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POTENTIAL OF BENZIMIDAZOLE AS ANTI-DIABETIC AGENT: REVIEW

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ABSTRACT

Benzimidazole is aromatic, nitrogen containing compound and privileged scaffold with active pharmacophore in medicinal chemistry. They exhibit immense pharmacological and biological activities which resulted in development of several classes of drugs. The review confers about the synthesis of benzimidazole derivatives as target agents for anti-diabetic activity by inhibiting enzyme α-amylase and α-glycosidase. Diabetes mellitus is chronic metabolic disease, mainly hyperglycemia results in deficiencies like insulin secretion or insulin action or both. Research describes that α- Glycosidase inhibitors (AGI's) and α-amylase inhibitors (AAI's) are unique class of drugs that are capable to reduce type II diabetes.

KEYWORDS: Benzimidazole, Anti-diabetic, α-amylase inhibition, α-glycosidase inhibition.

INTRODUCTION

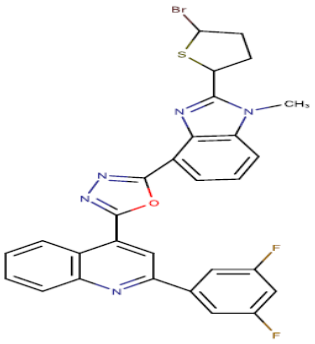
Diabetes mellitus is chronic metabolic disease, mainly hyperglycemia results in deficiencies like insulin secretion or insulin action or both.[1] Chronic hyperglycemia is associated with long lasting damage, dysfunction, failure or malfunction of several organs results in nephropathy, retinopathy, neuropathy, foot ulcer among other symptoms.[2] Diabetes is divided as Type I and Type II. Type I diabetes is caused by pancreatic cells injury which is due to insulin cannot be produced. Type II diabetes caused by insulin resistance or insufficient insulin action.[3,4] International Diabetes Federation in 2019 reported that about 463 million people were suffering from diabetes and this number supposed to increased. It is estimated that 576 million people may suffer diabetes in 2030 and 700 million in 2045.

According to WHO, deaths from diabetes have increased by 70% globally between years 2000-2019. There has also been 80% rise in deaths among males.[5,6]

Benzimidazole is aromatic nitrogen containing heterocyclic compound and privileged scaffold with active pharmacophore in medicinal chemistry.[7] They exhibit an immense pharmacological and biological activities including antiulcer,[8] antihypertensive,[9] antifungal,[10,11] anticancer,[12] anthelmintic,[13] antibacterial,[14] cytotoxic and antitumor,[15] DNA binding enzyme inhibitor,[16,17] HIV I induced cytopathic inhibitors,[18] anti-inflammatory,[19] antiviral,[20] antihistaminic,[21] antitubercular,[22] antiprotozoal,[23] antileishmanial,[24] antioxidant,[25] antimycobacterial.[26] Recently, benzimidazole nucleus was described as novel Zika inhibitors,[27] inhibitors targeting HCV N55B polymerase,[28] antileukemic agents,[29] antihepatitic C.[30] Benzimidazole is a privileged nucleus i.e. among the topmost ring systems used in small molecule drugs listed by the US FDA.

Diabetes can be treated by inhibition of α-amylase and α-glucosidase enzyme which are involved in carbohydrate digestion. Digestive enzyme, α amylase (a calcium metalloenzyme) secreted by pancreas and salivary gland which is involved in cleavage of α-1,4 glycosidic linkages of starch, glycogen, amylase and amylopectin. A-amylase is in brush borders of small intestine which releases glucose molecule by hydrolysis of oligosaccharides and disaccharides.[31] α- Glycosidase inhibitors (AGI's) and α-amylase inhibitors (AAI's) are unique class of drugs that can reduce type II diabetes by slowing the action of certain chemicals that break down food to release glucose (sugar) to blood.[32] The prime challenge to global healthcare system is to the development of novel α-glycosidase and α-amylase inhibiting agents which are capable of curing diabetes Type II. Literature shows that Benzimidazole and Benzimidazole derivatives (scaffolds) shows novel and potent action as anti-diabetic drugs.

