Design and synthesis of phenoxymethybenzoimidazole incorporating different aryl thiazole-triazole acetamide derivatives as α-glycosidase inhibitors

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Abstract
A novel series of phenoxymethybenzoimidazole derivatives (9a-n) were rationally designed, synthesized, and evaluated for their 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). Enzyme kinetic studies on 9c, 9g, and 9m as the most potent compounds revealed that these compounds were uncompetitive inhibitors into α-glycosidase. Docking studies confirmed the important role of benzoimidazole and triazole rings of the synthesized compounds to fit properly into the α-glycosidase active site. This study showed that this scaffold can be considered as a highly potent α-glycosidase inhibitor.

Keywords α-Glycosidase · Synthesis · Benzimidazole · Triazole-acetamide · Enzyme inhibition

Introduction
Diabetes mellitus (DM) recognizes as one of the most extensive global health emergencies in the twenty-first century affecting more than 400 million people worldwide, and it is estimated that the number will reach around 600 million by 2035 [1].

DM is a chronic metabolic disorder leading to hyperglycemia with the problem in the metabolism of carbohydrates, lipids, and proteins [2]. DM is categorized into two major sub-types type 1 DM and type 2 DM. Type 1 DM is an autoimmune disorder that the immune system mistakenly attacks the β cells of the pancreas which reduces or impairs the production of insulin [3]. Type 2 DM, with more than
90–95% of the cases, characterized by insulin resistance in target tissues, mainly skeletal muscle, adipose tissue, and liver. To fight back against insulin resistance, β-cells overwork to produce more insulin, and gradually the β-cells of the pancreas are destroyed, and insulin secretion is reduced and diminished [4]. DM is associated with a lot of complications including heart disease, stroke, blindness, renal failure, foot amputation, and even death [5]. The main medical approach to control the progress of DM and its complications focuses on the reduction of the postprandial glucose level in blood via regulating and/or inhibiting carbohydrate hydrolytic enzymes [6, 7].

α-Glycosidase (EC.3.2.1.20) is an important membrane-bound intestinal hydrolytic enzyme playing a vital role in the digestion of carbohydrates [8–10]. It hydrolyzes oligosaccharides, trisaccharides, and disaccharides to glucose and other monosaccharides at their non-reducing ends (α-glycosidic bonds) after hydrolysis of polysaccharides to oligosaccharides by α-amylase. As a result, α-glycosidase inhibitors transfer the undigested carbohydrate into the distal part of the small intestine and colon, delay the process of carbohydrate absorption in the gastrointestinal tract, and reduce postprandial hyperglycemia [4, 11, 12].

Acarbose, miglitol, and voglibose used as α-glycosidase inhibitors, mostly obtained from natural sources due to multiple complicated syntheses steps [13]. Also, administration of these inhibitors can bring undesirable side effects including serious gastrointestinal disorders such as diarrhea and flatulence. For this reason, several research groups have investigated the efficiency of small molecules possessing potent α-glycosidase inhibitory potential including imidazole [14], pyrazoles [15], quinazolinone [16], isatin[17], pyrimidine[18], xanthone [19], azole [20], and macrocyclic compounds [21, 22].

Considering the important properties of triazoles such as easy synthetic protocol and promising anti-diabetic properties [23] as well as imidazole and its derivatives as one of the most important nitrogen-containing heterocyclic scaffolds in medicinal chemistry [24, 25], the current study is conducted to evaluate anti-α-glycosidase properties of newly designed phenoxy methyltriazole coupled different thiourea-triazole acetamide (9a-n) derivatives. Kinetic studies of the most potent compounds were also performed to evaluate their inhibition pattern against α-glycosidase.

