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Azoles, A Potential Anti Diabetic Agents as α- Glucosidase Inhibitors: Past, Current & Future Prospects

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ABSTRACT

Diabetes is a chronic disordered metabolism disease, indicated by Elevated blood glucose level. Various methods such as Fasting plasma glucose level Oral glucose tolerance test (OGTT) and HbA_{1c} test , have been used to diagnose elevated blood glucose level in the body. A better medication is the only solution to control this disease. For this at present, α-Glucosidase inhibitors are recently used as a first line drug with safer efficacy. During study many previous study it was found that various chemical moieties were involved in the synthesis of α-Glucosidase inhibitors for the treatment of diabetes. Compound bearing azole moiety were one of them. This article compiled various recent researches which involved various types of compounds, having azole in their structure. Our main objective of this article is to focus on such facts, which can be used to design and synthesis of α- Glucosidase inhibitors bearing azole moiety, related to, which will further direct to the researchers in future.

Keywords: *Diabetes, α-Glucosidase inhibitors, Azole.*

1. INTRODUCTION

The main aim of this article to know about the therapeutic efficacy of azole compounds as α- Glucosidase inhibitors. This article included the SAR, computational design, synthesis and the α- Glucosidase inhibitory activity of different compounds containing azole moiety. In future, researchers may take help from this article for further study of compounds, having azole, in performing the various computational design study. They may also take help in the synthesis and in vitro α- Glucosidase inhibitory activity from this article.

Diabetes

Diabetes is a non- communicable chronic metabolic endocrine disorder, characterized by high blood sugar level in the body [1-2]. Deficiency of blood glucose metabolic hormone (Insulin), is the main reason of high blood sugar level in the body. Various processes such as transportation of glucose in adipose tissue, muscles and liver and glycogenesis, Insulin maintains the normal level of glucose in blood [3]. Insufficient or deficiency of insulin in the body causes diabetes mellitus [4]. Polyphagia (Frequent hunger), polyuria (frequent urination) and polydipsia (Frequent thirst) are the initial symptoms of diabetes mellitus in human body [4]. Other than the above symptoms, diabetes can be diagnosed by the estimation of fasting plasma glucose (FPG) level, Oral glucose tolerance test (OGTT) and HbA_{1c} test. Fasting plasma glucose level more than 126mg/dl and OGTT, equal to or greater than 200 mg/dl and HbA_{1c} is equal to or greater than 48mmol/mol (6.5%), is diagnosed as diabetes [5]. Other diagnosis techniques for diabetes mellitus are urine sugar [6], blood sugar[7], renal threshold of glucose [8], diminished and increased glucose tolerance [9], cortisone stressed glucose tolerance test [10] and renal

glycosuria [11]. Diabetes mellitus can be further classified in to three types on the basis of type of insulin deficiency or increasing blood glucose level. Type 1 diabetes, Type 2 diabetes and gestational diabetes [12]. In type 1 diabetes (Insulin dependent diabetes mellitus or juvenile diabetes), body fails to produce insulin due to autoimmune β cell destruction [13]. The main cause of type 2 diabetes (Non insulin dependent diabetes {NIDDM}), is the loss of insulin secretion from the β cell [14]. Gestational diabetes mellitus (considered as third type of diabetes) is diagnosed on the 2nd or 3rd trimester during pregnancy [15]. The detailed classification, occurrence and complication of diabetes are describe in figure 1[15].

At worldwide, 537 million adults (10.5%) of 20 to 79 age group are affected by diabetes. It is estimated that, by 2030, 643 million people and till 2045, approx 783 million people will be affected by diabetes[16]. This will be alarming threatening condition to the world wide population in future. At present there is no cure of diabetes but it can be treated and controlled by present medicinal System. In the present era, Oral hypoglycemic agents (α-glucosidase inhibitor [17], biguanide [18], sulfonylurea [19], thiazolidinediones [20], dipeptidyl peptidase – inhibitors [21]), insulin delivery devices [22] (insulin syringes, insulin pump, implantable pump inhaled insulin and pen devices) [23], stem cell therapy [24] , dietary management, artificial pancreas [25] are the main strategies for controlling the diabetic condition in human.

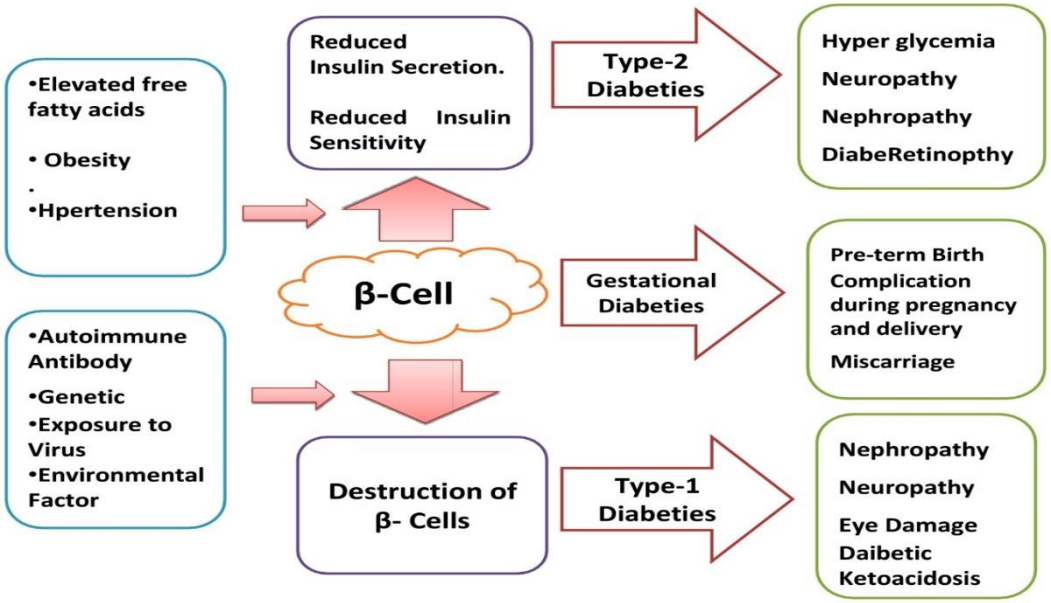


Figure 1: Types of Diabetes and their causes.

Physiology of Carbohydrate Digestion and absorption of Glucose in the blood

α- glucosidase and α- amylase are the two main enzymes, involved in the carbohydrate (starch) metabolism [26]. They convert complex carbohydrate in to the simpler carbohydrate (monosaccharide mainly glucose) [27]. α- Amylase converts complex carbohydrate in to disaccharide or trisaccharide followed by α- glucosidase converts these di or triaccharides in to monosaccharies and makes them suitable for absorption in the blood [28].

α-Glucosidase

α-Glcosidases are the enzymes which are present on the mucosal brush border of small intestine [29] and convert complex carbohydrate in to monosaccharide (conversion of di or trisaccharide in to monosaccharide or glucose) , which are readily absorbed in to the blood and reflect in the term of blood glucose concentration [30].

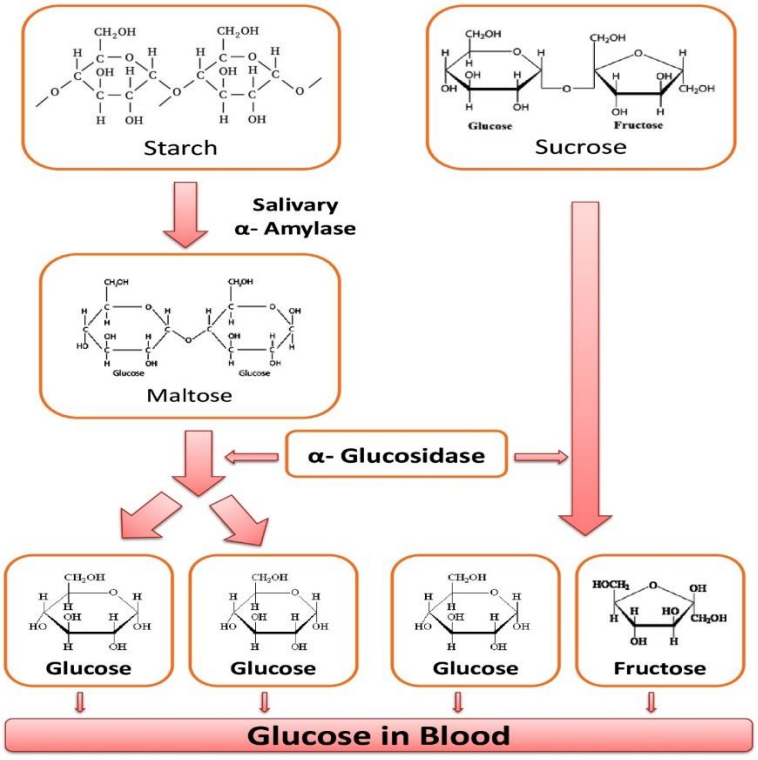


Figure 2 : Conversion of Complex Carbohydrate by α- Glucosidase

α-Glucosidase Inhibitors

α-Glucosidase inhibition is the main strategy, used to decrease the elevated postprandial blood

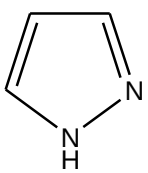
glucose level in the body [31]. It can be achieved by delaying the intestinal absorption of glucose in the blood by the inhibition of α-Glucosidas enzyme [32]. Most of the α-Glucosidase inhibitos work as pseudo-carbohydrates due to resemblances in their structure with the disaccharides or other saccharides which are normally hydrolysed by α-Glucosidase [33]. Due to resemblances in the structure, they easily attach on the attachment site of disaccharide or other saccharide on α-glucosidase, results in competitively inhibition of α-Glucosidase attachment site in the intestinal lumen [34] which delay or inhibit the conversion of disaccharides and oligosaccharides in to monosaccharide thus decrease the postprandial glucose concentration in blood [35]. Some examples of Alpha-glucosidase inhibitors (AGIs) are Acarbose [36], Voglibose [37] & Miglitol [38].

