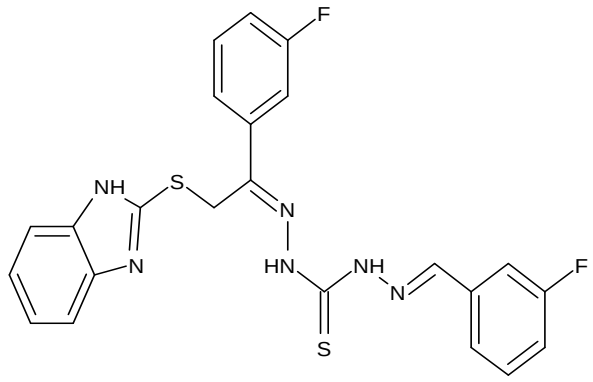
Vijayakumar and Ahamed were studied series of compounds for their potential anticancer, antidiabetic, antitumour and antiasthmatic properties. Compound (99) showed good antidiabetic activity.[18]



Laxmi Deswal *et. al.,* were synthesized novel 1,2,3-triazole derivatives attached to benzimidazoles and these compounds were tested for their ability to inhibit both α-amylase and α-glycosidase i.e. anti-diabetic action.[19]



Hayat Ullah *et. al.,* synthesized Benzimidazole Bearing Thiosemicarbazone Derivatives and screened against α-glucosidase and α-amylase enzymes. Derivatives 19 and 20 were found to be the most potent among the series when compared with standard drug acarbose.[21]



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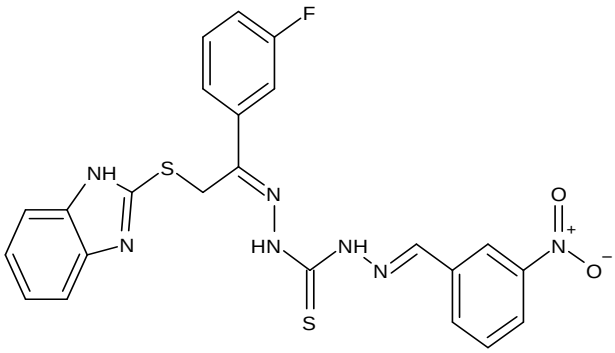
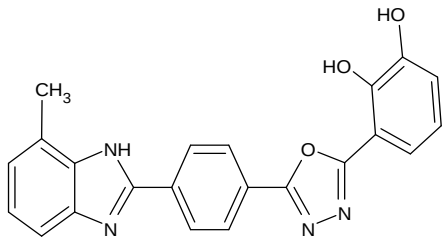
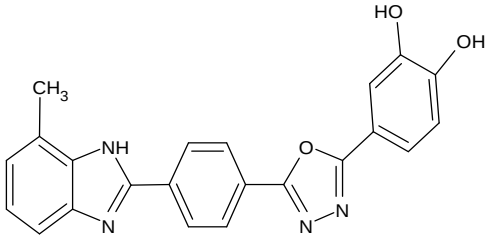


20

Muhammad Taha *et. al.*, synthesized twenty-six analogs of benzimidazole based oxadiazole and evaluated against alpha-glycosidase enzyme. Analog 1, 2, 3 and 14 with IC_{50} values 4.6± 0.1, 9.50± 0.3, 2.6 ±0.1 and 9.30± 0.4 µM respectively showed excellent inhibitory potential than reference drug acarbose (IC_{50} = 38.45 ±0.80 µM).[22]



1



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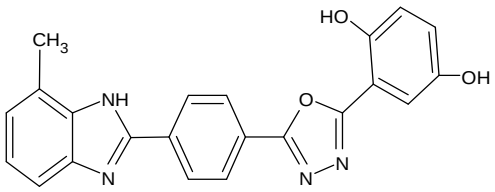

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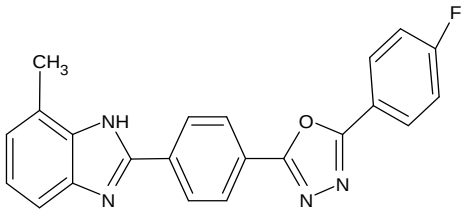
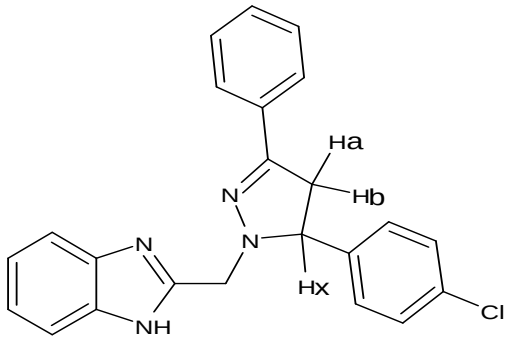