Bhardwaj et. Al. (2018) were synthesized benzimidazole- quinolinyloxadiazole hybrids. Among which compound 30 a and 30 b exhibits promising anti-diabetic activity i.e. α-glycosidase inhibition. Compound 30 a and 30 b were most potent with IC_{50} values 0.395±0.05 and 0.386±0.02 µm when compared with standard acarbose (IC_{50} = 942.57 ± 157 µm).[33]



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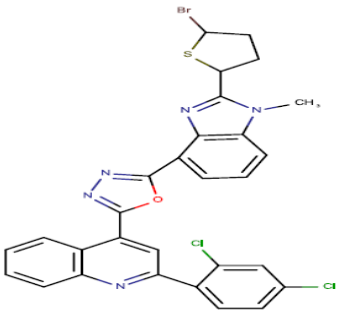
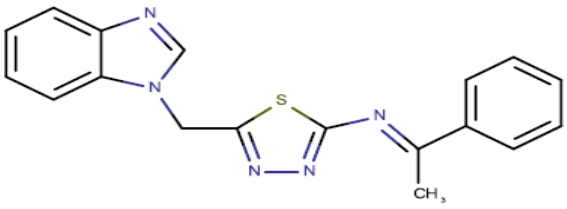
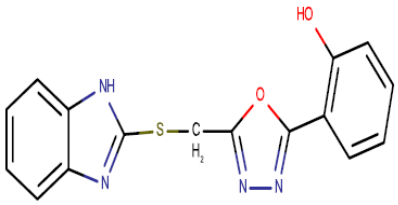


30 B

Sandhya M J Nair were synthesized compound based on Libdock score, was selected for in vitro anti-diabetic and it shows 49.25% inhibition at 100 µm concentration while reference acarbose shows 68.61% inhibition at 100 µm concentration.[34]



Ramya V. Shingalapur et. Al. They synthesized 2- mercapto benzimidazole derivative and checked for antidiabetic activity. The compounds a-d shows better reduction in blood glucose levels on 9th day when compared with glibenclamide.[35]



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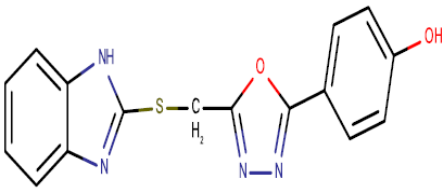

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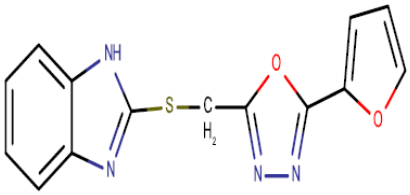

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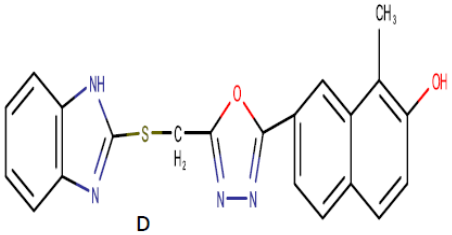
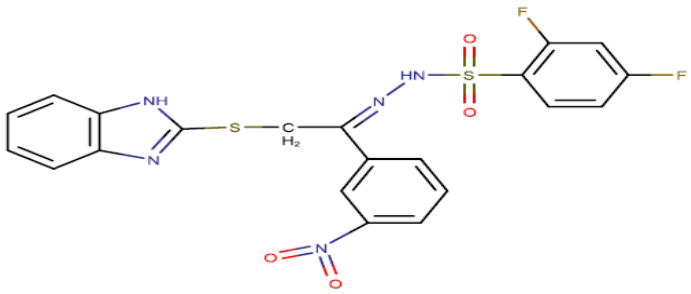


D

Shafqat Hussain et. Al. synthesized 2-mercaptobenzimidazole analogues which having α-amylase inhibition potential. The Compounds shows IC_{50} value 0.90±0.05 µm when it is compared with standard acarbose having IC_{50} value 1.70±0.10 µm. These compounds are better potent than standard drug due to presence of more electronegative NO_2 group on phenyl ring and also having 2, 4 difluoro substituents on phenyl ring can create more polarity.[36]



Leila Dinparast et. Al. found out that Green, one pot, solvent free and selective synthesis of benzimidazole derivatives is done in which ZnO/ MgO, ZnO nano-particles are used catalyst. This compound shows α-glycosidase inhibitory activity. Also In- silico studies were performed and QSAR model was established to find correlation between observed bioactivity and structural properties of synthesized compound.[37]