Now a days, α-Glucosidase inhibition is the main attracting strategy for the treatment of diabetes. Many researchers have synthesized and evaluated many compound as α-Glucosidase inhibitors. Researchers showed very much interest to synthesized the compounds which were based on azole compounds.

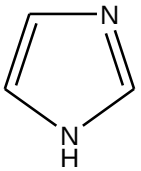
Azole

Azoles are chemically heterocyclic compound which have significant pharmacological importance. Azole is a word made by combination of two words- 'Aza' and Ole. In the nomenclature of heterocyclic system, Aza word mainly used for nitrogen atom and 'Ole' word is used for the 5 member unsaturated heterocyclic ring compounds. So a group of 5 member heterocyclic compounds, having nitrogen atom and also have one other atom than Carbon (nitrogen or oxygen or sulphur) is known as azoles [39]. On the basis of above discussion, some examples of Azoles [40] are-

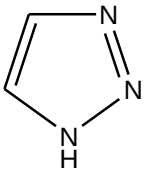
Only Nitrogen atom:



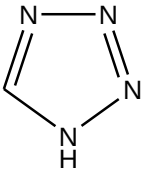
Pyrazole



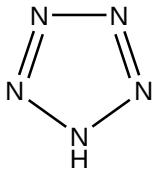
Imidazole



1,2,3- Triazole

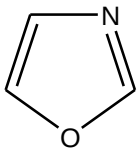


1,2,4-Triazole

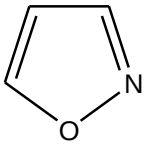


Pentazole

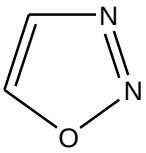
N,O Compounds



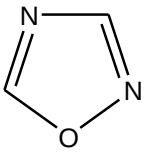
Oxazole



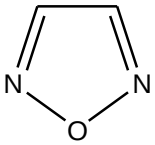
Isoxazole



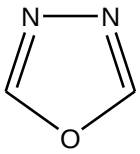
1,2,3-Oxadiazole



1,2,4-Oxdiazole

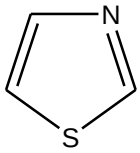


1,2,5-Oxadiazole

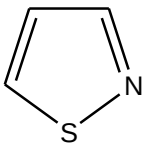


1,3,4-Oxadiazole

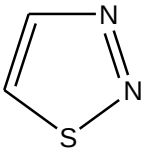
N,S compounds



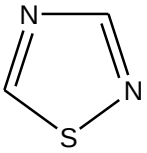
Thiazole



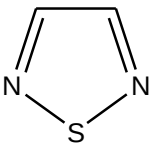
Isothiaole



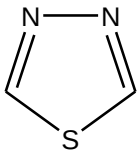
Thiadiazole



1,2,4-Thiadiazole



1,2,5-Thiadiazole



1,3,4-Thiadiazole

Azole Derivatives As α-Glucosidase Inhibitors

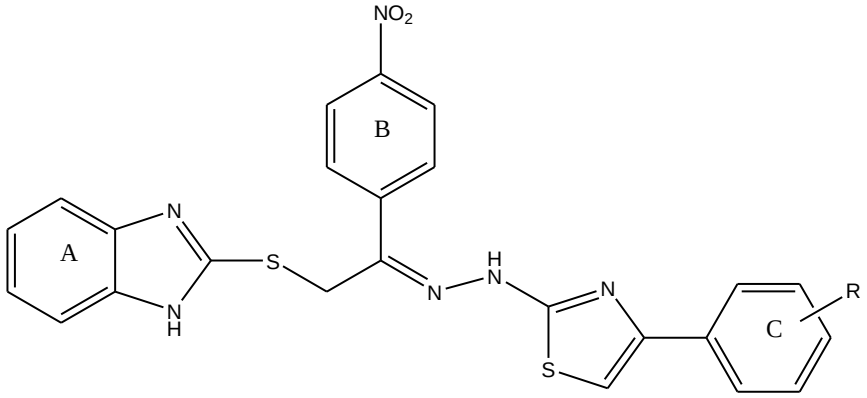
Hussain R et al (2022) synthesize derivatives of (*E*)-1-(2-(1H-benzo[*d*]imidazol-2-ylthio)-1-(4-nitrophenyl)ethylidene)-2-(4-phenylthiazol-2-yl)hydrazine (1-17) and tested them for their ability to inhibit alpha-glucosidase inhibitor, using acarbose as standard drug. All 17 compounds showed good to moderate inhibitory activity against α-glucosidase . Compound 3 that is [(E)-1-(2-(1H-benzo[d]imidazol-2-ylthio)-1-(4-nitrophenyl) ethylidene)-2-(4-(4-fluorophenyl)thiazol-2-yl)hydrazine)] having 4-fluoro group showed best inhibitory activity against α-glucosidase. After testing, a structure activity relationship (SAR) study was also carried out according to this-

I. Compounds having smaller substituent (-F, -Cl) and capability of forming hydrogen bonding, enhanced the inhibitory potential.

II. Compounds having bulky substituent (-Br) and incapability of forming hydrogen bonding, showed lower potency for inhibitory α-glucosidase activity.

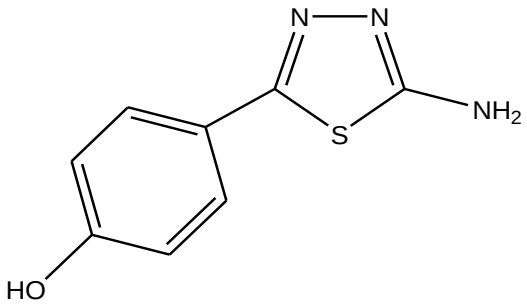
III. Introduction of Electron withdrawing groups (–F and –NO2) enhanced for inhibitory α-glucosidase activity.

IV. Attachment of both Electron withdrawing groups (-NO2) and bulky substitutent (-CH3 and –Br), reduce the α-glucosidase inhibitory activity [41].



(1)

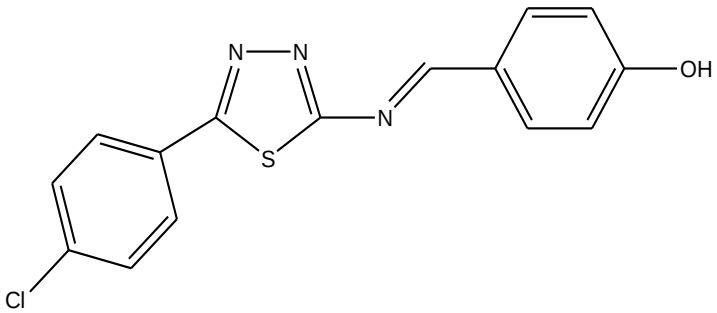
Tariq M et al. (2018) synthesized and evaluated total 22 compounds having 2-amino thiadiazole (1-13) and 2-amino thiadiazole based schiff base (14-22) for α-glucosidase inhibitory activity. All compounds have showed various degree of α-glucosidase inhibitory activity with IC_{50} ranging from 2.30 ±0.1 to 38.30 ±0.7µM in comparison to standard drug Acarbose having IC_{50} value39.60 ±0.70 µM. Compound. After inhibitory activity evaluation, A SAR study was also performed which suggested that the inhibitory activity of synthesized compound depends upon the substituent attached on phenyl ring. Among 2-amino thiadiazole, compound 6 (4-(5-amino-1,3,4-thiadiazol-2-yl)phenol), having 4-hydroxyl group (4-OH group) found to be more potent. Docking analysis of compound 6 (Docking score-5.231) showed that it form mainly 3 hydrogen bonds with binding site residues Glu276 and Asp408 by its hydroxyl and amine group[42].



Compound 6 [4-(5-amino-1,3,4-thiadiazol-2-yl)phenol]

(2)

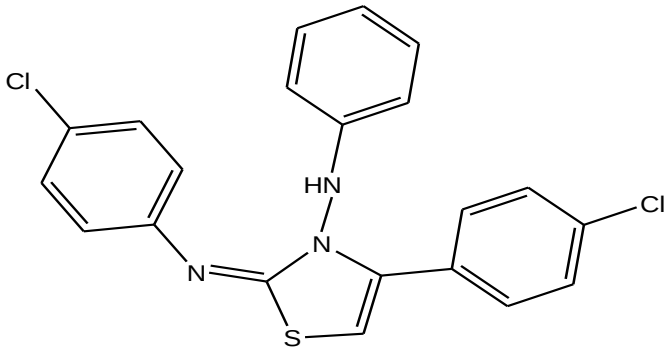
Among 2-amino thiadiazole based shciff base compounds (14-22), compound 14 was found to be most active compound with IC50 value 2.30±0.1 µM. The docking study of compound 14 (Docking Score -5.743) suggest that chlorobenzene moiety and three arene mainly establish hydrogen bonding ith active site of enyme.. Cholorobenene moiety of compound 14 interact with active site Pro309 residue by Hydrogen donar relationship and three arene-hdrogen bond were establish with Phe157, Tyr71 and Arg312.This whole study suggest compound bearing –OH, -NO2 and –Cl group showed good inhibitory activity in vitro as well as in silico [42].