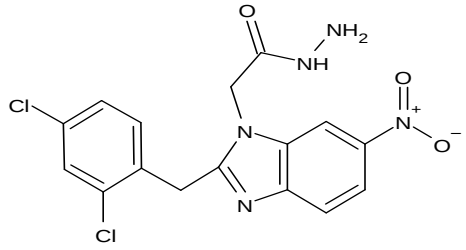
14

Farhat Ibraheem *et. al.*, synthesized novel benzimidazole-pyrazoline hybrid molecules and screened against alpha-glycosidase enzyme. Compound 5d appeared as effective inhibitor with IC50 = 50.06µM as compared to reference drug (acarbose) having IC_{50} = 58.8µM.[23]

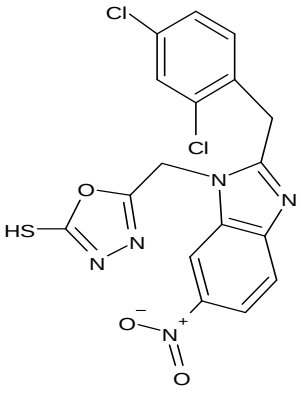


5d

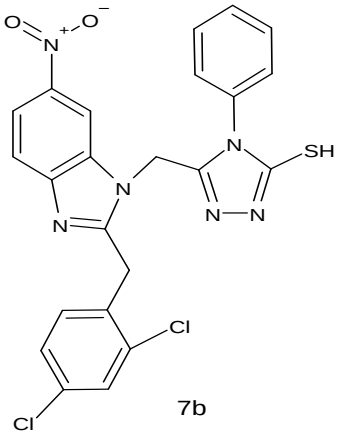
Musa Ozil *et. al.*, a novel series of benzimidazole derivative and investigated for α-glucosidase inhibitor activity. Compounds 4b, 5b and 7b were potent inhibitors.[24]



4b

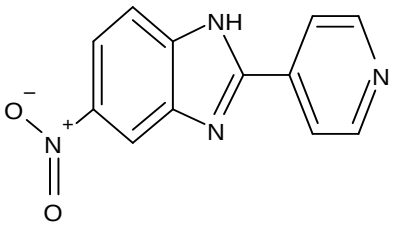


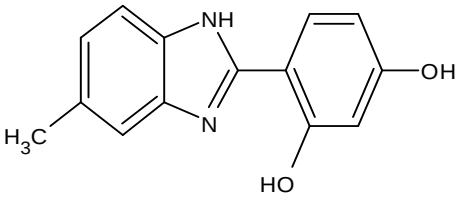
5b



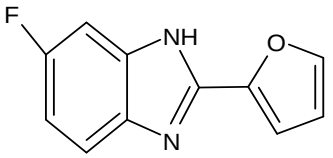
7b

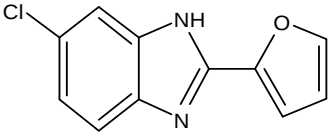
Jaldi *et. al.*, synthesised 2-substituted benzimidazole compounds and assessed their effectiveness in inhibiting yeast and rat intestinal α-glycosidase. Among these, compound A inhibits yeast and rat intestinal α-glycosidase enzyme by 95.6% and compound B by 76%. The most effective inhibitor of intestinal α-glycosidase, according to the IC_{50} value 99.4μM is compound A.[25]

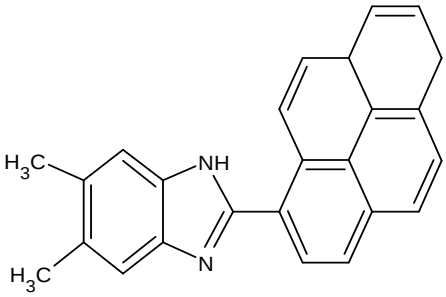




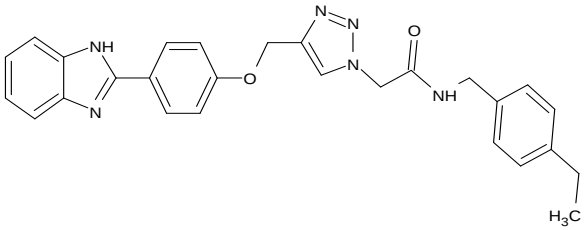
Akinsola Akande *et. al.*, carried out synthesis of heteroarylated benzimidazole and screened for α-amylase inhibitory activity and antioxidant properties. All compounds show moderate α-amylase inhibition and ABTS and DPPH radical scavenging ability compared to the standard forms ascorbic acid and acarbose. 2-furynyl and 2-methylated 2-furynyl are followed by 2-benzyloxyphenol, 2-pyrenl, and 2-anthracnyl substituted benzimidazole. According to the literature, this compound can be used in subsequent studies to produce effective and potent α-amylase inhibition as well as ABTS and DPPH radical scavengers.[26]