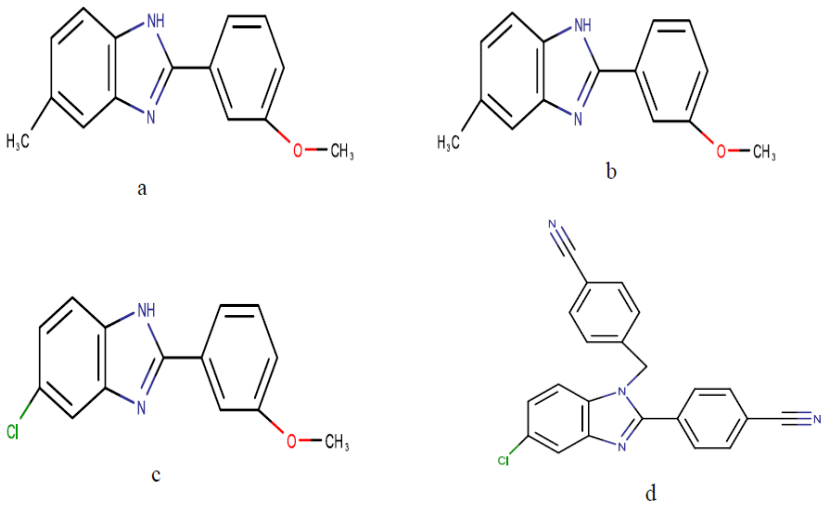
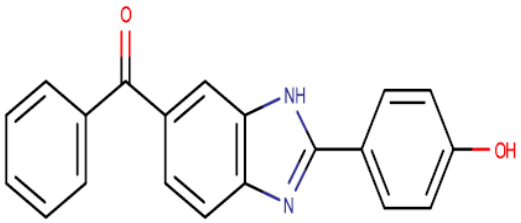


Table no. 1: Compounds with their IC_{50} values.

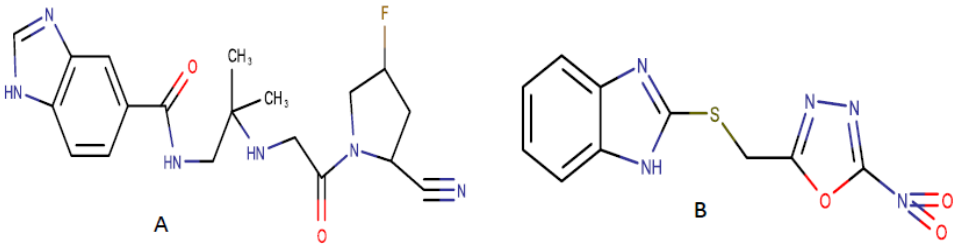
Compounds	IC $_{50}$ values (µm)
a	165.9 ±13.1
b	119.7±1.6
c	168.4±3.6

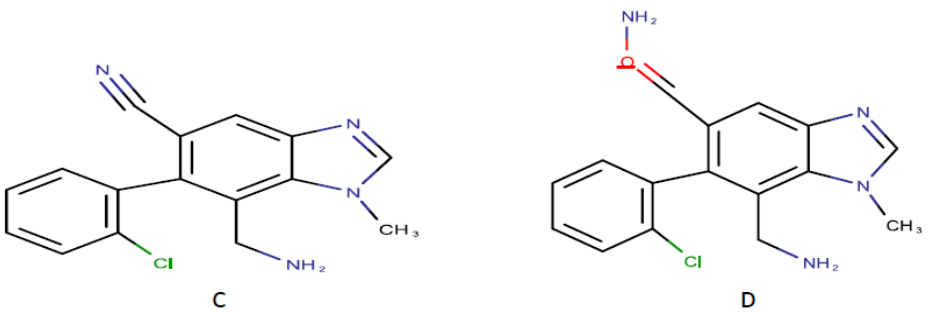
d	60.7±1.7
Acarbose	47.7±1.7

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. Given compound shows best activity having -OH group at para position of phenyl group and exhibiting α-amylase inhibition (IC_{50}=12.9±0.38 µm) and α-glycosidase inhibition (IC_{50}=11.02±0.04 µm) when compared with acarbose as standard reference drug.[38]

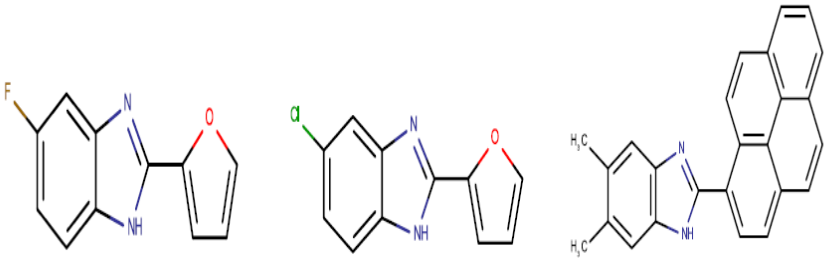


Olayinka Ajani et. Al. introduced compound A shows promising anti-diabetic agent due to the inhibition of DPP- IV at IC_{50} 5.7 nm. According to oral glucose tolerance test, compound B shows excellent anti-diabetic activity as better reduction in blood glucose level on 9th day when compared with glibenclamide. Compound C & D shows highly promising anti-diabetic compound with IC_{50} 0.008µm& 0.032 µm respectively.[39]