Compound 14 [4-((*E*)-(5-(4-chlorophenyl)-1,3,4-thiadiazol-2-ylimino)methyl)phenol]

(3)

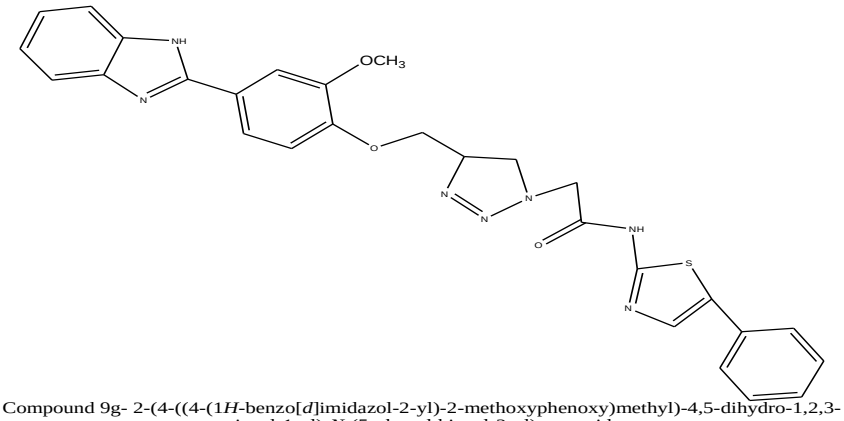
Mohammed K et al. synthesized 24 new thiazole derivatives Via 'One Pot' multicomponent reaction and evaluated for α-glucosidase inhibitory activity.. The structure of all synthesized compounds were confirmed by 1H-NMR, 13C-NMR and EIMS techniques. After In vitro α-glucosidase inhibitory compound 12 [N-((2E)-2-(4-chlorophenylimino)-4-(4-chlorophenyl) thiazol-3(2H)-yl)benzenamine, having para chloro substitution on two places , showed best activity with IC 50 =9.06±0.10 µM as compared with standard drug Acarbose with IC50=38.25±0.12 µM. Other compounds bearing chloro group also showed good α-glucosidase inhibitory activity suggest that chloro group is playing very important role in the inhibitory activity of α-glucosidase. After docking analysis compound 12 also shoed best interaction with enme (Docking score -11.8617). It made two π-interactions with binding pocket of enzyme. Aniline moiety of compound 12, made arene – arene interaction with Phe157 and chlorobenzene made arene arene interaction with Phe300 [43].



Compound 12- *N*-((2*E*)-2-(4-chlorophenylimino)-4-(4-chlorophenyl)thiazol-3(2*H*)-yl)benzenamine

(4)

Nasli A et. Al. (2022) rationally esigned, synthesized and evaluated some phenoxymethylbenzimidaole derivatives [9(a-n)] for α-glucosidase inhibitor activity. The final compound are synthesized by the reaction of benzene-1,2-diamine and –(prop-2-yn-1-yloxy)benzaldehyde in presence of $Na_2S_2O_3$ at 100^0C for 4hr. The obtained product was recrystallied with ethanol. The synthesized compounds were evaluated for in vitro α-Glucosidase inhibitory activity. Compound 9g Compound 9g- 2-(4-(4-(1H-benzo[d]imidazol-2-yl)-2-methoxyphenoxy)methyl)-4,5-dihydro-1,2,3-triazol-1-yl)-N-(5-phenylthiazol-2-yl)acetamide (IC50=6.31±0.03) as found to be most active compound in comparison to standard drug Acarbose with IC50= 750.0±10.0). Docking study as also performed on most active compounds b using Gold docking program suggest that compound 9g score Gold Score 70.16. Various type of interaction were found between 9g and receptor. Benzimidaole of 9g interact with receptor part by hydrogen bond, pi-Pi stacking with Asp616 and Phe649 respectively. Methoxyphenoxymethyl of compound 9g interact with hydrogen bond by Ap616 and Adp282 [44].

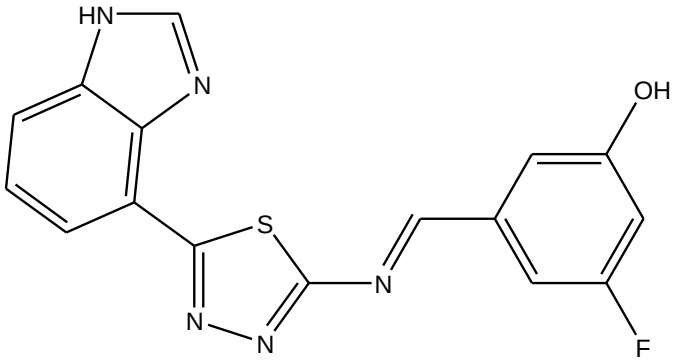


Compound 9g- 2-(4-((4-(1*H*-benzo[*d*]imidazol-2-yl)-2-methoxyphenoxy)methyl)-4,5-dihydro-1,2,3-triazol-1-yl)-*N*-(5-phenylthiazol-2-yl)acetamide

(5)

Shoaib et. al. (2023) synthesized 17 compounds, based on benzimidaole-thiadiazole hybrid and evaluated them against the inhibitory activity of α-glucosidase. All the compound showed moderate to good activity with the comparison of standard drug 'Acarbose'. Compound 2 [3-((E)-(5-(1H-benzo[d]imidazol-4-yl)-1,3,4-thiadiazol-2-ylimino)methyl)-5-fluorophenol], having –OH group and –F group, showing best inhibitory activity with IC_{50} value 2.10±0.10 in comparison to standard

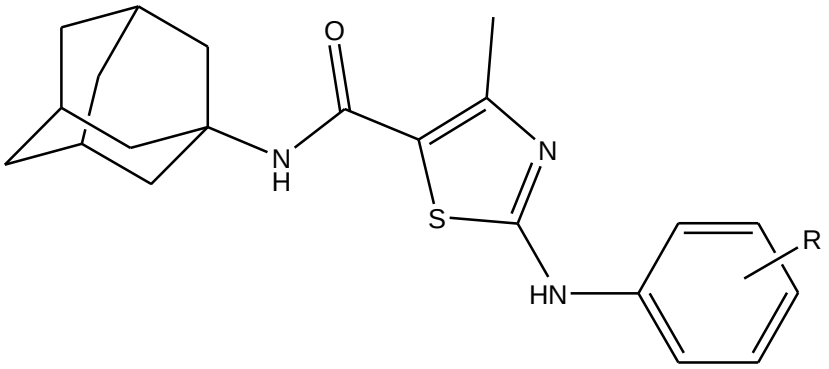
drug acarbose with IC_{50} value 5.30 ± 0.12.Structure activity relationship suggested that the compound bearing hydroxyl group make hydrogen bonding with active site and showed much better binding with active site. Replacing of other substituent like chlorine with fluorine showed better interaction and binding with receptor site due to smaller size and strong hydrogen bonding [45].



Compound 2- 3-((*E*)-(5-(1*H*-benzo[*d*]imidazol-4-yl)-1,3,4-thiadiazol-2-ylimino)methyl)-5-fluorophenol

(6)

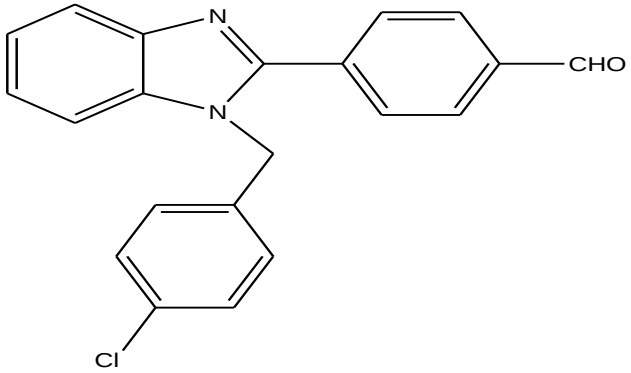
Zahra FT et al. (2023) synthesized a series of 10 compound (6a-j) having N-aryl amino thiazole derivatives clubbed with new amantadine. All the copund were evaluated against in vitro α- Glucosidase inhibition asaay. The activity of all compounds were reported in terms of IC_{50} value. Compound 6c showed best inhibitory activity against α- Glucosidase with IC_{50} value 38.73±0.80 as compared to standard drug Acarbose with IC50 value 1.21±0.16. Docking study as also performed for active compound. Compoud 6a, 6b and 6e showed the best interaction, in the term of lowest energy -3.6, -0.7 and -1.5 kcal mol^{-1}. These compounds showed dual interaction with the receptor by the interaction with the amino acid (receptor) ARG-609, ARG-587 and THR-384. A SAR study was also generated as per the result of α- Glucosidase inhibition activity. As per the SAR study, the bromo group at para postion showed best activity against α- Glucosidase inhibition in coparison to other halogen group (chloro) at meta position1 [46].



R=4-NO_2 (6b)
R=4-Br (6c)
R= 4-OMe (6d)
R=2-OMe (6e)
R=3-Cl (6f)
R=2-Cl (6g)
R= 3-F (6i)

(7)

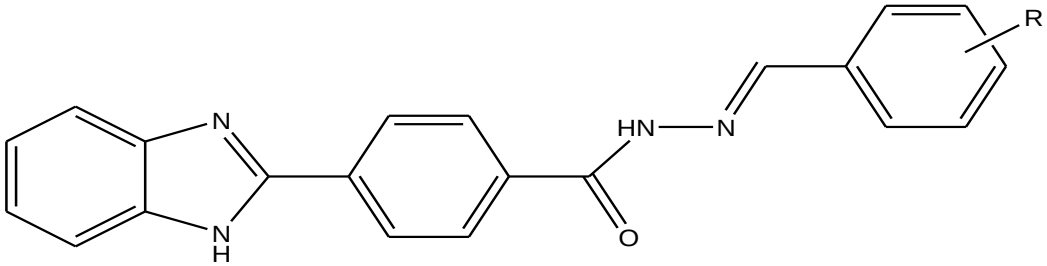
Mall, R. et al. (2017) synthesized and evaluated a series based on N-substituted-benzimidazolyl linked para substituted benzylidene and evaluated the synthesized compound for in vitro alpha glucosidase activity. LC-MS, 1H-NMR, 13CNMR and FT-IR are the techniques which are used for the confirmation of structure of synthesized compounds. Compound 4-(1-(4-chlorobenzyl)-1H-benzo[d]imidazol-2-yl) benzaldehyde showed the best in vitro inhibitory activity against α-amylase and α-glucosidase with an IC50 value of 0.54 ± 0.01 µM. Docking study was also performed in which the protein, PDB code: 3TOP was used as a receptor site for the interaction of different synthesized compound with standard drug Acarbose. The result of docking study was represented in terms of binding affinities (G score values and hydrogen bond interactions). Compound 4-(1-(4-chlorobenzyl)-1H-benzo[d]imidazol-2-yl) benzaldehyde gave the best docking result among the all synthesized compound [47].