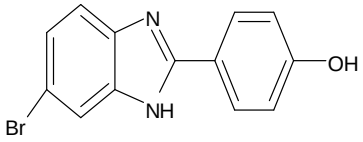


Nafise Asemanipoor *et. al.*, carried out synthesis of new benzimidazole-1,2,3-triazole hybrids as potential α-glucosidase inhibitors. The synthesized compounds (IC_{50} values ranging from 25.2 ± 0.9 to 176.5 ± 6.7 μM) exhibited more inhibitory activity in comparison to standard drug acarbose (IC_{50} = 750.0 ± 12.5 μM). Compound 8c is the most potent one.[27]

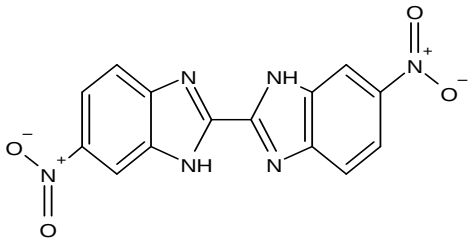


Tanzila Arshad *et. al.*, carried out *in vitro* evaluation and molecular docking studies of 5-bromo-2-aryl benzimidazoles as α-glucosidase inhibitors. Compound 17 (IC_{50} = 8.34 ± 0.02 μM) found excellent inhibition as

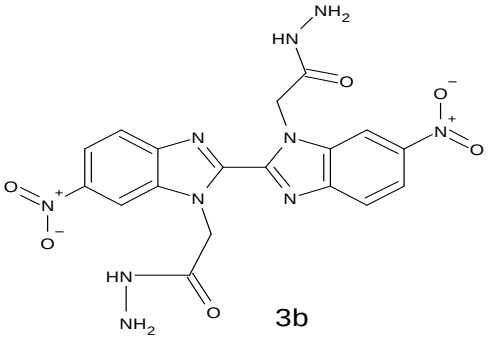
compared to standard acarbose (IC_{50} = 38.25 ± 0.12 µM).[28]



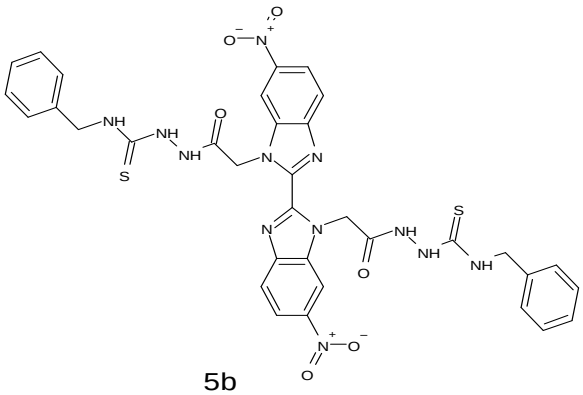
Musa Ozil *et. al.*, synthesized a series of bisbenzimidazole derivatives and screened for α-glucosidase inhibition. The IC_{50} value of derivatives ranging between 0.44 ± 0.04 and 6.69 ± 0.01 µM when compared to the standard acarbose (IC_{50}- 13.34 ± 1.26µM). Among the tested compounds 1b, 3b, 4b and 5b showed the most significant α-glucosidase inhibition.[29]



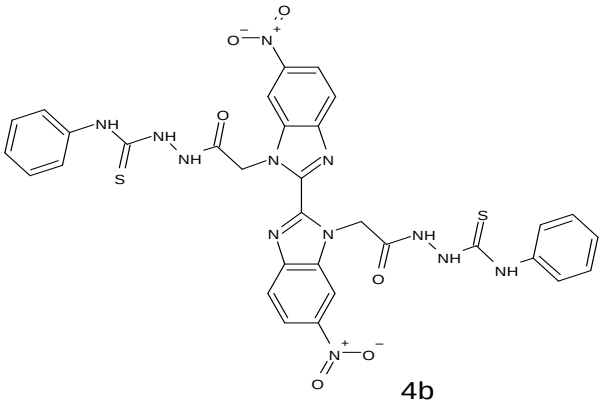
1b



3b



5b



4b

CONCLUSION

Benzimidazole modifications showed beneficial biological effects. In this review, a variety of new benzimidazole scaffolds that inhibit the enzymes α-amylase and α-glycosidase are described. These scaffolds have anti-diabetic characteristics. Other researchers will benefit from this as they develop crucial SAR studies on benzimidazole derivatives. For the treatment of type II diabetes, a number of drugs have been introduced with promising potential activity. Hence, the search for novel benzimidazole pharmacophores that are potent, pharmacologically efficient, and secure as anti-diabetic medicines is encouraged.

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