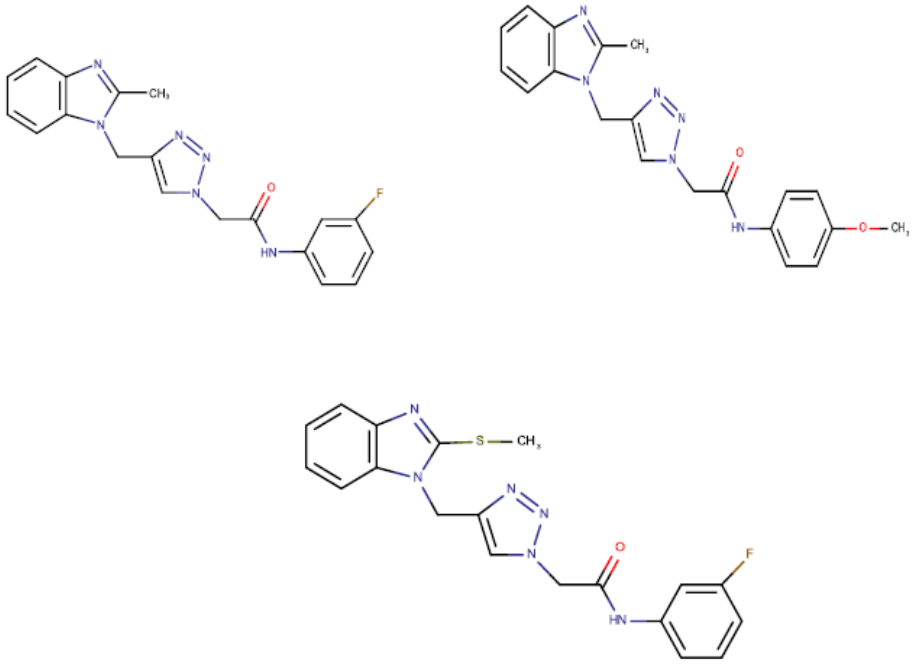




Akinsola Akande et. Al. Carried out synthesis of heteroarylated benzimidazole and screened for α-amylase inhibitory activity and antioxidant properties. All compounds shows moderate α-amylase inhibition as well as ABTS and DPPH radical scavenging potential when compared with standard acarbose and ascorbic acid respectively. 2-furynyl/ 2- methylated furynyl> 2-benzyloxyphenol > 2-pyrenl ⩭ 2- anthracnyl substituted benzimidazole. Literature says that this compound can be used for further future research to obtain good and potent α-amylase inhibition and ABTS and DPPH radical scavengers.[40]

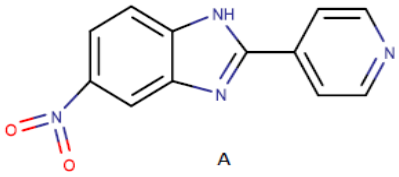


Laxmi Deswal et. Al. were synthesized novel benzimidazole tethered 1,2,3-triazole derivatives are most active compound were synthesized and evaluated for α-amylase inhibition and α-glycosidase inhibition i.e. anti-diabetic activity.[41]



Jaldi et al. Were prepared 2-substituted benzimidazole derivatives and evaluated activity on yeast and rat intestinal α-glycosidase inhibition. Among which compound A shows 95.6%

inhibition and compound B shows 76% inhibition of yeast and rat intestinal α-glycosidase enzyme. Compound A is most potent inhibitor for intestinal α-glycosidase with IC_{50} value 99.4μM.[42]



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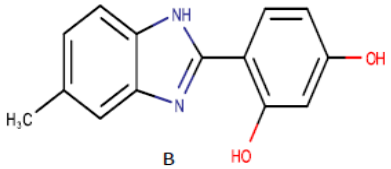

B

The prime challenge to global healthcare system is to the development of novel α-glycosidase and α-amylase inhibiting agents which are capable of curing diabetes Type II. Literature shows that Benzimidazole and Benzimidazole derivatives (scaffolds) shows novel and potent action as anti-diabetic agents.

CONCLUSION

The review gives an account on several novel benzimidazole scaffolds that possess anti-diabetic activity by inhibiting enzyme α-amylase and α-glycosidase. This will aid other researcher to develop important SAR study on benzimidazole derivatives. Various agents who show good potential activity that they were marketed for treatment of type II diabetes. So, further studies are recommended on the search of novel benzimidazole pharmacophores that are potent, pharmacological effective and safe as anti-diabetic agents.

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