4-(1-(4-chlorobenzyl)-1*H*-benzo[*d*]imidazol-2-yl)benzaldehyde

(8)

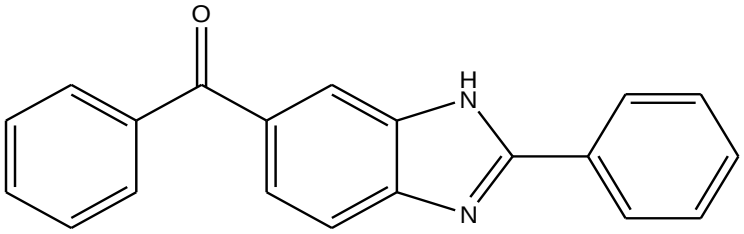
Mishra S. et al. (2020) design, synthesize and evaluated eleven compounds benzimidazoles derivatives for alpha-glucosidase activity. Initially, 60 compounds were designed using computation techniques including 3D QSAR, HQSAR, and Pharmacophore mapping. Docking studies were also performed for evaluation of best interaction on the above designed compounds. Amino acids LEU 520, ARG 335 and ASP 69 were found to be the main amino acid which are involved in the interaction with the designed compound. On the basis of docking study, Eleven compounds were selected for the synthesis and also evaluated for alpha- glucosidase activity. In vitro alpha- glucosidase activity showed that hydroxyl and alkyl groups (compound no. 3, 9 and 10) were found to be best active compounds and found five to eight folds more active with IC90 values (in the range of 6.02 ± 1.10 to 33.25 ± 1.20 µg/ml), in comparison with the standard drug, Acarbose (IC90= 290.55 ± 0.081 µg/ml) [48].



Derivatives of (*E*)-4-(1*H*-benzo[*d*]imidazol-2-yl)-*N*'-benzylidenebenzohydrazide

(9)

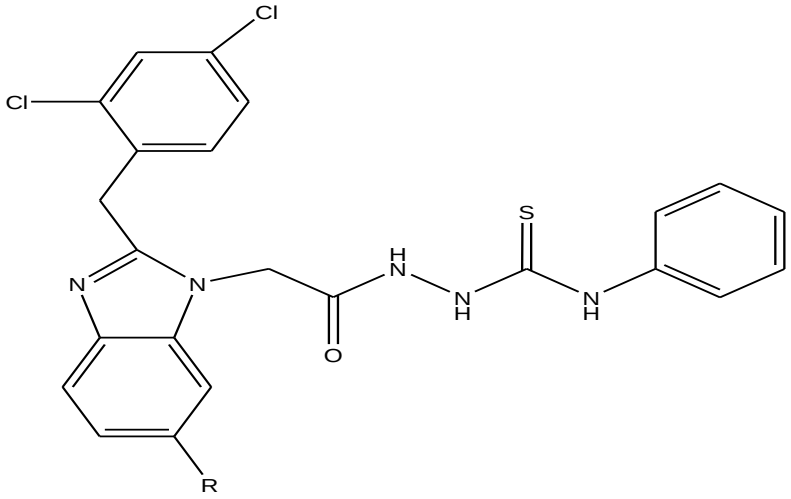
Aroura L.M. et al. (2021) synthesized and evaluated a series of derivatives of phenyl(2-phenyl-1*H*-benzo[*d*]imidazol-6-yl)methanone (3a-h) as antidiabetic agents. The above derivatives were synthesized by the reaction of 3,4-diaminobenzophenone with arylaldehyde in the presence of ammonium chloride or a mixture of ammonium chloride and sodium metabisulfite as catalyst. Antidiabetic activity of the synthesized compounds was performed by using *in vitro* antidiabetic assay of α-amylase and α-glucosidase. Compound **3f (**2-(4-hydroxyphenyl)-1*H*-benzo[*d*]imidazol-6-yl)(phenyl) containing hydroxyl motif at *para*-position of phenyl was found to be more active inhibitor against α- amylase (IC50 = 12.09 ± 0.38 µM) and α-glucosidase (IC50 = 11.02 ± 0.04 µM) comparable to the reference drug acarbose. Docking study was also performed on the above compounds with human pancreatic α-amylase (HPA) and human lysosomal acid-α-glucosidase (HLAG) active sites for confirmation of result [49].



Derivatives of phenyl(2-phenyl-1*H*-benzo[*d*]imidazol-6-yl)methanone

(10)

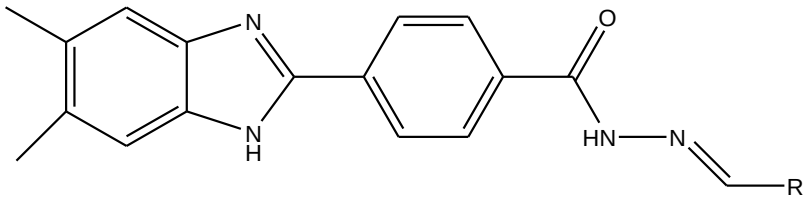
Ozil et al (2016) synthesized a series of benzimidazole derivatives by the reaction of o-phenylenediamine and 4-nitro-o-phenylenediamine with iminoester hydrochlorides. Acidic proton in benzimidazole was exchanged with ethyl bromoacetate, then ethyl ester group was transformed into hydrazide group. Cyclization using CS2/KOH leaded to the corresponding 1,3,4-oxadiazole derivative, which was treated with phenyl isothiocyanate resulted in carbothioamide group, respectively. As the target compounds, triazole derivative was obtained under basic condition and thiadiazole derivative was obtained under acidic condition from cyclization of carbothioamide group. Most reactions were conducted using both the microwave and conventional methods to compare yields and reaction times. All compounds obtained in this study were investigated for a-glucosidase inhibitor activity. Compounds 6a, 8a, 4b, 5b, 6b and 7b were potent inhibitors with IC50 values ranging from 10.49 to 158.2 lM. This has described a new class of a-glucosidase inhibitors. Molecular docking studies were done for all compounds to identify important binding modes responsible for inhibition activity of a-glucosidase [50].



Derivatives of 1-(2-(2-(2,4-dichlorobenzyl)-1*H*-benzo[*d*]imidazol-1-yl)acetyl)-4-phenylthiosemicarbazide

(11)

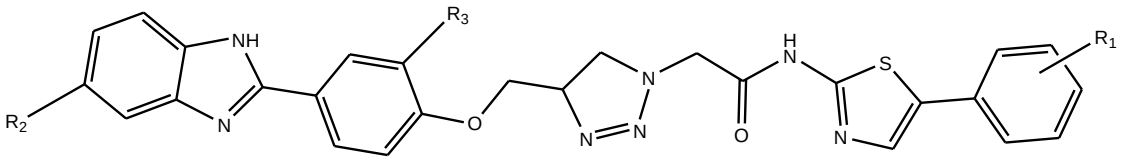
Zawawi et al. (2016) synthesized 26 derivatives of 4-(5,6-dimethyl-1H-benzo[d]imidazol-2-yl)benzohydrazide Schiff bases (**1-26**) and evaluated them for α glucosidase inhibitory activity with IC50 values between 8.40 ± 0.76 - 179.71 ± 1.11 µM when compared with standard acarbose. In this assay, seven compounds that showed highest inhibitory effects than the rest of benzimidazole series were identified. All the synthesized compounds were characterized by different spectroscopic methods adequately[51].



Derivatives of (*E*)-*N*'-ethylidene-4-(5,6-dimethyl-1*H*-benzo[*d*]imidazol-2-yl)benzohydrazide

(12)

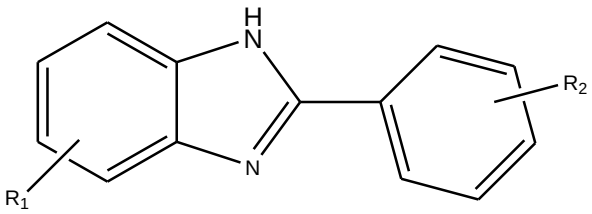
Esfahani et al. (2022) rationally designed, synthesized some phenoxymethy benzoimidazole derivatives (9a-n) and evaluated them for α-glycosidase inhibitory activity. All tested compounds displayed promising α-glycosidase inhibitory potential with IC50 values in the range of 6.31 to 49.89 µM compared to standard drug acarbose (IC50=750.0} 10.0 µM). Compound 9c (2-{4-[4-(1H-1,3-benzodiazol-2-yl) phenoxy- methyl]-1H-1,2,3–triazol-1-yl}-N-[2-(4-bromophenyl)-1,3-thiazol-5-yl]ac-tamide), 9g (2-{4-[4-(1H-1,3-benzodiazol-2-yl)-2-methoxyphenoxymethyl]-1H-1,2,3-triazol-1-yl}-N-(2-phenyl-1,3-thiazol-5-yl)acetamide), and 9m (2-{4-[4-(6-Methyl-1H-1,3-benzodiazol-2-yl) phenoxymethyl]-1H-1,2,3-triazol-1-yl}-N-[2-(4-methylphenyl)-1,3-thiazol-5-yl]acetamide) were found as the most potent compounds by enzyme kinetics study. Docking studies also performed for confirmation of the result and also suggest the important role of benzoimidazole and triazole rings of the synthesized compounds to fit properly into the α-glycosidase active site [52].



Derivatives of 2-(4-((4-(1*H*-benzo[*d*]imidazol-2-yl)phenoxy)methyl)-4,5-dihydro-1,2,3-triazol-1-yl)-*N*-(5-phenylthiazol-2-yl)acetamide

(13)

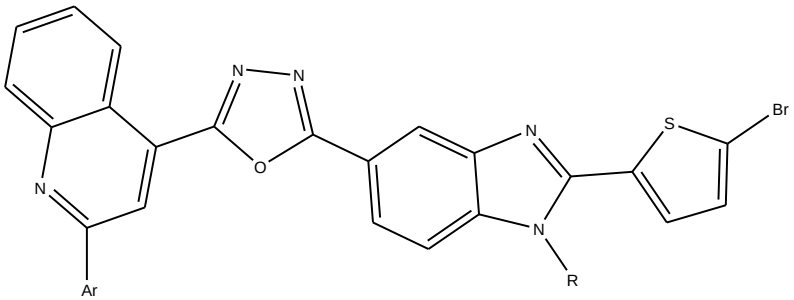
Dinparast et al. (2016) synthesized some benzimidazole derivatives by green, one-pot, solvent-free synthesisand evaluated them for their α-glucosidase inhibitory potential. The reactions were catalyzed by ZnO/MgO containing ZnO nanoparticles as a highly effective, non-toxic and environmentally friendly catalyst. Characterized of synthesized compound ere done by using spectroscopic technics (FT-IR, 1HNMR, 13CNMR). Compounds 3c (2-(4-methoxyphenyl)-1H-benzo [d] imidazole), 3e (2-(4-methoxyphenyl)-5-methyl-1H-benzo[d]imidazole), 3l (5-chloro-2-(4-methoxyphenyl)-1H-benzo[d]imidazole) and 4n (1-(4-isocyanobenzyl)-5-chloro-2-(4-chlorophenyl)-1H-benzo[d]imidazole) were potent inhibitors with IC50 values ranging from 60.7 to 168.4 mM. In silico studies were performed . Developed linear QSAR model based on density and molecular weight could predict bioactivity of newly synthesized compounds well. Molecular docking studies revealed the availability of some hydrophobic interactions[53].



3a-3n

(14)

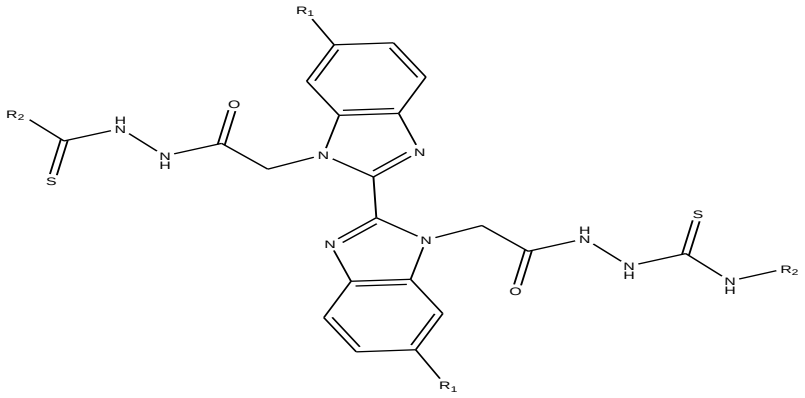
Bharadwaj et al. (2018) synthesized, characterized (FT-IR, 1H NMR, mass spectroscopy and single crystal X-ray diffraction methods) some novel benzimidazole-containing quinolinyl oxadiazoles derivatives and evaluated them for antidiabetic, anticoagulant, and antiplatelet activity. These compounds were also evaluated for in vitro α-glucosidase inhibitory assay and showed the activity in the range of IC50 = 0.66 ± 0.05 to 3.79 ± 0.46 μg/mL. Molecular docking studies, performed on these compounds, revealed that benzimidazole-containing quinolinyl oxadiazoles can correctly dock into the target receptor protein of the human intestinal α-glucosidase, while their bioavailability/drug-likeness was predicted to be acceptable but requires further optimization. These findings suggest that benzimidazole containing quinolinyl oxadiazoles acted as α-glucosidase inhibitors to develop novel therapeutics for treating type-II diabetes mellitus and also can act as lead molecules in drug discovery as potential antidiabetic and antithrombotic agents [54].



Derivatives of 4-(5-(2-(5-bromothiophen-2-yl)-1-methyl-1*H*-benzo[*d*]imidazol-5-yl)-1,3,4-oxadiazol-2-yl)quinoline

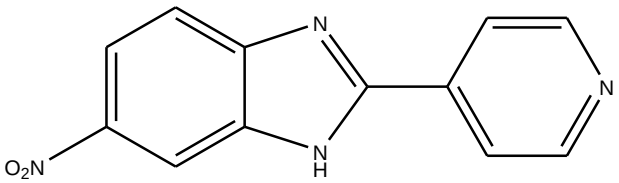
(15)

Ozil et al. (2016) synthesized and evaluated a series of bisbenzimidazole derivatives starting from o-phenylenediamine and 4-nitro-o-phenylenediamine with oxalic acid for inhibitory activities against α-glucosidase. The results showed different range of α -glucosidase inhibitory potential with IC50 value ranging between 0.44 ± 0.04 and 6.69 ± 0.01 lM when compared to the standard acarbose (IC50, 13.34 ± 1.26 lM). Molecular docking studies were done for all compounds to identify important binding modes responsible for inhibition activity of α –glucosidase [55].



(16)

Kumar et al.(2010) synthesized and evaluated some benzimidazole derivatives from the reaction of *o*-phenylenediamine and aromatic and heteroaromatic carboxaldehydes in very good yields, using $PdCl_2(CH_3CN)_2$ as the catalyst and evaluated for their activity on yeast and rat intestinal α-glucosidase inhibition and cytotoxic activity against colon carcinoma cell line HT29. Compound **3e (**6-Nitro-2-(4-pyridyl)-1H-benzo[*d*]imidazole) exhibited 95.6% and 75.3% inhibition of yeast and rat intestinal α-glucosidase enzyme, while showing 74.8% cytotoxic activity against the HT-29 cell line at primary screening concentrations of 2.1 mM for yeast and rat intestinal α-glucosidase enzyme and 0.2 mM for cytotoxic activity against the HT-29 cell line, respectively. Compound **3c (**4-(6-methy l-1*H*-benzo[*d*] imidazo l-2-yl)-1,3-Benzenediol) displayed 76% and 34.4% inhibition of yeast and rat intestinal α-glucosidase enzyme, and 80.4% cytotoxic activity against the HT-29 cell line at similar primary screening concentrations. The IC50 value for the most potent intestinal α-glucosidase inhibitor compound **3e (**6-Nitro-2-(4-pyridyl)-1H-benzo[*d*]imidazole) was found to be 99.4 µM. The IC50 values for the most active cytotoxic compounds **3c(**4-(6-methy l-1*H*-benzo[*d*] imidazo l-2-yl)-1,3-Benzenediol) and **3e (**6-Nitro-2-(4-pyridyl)-1H-benzo[*d*]imidazole) were 82 µM and 98.8 µM, respectively. Both compounds displayed significant antihyperglycemic activity in starch-induced postprandial hyperglycemia in rats. This is the first report assigning yeast and rat intestinal α-glucosidase enzyme inhibition, cytotoxic activity against the HT-29 cell line, and antihyperglycemic activity to benzimidazole compounds **3c** and **3e [56].**



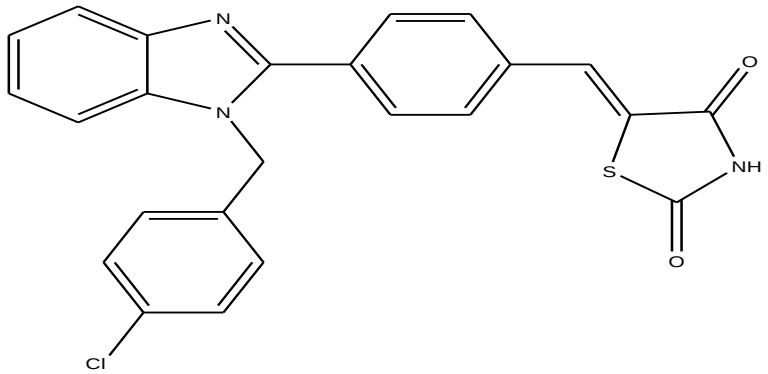
6-nitro-2-(pyridin-4-yl)-1*H*-benzo[*d*]imidazole

(17)

Yan et al.(2019)[35] synthesized and evaluated a series of tricyclic benzimidazole-iminosugars 1(a–f) (derivatives of 1*S*,2*R*,3*S*,4*S*)-1-(hydroxymethyl)-1,2,3,4-tetrahydrobenzo [4,5] imidazo [1,2-*a*]pyridine-2,3,4-triol) and 2(a–f) (derivatives of 1*S*,2*R*,3*S*,4*S*)-1-(hydroxymethyl)-7,8-dimethyl-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-*a*]pyridine-2,3,4-triol) for against five glycosidases. The synthesis initiated from the benzyl protected sugar (aldehyde), reacted with 1,2 diaminobenzene to afford aldo-benzimidazole by the iodine-induced oxidative condensation. Then, tricyclic compound was snthesized by the key Mitsunobu reaction. After removal of the benzyl group in CF_3SO_3H, the target tricyclic benzimidazole-iminosugars 1 and 2 were synheszied. The results of the glycosidase inhibitory activities of 1 and 2 showed that three compounds derived from D-ribose exhibited specific and good inhibitory effects on β glucosidase. Among them, 1e was the best one with IC50 value of 5.37 µM. All hydroxyl groups on β-position would be favourable to the inhibitory activity of such tricyclic benzimidazole-iminosugars against β-glucosidase [57].

Singh et al.(2018) synthesized and evaluated a novel series of *N*-substituted-benzimidazolyl linked *para* substituted

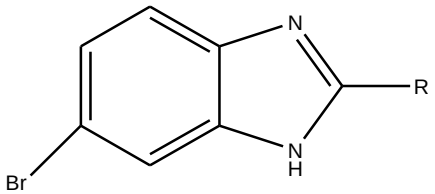
benzylidene based molecules containing three pharmacologically potent hydrogen bonding parts namely; 2,4-thiazolidinedione (TZD: a 2,4-dicarbonyl), diethyl malonate (DEM: a 1,3-diester and an isooxazolidinedione analog) and methyl acetoacetate (MAA: a *β*-ketoester) (**6a–11b**) for *in vitro* *α*-glucosidase inhibition. Characterization of synthesied compound were performed (LC–MS, ^{1}H NMR, ^{13}C NMR, FT-IR). In vitro evaluation of these compounds revealed that the compound **9b** **(**5-{4-[1-(4-chlorobenzyl)-1*H*-benzimidazol-2-*yl*]benzylidene}-1,3-thiazolidine-2,4-dione) showed maximum inhibitory potential against α-amylase and α-glucosidase, giving an IC_{50} value of 0.54 ± 0.01 µM. Docking study as also performed which showed the binding affinities in terms of G score values and hydrogen bond interactions between all the synthesized compounds and the AA residues in the active site of the protein (PDB code: 3TOP) to that of Acarbose (standard drug) were explored with the help of molecular docking studies. Compound **9b (**5-{4-[1-(4-chlorobenzyl)-1*H*-benzimidazol-2-*yl*]benzylidene}-1,3-thiazolidine-2,4-dione) was selected as promising candidate of this series [58].



Compound 9b- (*Z*)-5-((4-(1-(4-chlorobenzyl)-1*H*-benzo[*d*]imidazol-2-yl)phenyl)methylene)thiazolidine-2,4-dione

(18)

Arshad et al.(2016) synthesized and evaluated 5-bromo-2-aryl benzimidazole derivatives **1**–**25** for their in vitro *α*-glucosidase inhibitory activities.. Characterization of synthesized compounds were performed by EIMS, HRMS, ^{1}H-NMR, and ^{13}C-NMR. Molecular docking study was also performed on the selected compounds **1**, **4**, **7**, and **17** having varying substitution pattern. Twenty-three compounds out of twenty-five showed excellent to moderate activity in the range of IC_{50} = 12.4–103.2 µM. Inhibitory results were compared with the standard drug acarbose (IC_{50} =38.25± 0.12 µM). Compounds **1 (**2-(5-Bromo-1H-benzo[d]imidazol-2-yl)-5-methoxyphenol, IC_{50} = 37.82 ± 0.08 µM) , **9 (**2-(5-Bromo-1H-benzo[d]imidazol-2-yl)phenol, IC_{50}= 37.76± 0.05µM), **12 (**5-Bromo-2-(4-butoxyphenyl)-1H-benzo [*d*] imidazole**,** IC_{50} = 24.96 ± 0.09 µM), **16 (**5-Bromo-2-(3-bromophenyl)-1*H*-benzo[*d*]imidazole**,** IC_{50} = 21.15 ± 0.08 µM) and **17 (**4-(5-Bromo-1H-benzo[d]imidazol-2-yl)phenol, IC_{50} = 8.34 ± 0.02 µM) showed excellent inhibition as compared to standard drug acarbose (IC_{50} = 38.25 ± 0.12 µM). Especially, compound **17** **(**4-(5-Bromo-1*H*-benzo[*d*]imidazol-2-yl)phenol, IC_{50} = 8.34 ± 0.02 µM) was found to be five-fold more active than the standard [59].

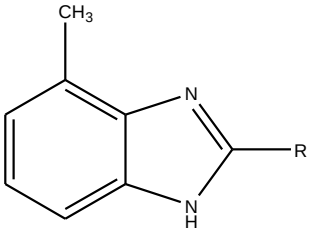


Substituted 6-bromo-1*H*-benzo[*d*]imidazole Derivatives

(19)

Taha et al. (2016) synthesized and evaluated some substituted 7-methyl-1*H*-benzo[*d*]imidazole analogs (1-27) for their α-glucosidase inhibitory activity. After synthesis these compounds were characterized by EI-MS and ^{1}H NMR. Compound 25 (2-(2′ -Chlorophenyl)-7-methyl-1*H*-benzo[*d*]imidazole), 19 (2-(2′-Hydroxyphenyl)-7-methyl-1H-benzo [*d*] imidazole), 10 (2-(3′,4′-dihydroxyphenyl)-7-methyl-1H-benzo[d]imidazole) and 20 (2-(2′-Hydroxy-4′-methoxy phenyl)-7-methyl-1H-benzo[d]imidazole) had best inhibitory activities with IC50 values 5.30 ± 0.10, 16.10 ± 0.10, 25.36 ± 0.14 and 29.75 ± 0.19 respectively against α-glucosidase. Compound 6 (2-(4′-Nitrophenyl)-7-methyl-1H-benzo[d]imidazole) and 12 (7-methyl-2-(pyridin-3′-yl)-1H-benzo[*d*]imidazole) have no inhibitory activity against α-glucosidase enzyme among the series. Further studies showed that the compounds are not showing any cytotoxicity effect. The docking studies of the compounds as well as the experimental activities of the compounds correlated well. From the molecular docking studies, it was observed that

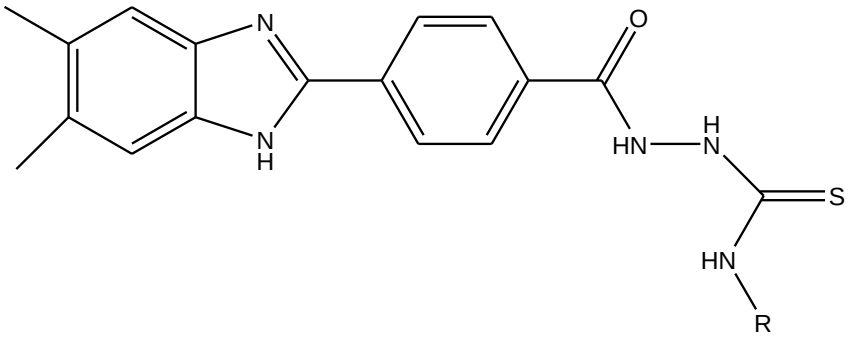
the top ranked conformation of all the compounds fit well in the active site of the homology model of α-glucosidase [60].



Substituted 4-methyl-1*H*-benzo[*d*]imidazole Derivative

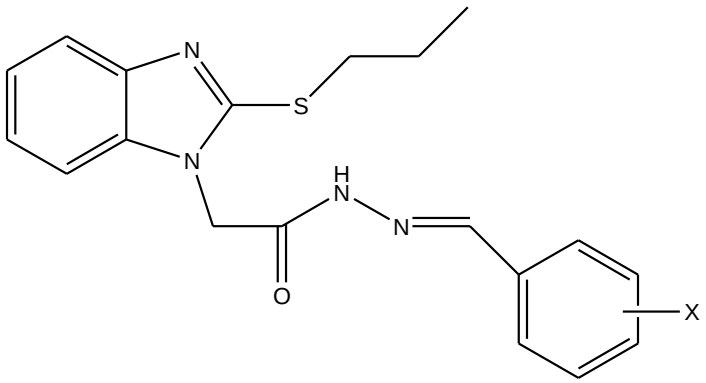
(20)

Zawawi et al.(2017) synthesized and evaluated thiourea derivatives bearing benzimidazole nucleus (1-17) α-glucosidase inhibition. Characterized of the synthesized compounds were done by ^{1}H NMR, ^{13}C NMR and EI-MS. In vitro screening of 17 thiourea bearing benzimidazole derivatives were done by using Baker's yeast α-glucosidase enzyme. Compounds 1-17 exhibited good to moderate α-glucosidase inhibitory activity with IC50 values between 35.83±0.66 - 297.99±1.20 µM which are more better than the standard acarbose (IC50 = 774.5±1.94 µM). Compound 10 (*N*-(4-bromophenyl)-2-(4-(5,6-dimethyl-1H-benzo[d]imidazol-2-yl)benzoyl) hydrazine carbo thioamide) and 14 (2-(4-(5,6-dimethyl-1H-benzo[d]imidazol-2-yl)benzoyl)-N-(4-nitrophenyl) hydrazinecarbothioamide) showed significant inhibitory effects with IC50 value 50.57±0.81 and 35.83±0.66 µM, respectively better than the rest of the series. Structure activity relationships were established. Molecular docking studies were performed to understand the binding interaction of the compounds [61].



(21)

Ali et al.(2018)[40] synthesized a new series of N-acylhydrazone derivatives (4-17). FT-IR, Mass and 1HNMR techniques were used as the spectral techniques. After synthesis, the synthesized compounds were also evaluated for in vitro free radical scavenging and α-glucosidase inhibition activity and ascorbic acid and acarbose were used as a standard drug, respectively. Compound 13 (N-(4-formylbenzylidene)-2-(2-(tetradecylthio)-1H-benzo[d] imidazol-1-yl)acetohydrazide) wre found to be most active compound with IC50=131.50 µM (DPPH scavenging assay) and IC_{50}=352 µg/ml (α-glucosidase inhibition). Docking analysis was also performed by using Molecular Operating Environment (MOE 2016.08) on the above compounds. A homology model for α-glucosidase was constructed and validated using Ramachandran plot [62].



(22)

2. CONCLUSION

Diabetes mellitus is a complex metabolic disorder affecting a very large population of worldwide. Unbalanced diet, obesity make diabetic to a large population of world. It is assuming that till 2040, one person out of 10 people will be affected from diabetes. For avoiding such condition it is essential to search some effective antidiabetic agents. Recently it proves that α-glucosidase inhibitors, play an important role in the management of diabetes. In some couple of past decades, various synthetic and pharmacological studies in the field of α- glucosidase inhibitors have tried to unwind the increasing complexities of diabetes. Better understand of etiology and pathogenesis of this dangerous disease, help in the discovery of new therapeutic agents. Understanding the seriousness and complexity of this disease, a very large number of therapeutic agents, based on α- glucosidase inhibiton approach were developed in some couple of past decades. Data between the year of 2000 to 2023 suggested that newly discovered compounds have shown better therapeutic efficacy towards the α-glucosidase inhibiton.

As the various previous researches suggest that the various disaccharide bind to the α- glucosidase for conversion of simpler monosaccharide and the various compound which mimic the structure of these disaccharide, show better α- glucosidase inhibition activity. Aside from this consideration it was also proved that the compounds bearing azole moiety, also show better therapeutic efficacy against α- glucosidase inhibition.

In this paper, some recent researches, including computational design, synthesis, in vitro, in vivo biological activity of such compounds which have azole moiety in their structure and showing better therapeutic efficacy, regarding the α- glucosidase inhibiton, have been reported which will help the researchers to discover better therapeutic agents in the future.

ABBREVIATIONS

OGTT: Oral glucose tolerance test; $HbA_{1C:}$ Hemoglobin A1C (Glycated hemoglobin), SAR: Structure Activity Relationship

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EFERENCES

[1] Hameed I, Masoodi SR, Mir SA, Nabi M, Ghazanfar K, Ganai BA. (2015) Type 2 diabetes mellitus: From a metabolic disorder to an inflammatory condition. World J Diabetes. 2015 May 15;6(4):598-612. doi: 10.4239/wjd.v6.i4.598.

[2] American Diabetes Association. Diagnosis and classification of diabetes mellitus.2009 Diabetes Care. 32 Suppl 1(Suppl 1):S62-7. doi: 10.2337/dc09-S062.

[3] Rahman MS, Hossain KS, Das S, Kundu S, Adegoke EO, Rahman MA, Hannan MA, Uddin MJ, Pang MG. (2021) Role of Insulin in Health and Disease: An Update. Int J Mol Sci. 15;22(12):6403. doi: 10.3390/ijms22126403.

[4] Banday MZ, Sameer AS, Nissar S. (2020) Pathophysiology of diabetes: An overview. Avicenna J Med. Oct 13;10(4):174-188. doi: 10.4103/ajm.ajm_53_20.

[5] Singh N, Kesherwani R, Tiwari AK, Patel DK (2016) A review on diabetes mellitus. J. Pharm. Innov. (7): 36-40.

[6] Marsden J, Pickering D. (2015) Urine testing for diabetic analysis. Community Eye Health. 2015;28(92):77. PMID: 27418731; PMCID: PMC4944103.

[7] Kaur G, Lakshmi PVM, Rastogi A, Bhansali A, Jain S, Teerawattananon Y, Bano H, Prinja S. (2020)Diagnostic accuracy of tests for type 2 diabetes and prediabetes: A systematic review and meta-analysis. PLoS One. 20;15(11):e0242415. doi: 10.1371/journal.pone.0242415.

[8] Hieshima K, Sugiyama S, Yoshida A, Kurinami N, Suzuki T, Ijima H, Miyamoto F, Kajiwara K, Jinnouchi K, Jinnouchi T, Jinnouchi H. (2020) Elevation of the renal threshold for glucose is associated with insulin resistance and higher glycated hemoglobin levels. J Diabetes Investig. 2020 May;11(3):617-625. doi: 10.1111/jdi.13191. Epub 2020 Jan 15.

[9] Mitrakou A, Kelley D, Mokan M, Veneman T, Pangburn T, Reilly J, Gerich J. (1992) Role of reduced suppression of glucose production and diminished early insulin release in impaired glucose tolerance. N Engl J Med. 2;326(1):22-9. doi: 10.1056/NEJM199201023260104.

[10] Pasieka AM, Rafacho A. 2016 Impact of Glucocorticoid Excess on Glucose Tolerance: Clinical and Preclinical Evidence. Metabolites. 3;6(3):24. doi: 10.3390/metabo6030024.

[11] Seager LH. (1965) Renal Glycosuria With a False-Positive Glucose Tolerance Test. ***JAMA.*** 193(5):392–393. doi:10.1001/jama.1965.03090050068024

[12] International Diabetes Federation. IDF Diabetes Atlas. 6th ed. Brussels, Belgium: International Diabetes Federation; 2013. Available from: http://www.idf.org/diabetesatlas.

[13] DiMeglio LA, Evans-Molina C, Oram RA. (2018) Type 1 diabetes. Lancet. 16;391(10138):2449-2462. doi: 10.1016/S0140-6736(18)31320-5.

[14] Olokoba AB, Obateru OA, Olokoba LB. (2012) Type 2 diabetes mellitus: a review of current trends. Oman Med J. 27(4):269-73. doi: 10.5001/omj.2012.68.

[15] Modzelewski R, Stefanowicz-Rutkowska MM, Matuszewski W, Bandurska-Stankiewicz EM. (2022) Gestational Diabetes Mellitus-Recent Literature Review. J Clin Med. 28;11(19):5736. doi: 10.3390/jcm11195736.

[16] Kumar A, Gangwar R, Zargar AA, Kumar R, Sharma A (2024) Prevalence of Diabetes in India: A Review of IDF Diabetes Atlas 10th Edition. Curr Diabetes Rev. 20(1):e130423215752. doi: 10.2174/1573399819666230413094200.

[17] Lebovitz HE. (1997) alpha-Glucosidase inhibitors. Endocrinol Metab Clin North Am. 26(3):539-51. doi: 10.1016/s0889-8529(05)70266-8.

[18] Di Magno L, Di Pastena F, Bordone R, Coni S, Canettieri G. (2022) The Mechanism of Action of Biguanides: New Answers to a Complex Question. Cancers (Basel). 30;14(13):3220. doi: 10.3390/cancers14133220.

[19] Sola D, Rossi L, Schianca GP, Maffioli P, Bigliocca M, Mella R, Corlianò F, Fra GP, Bartoli E, Derosa G. (2015) Sulfonylureas and their use in clinical practice. Arch Med Sci. 12;11(4):840-8. doi: 10.5114/aoms.2015.53304.

[20] Lebovitz HE. Thiazolidinediones: the Forgotten Diabetes Medications. (2019)Curr Diab Rep. 27;19(12):151. doi: 10.1007/s11892-019-1270-y.

[21] Florentin M, Kostapanos MS, Papazafiropoulou AK. (2022) Role of dipeptidyl peptidase 4 inhibitors in the new era of antidiabetic treatment. World J Diabetes. 15;13(2):85-96. doi: 10.4239/wjd.v13.i2.85.

[22] Shah RB, Patel M, Maahs DM, Shah VN (2016) Insulin delivery methods: Past, present and future. Int J Pharm Investig. 6(1):1-9. doi: 10.4103/2230-973X.176456.

[23] The World Health Report. Shaping the future, 2003.

[24] Mishra V, Nayak P, Sharma M, Albutti A, Alwashmi ASS, Aljasir MA, Alsowayeh N, Tambuwala MM (2021) Emerging Treatment Strategies for Diabetes Mellitus and Associated Complications: An Update. Pharmaceutics. 27;13(10):1568. doi: 10.3390/pharmaceutics13101568.

[25] Bowen R 2006 *"Dietary Polysaccharides". Arbl.cvmbs.colostate. edu.* http://www.vivo.colostate.edu/hbooks/pathphys/digestion/basics/polysac.html.

[26] Barmak A. Niknam K. Gholamhossein MG (2019) Synthesis, Structural Studies, and α-Glucosidase Inhibitory, Antidiabetic, and Antioxidant Activities of 2,3-Dihydroquinazolin-4(1H)-ones Derived from Pyrazol-4-carbaldehyde and Anilines" ACS Omega 4:18087-18099.

[27] Assefa ST, Yang EY, Chae SY, Song M, Lee J, Cho MC, Jang S. (2019) Alpha Glucosidase Inhibitory Activities of Plants with Focus on Common Vegetables. Plants (Basel). 18;9(1):2. doi: 10.3390/plants9010002.

[28] Liu Z Shutao M S. (2017) Recent Advances in Synthetic a-Glucosidase Inhibitors" Chem Med Chem, 12, 819-829.

[29] Alqahtani AS, Hidayathulla S, Rehman MT, ElGamal AA, Al-Massarani S, Razmovski-Naumovski V, Alqahtani MS, El Dib RA, AlAjmi MF. Alpha-Amylase and Alpha-Glucosidase Enzyme Inhibition and Antioxidant Potential of 3-Oxolupenal and Katononic Acid Isolated from *Nuxia oppositifolia*. Biomolecules. 2019 Dec 30;10(1):61. doi: 10.3390/biom10010061.

[30] Assefa ST, Yang EY, Chae SY, Song M, Lee J, Cho MC, Jang S. (2019) Alpha Glucosidase Inhibitory Activities of Plants with Focus on Common Vegetables. Plants (Basel). 18;9(1):2. doi: 10.3390/plants9010002.

[31] Kashtoh H, Baek KH. (2022) Recent Updates on Phytoconstituent Alpha-Glucosidase Inhibitors: An Approach towards the Treatment of Type Two Diabetes. Plants (Basel). 14;11(20):2722. doi: 10.3390/plants11202722.

[32] Derosa G Maffioli P. (2012) α-Glucosidase inhibitors and their use in clinical practice" Arch Med Sci 9;8(5); 899-906.

[33] Hossain U, Das AK, Ghosh S, Sil PC. (2020)An overview on the role of bioactive α-glucosidase inhibitors in ameliorating diabetic complications. Food Chem Toxicol. 145:111738. doi: 10.1016/j.fct.2020.111738.

[34] Sharma, R., Prasad Y, Mishra, GP, Chaturvedi, SC. (2013) Some substituted 1,3,4-thiadiazoles: a novel centrally acting agents. Medicinal Chemistry Research, DOI – 00044-013-626-0.

[35] Ghani U. (2015) Re-exploring promising α-glucosidase inhibitors for potential development into oral anti-diabetic drugs: Finding needle in the haystack. Eur J Med Chem. 20;103:133-62. doi: 10.1016/j.ejmech.2015.08.043.

[36] McIver LA, Preuss CV, Tripp J.(2024) Acarbose. 21. In: StatPearls [Internet]. Treasure Island (FL)–. PMID: 29630266.

[37] Dabhi AS, Bhatt NR, Shah MJ. (2013) Voglibose: an alpha glucosidase inhibitor. J Clin Diagn Res. 7(12):3023-7. doi: 10.7860/JCDR/2013/6373.3838.

[38] Sels JP, Huijberts MS, Wolffenbuttel BH. (1999) Miglitol, a new alpha-glucosidase inhibitor. Expert Opin Pharmacother. 1(1):149-56. doi: 10.1517/14656566.1.1.149.

[39] Kuznetsov AE. (2021) Introductory Chapter: Azoles, Their Importance, and Applications. 1-8. doi: 10.5772/intechopen.98426

[40] Mishra, GP, Sharma, R.(2015), Identification of potential PPAR-γ agonists as hypoglycemic agents: molecular docking approach. Interdisciplinary Sciences: Computational Life Sciences , 8(3), 220-8, doi:10.1007/s12539-015-0126-7.

[41] Hussain R, Iqbal S, Shah M, Rehman W, Khan S, Rasheed L, Rahim F, Dera AA, Kehili S, Elkaeed EB (2022) Synthesis of Novel Benzimidazole-Based Thiazole Derivatives as Multipotent Inhibitors of α-Amylase and α-Glucosidase: In Vitro Evaluation along with Molecular Docking Study. *Molecules* 27(19):6457. doi:10.3390/molecules27196457

[42] Javid MT, Rahim F, Taha M, Rehman HU, Nawaz M, Wadood A, Imran S, Uddin I, Mosaddik A, Khan KM (2018) Synthesis, in vitro α-glucosidase inhibitory potential and molecular docking study of thiadiazole analogs. Bioorg Chem. 78:201-209. doi: 10.1016/j.bioorg.2018.03.022.

[43] Khan KM, Qurban S, Salar U, Taha M, Hussain S, Perveen S, Hameed A, Ismail NH, Riaz M, Wadood A. (2016) Synthesis, in vitro α-glucosidase inhibitory activity and molecular docking studies of new thiazole derivatives. Bioorg Chem. 68:245-58. doi: 10.1016/j.bioorg.2016.08.010.

[44] Nasli EA, Iraji A, Alamir A, Moradi S, Asgari MS, Hosseini S, Mojtabavi S, Nasli-Esfahani E, Faramarzi MA, Bandarian F, Larijani B, Hamedifar H, Hajimiri MH, Mahdavi M.(2022)Design and synthesis of phenoxymethybenzoimidazole incorporating different aryl thiazole-triazole acetamide derivatives as α-glycosidase inhibitors. Mol Divers. 26(4):1995-2009. doi: 10.1007/s11030-021-10310-7.

[45] Khan S, Iqbal S, Taha M, Hussain R, Rahim F, Shah M, Awwad NS, Ibrahium HA, Alahmdi MI, Dera AA, Ullah H, Bahadur A, Aljazzar SO, Elkaeed EB, Rauf M. (2023) Synthesis, *in vitro* biological assessment, and molecular docking study of benzimidazole-based thiadiazole derivatives as dual inhibitors of α-amylase and α-glucosidase. Front Chem. 5;11:1125915. doi: 10.3389/fchem.2023.1125915.

[46] Zahra FT, Saeed A, Ahmed A, Ismail H, Ijaz MU, Albericio F (2023) Synthesis of amantadine clubbed *N*-aryl amino thiazoles as potent urease, α-amylase & α-glucosidase inhibitors, kinetic and molecular docking studies. RSC Adv. 22;13(36):24988-25001. doi: 10.1039/d3ra05330j.

[47] Singh G, Singh A, Verma RK, Mall R, Azeem U. Synthesis (2018) biological evaluation and molecular docking studies of novel benzimidazole derivatives. Comput Biol Chem. 72:45-52. doi: 10.1016/j.compbiolchem.2017.12.010.

[48] Mishra S, Dahima R. Sharma R. (2020) Synthesis and Biological Evaluation of Benzimidazoles as target for α-Glucosidase inhibitors J. Drug Deliv. Ther. 10(2-s), pp. 43-49. doi: 10.22270/jddt.v10i2-s.4019

[49] Aroua LM, Almuhaylan HR, Alminderej FM, Messaoudi S, Chigurupati S, Al-Mahmoud S, Mohammed HA. (2021) A facile approach synthesis of benzoylaryl benzimidazole as potential α-amylase and α-glucosidase inhibitor with antioxidant activity. Bioorg Chem. 114:105073. doi: 10.1016/j.bioorg.2021.105073

[50] Özil M, Emirik M, Etlik SY, Ülker S, Kahveci B. (2016) A simple and efficient synthesis of novel inhibitors of alpha-glucosidase based on benzimidazole skeleton and molecular docking studies. Bioorg Chem. 68:226-35. doi: 10.1016/j.bioorg.2016.08.011.

[51] Z Zawawi NK, Taha M, Ahmat N, Wadood A, Ismail NH, Rahim F, Azam SS, Abdullah N. (2016) Benzimidazole derivatives as new α-glucosidase inhibitors and in silico studies. Bioorg Chem. 64:29-36. doi: 10.1016/j.bioorg.2015.11.006.

[52] Nasli Esfahani A, Iraji A, Alamir A, Moradi S, Asgari MS, Hosseini S, Mojtabavi S, Nasli-Esfahani E, Faramarzi MA, Bandarian F, Larijani B, Hamedifar H, Hajimiri MH, Mahdavi M. (2022) Design and synthesis of phenoxymethybenzoimidazole incorporating different aryl thiazole-triazole acetamide derivatives as α-glycosidase inhibitors. Mol Divers. 26(4):1995-2009. doi: 10.1007/s11030-021-10310-7.

[53] Dinparast L, Valizadeh H, Bahadori MB, Soltani S, Asghari B , Rashidi MR. 2016 Design, synthesis , a-glucosidase inhibitory activity, molecular docking and QSAR studies of benzimidazole derivatives" J. Mol. Struct.: 1114:84-94. doi: 10.1016/j.molstruc.2016.02.005

[54] Bharadwaj SS, Poojary B, Nandish SKM, Kengaiah J, Kirana MP, Shankar MK, Das AJ, Kulal A. Sannaningaiah D (2018) Efficient Synthesis and in Silico Studies of the Benzimidazole Hybrid Scaffold with the Quinolinyloxadiazole Skeleton with Potential α- Glucosidase Inhibitory, Anticoagulant, and Antiplatelet Activities for Type-II Diabetes Mellitus Management and Treating Thrombotic Disorders" ACS Omega, 31:2562-12574. doi: 10.1021/acsomega.8b01476

[55] Özil M, Emirik M, Beldüz A, Ülker S. (2016) Molecular docking studies and synthesis of novel bisbenzimidazole derivatives as inhibitors of α-glucosidase. Bioorg Med Chem. 1;24(21):5103-5114. doi: 10.1016/j.bmc.2016.08.024.

[56] Kumar JA, Tiwari AK, Ali AZ, Madhusudhana K, Reddy BS, Ramakrishna S, China Raju B. (2010) New antihyperglycemic, alpha-glucosidase inhibitory, and cytotoxic derivatives of benzimidazoles. J Enzyme Inhib Med Chem. 25(1):80-6. doi: 10.3109/14756360903017122.

[57] Yan L, Lui H, Sun J, Gao L, Lu X, Li X, Chen H. 2019 Synthesis of tricyclic benzimidazole-iminosugars as potential glycosidase inhibitors via a Mitsunobu reaction. Carbohydr Res. 1;485:107807. doi: 10.1016/j.carres.2019.107807.

[58] Singh G, Singh A, Verma RK, Mall R. Azeem U (2018) Synthesis, biological evaluation and molecular docking studies of novel benzimidazole derivatives Comput. Biol. Chem. 72: 45-52. doi: 10.1016/j.compbiolchem.2017.12.010

[59] Arshad T, Khan KM, Rasool N, Salar U, Hussain S, Tahir T, Ashraf M, Wadood A, Riaz M, Perveen S, Taha M, Ismail NH. (2016) Syntheses, in vitro evaluation and molecular docking studies of 5-bromo-2-aryl benzimidazoles as α-glucosidase inhibitors, Med Chem Res. 25 : 2058-2069. doi: 10.1007/s00044-016-1614-y

[60] Taha M, Ismail NH, Imran S, Mohamad MH, Wadood A, Rahim F, Saad SM, Rehman AU, Khan KM.(2016) Synthesis, α-glucosidase inhibitory, cytotoxicity and docking studies of 2-aryl-7-methylbenzimidazoles. Bioorg Chem. 65:100-9. doi: 10.1016/j.bioorg.2016.02.004.

[61] Zawawi NK, Taha M, Ahmat N, Ismail NH, Wadood A, Rahim F. (2017) Synthesis, molecular docking studies of hybrid benzimidazole as α-glucosidase inhibitor. Bioorg Chem. 70:184-191. doi: 10.1016/j.bioorg.2016.12.009.

[62] Ali M, Ali S, Khan M, Rashid U, Ahmad M, Khan A, Al-Harrasi A, Ullah F, Latif A. (2018) Synthesis, biological activities, and molecular docking studies of 2-mercaptobenzimidazole based derivatives. Bioorg Chem. 80:472-479. doi: 10.1016/j.bioorg.2018.06.032.