**Results and discussion**

**Rational study of the present work**

Benzimidazole-based compounds possess a wide range of pharmaceutical and biological activities, especially α-glycosidase inhibition [26]. Zawawi et al. screened a novel series of thiourea derivatives bearing benzimidazole with IC₅₀ values between 35.83 and 297.99 μM which was better than the standard drug acarbose with IC₅₀ = 774.5 μM. According to molecular docking study of the most potent compound (A, Fig. 1), imidazole moiety formed hydrogen bond with Glu 276, and phenyl rings showed arene–arene interaction with residue Phe 157 of the α-glycosidase active site [27]. In 2019, Taha et al. evaluated novel benzimidazole-based oxadiazole derivatives for their in vitro anti-α-glycosidase activity. Among the screened analogs, compound B showed excellent inhibitory potential with an IC₅₀ value of 2.6 ± 0.1 μM compared with acarbose (IC₅₀ = 38.45 ± 0.80 μM). According to the structure–activity relationship (SAR), the substitution of methyl and methoxy moiety on phenyl ring recorded hydrophobic interaction and decreased inhibitory potential significantly [28]. In another study, Rahim et al. introduced benzimidazole bearing bis-Schiff bases as α-glycosidase inhibitors. All derivatives displayed moderate to good inhibitory potential with an IC₅₀ ranging from 2.20 to 88.60 μM compared with standard drug acarbose (IC₅₀ = 38.45 μM). The great potential of analog C (IC₅₀ = 2.20 ± 0.1 μM) mainly seems to be due to methoxy and hydroxyl groups presented on two phenyl rings which might be involved in hydrogen bonding with the active site (Fig. 3) [29].

It was found that the benzimidazole ring as the basic skeleton of compounds was responsible for this promising α-glycosidase inhibition.

Triazole acetamide moiety has been already identified with α-glycosidase inhibitory potential. In this context, Wang et al. reported xanthone-triazole acetamide hybrids D with significant anti-α-glycosidase activities. Analog D showed high activities in promoting glucose uptake and low toxicity to the human normal hepatocyte cell line (Fig. 1) [30]. Another set of benzimidazole-1,2,3-triazole hybrids were screened as α-glycosidase inhibitors. In this respect, compound E depicted an IC₅₀ value of 25.2 ± 0.9 μM in comparison with standard drug acarbose (IC₅₀ = 750.0 ± 12.5 μM) [31]. In 2021, another set of indolinone-substituted phenoxy methyltriazole was synthesized and the most potent derivative in this set (Compound F) showed around a 46-fold improvement in the inhibitory activity against α-glycosidase, compared with acarbose [17].

Another interesting pharmacophore to design potent α-glycosidase inhibitors is aryl thiazole substituent. Compound G (IC₅₀ = 2.2 μM) with p-methoxy pendant displayed strong α-glycosidase inhibitory activity that fulfilled the conformational requirement to fit well in the active site of the enzyme [32]. A set of arylthiazole-pyridine derivatives were also screened as possible α-glycosidase inhibitors (Compound H). All analogs exhibited potent inhibition in the range of 1.40 to 236.10 μM compared to the standard
acarbose (IC₅₀ = 856.45 ± 5.60 μM) owing to interactions with Pro309, Phe157, and Asn347 residues [33].

Keeping the above-mentioned importance of benzimidazole, triazole, and aryl thiazole moieties in the design of new α-glycosidase inhibitors, herein, the hybridization strategy of these pharmacophores was applied to design novel phenoxy methybenzoimidazole bearing different aryl thiazole-triazole acetamide derivatives. Various substituents were performed on benzimidazole, triazole, and aryl thiazole moieties to define beneficial SARs as α-glycosidase inhibitors.

**Chemistry**

The synthesis of compounds 9a-n is schematically presented in scheme 1. The methyl group of commercially available acetophenone derivatives (1) was reacted with n-bromosuccinimide in the presence of p-toluenesulfonic acid to give α-bromoacetophenone derivatives (2). Then compound 2 reacted with thiourea in ethanol to give 4-arylthiazol-2-amines (3). The reaction of intermediate 3 with 2-chloroacetyl chloride gave compound 4. On the other hand, different phenylenediamines 6 reacted with 4-(prop-2-ynyloxy)benzaldehyde derivatives 7 in the presence of Na₂S₂O₅ in DMF at 100 °C to give the corresponding compound 8. The target compounds 9a-n were synthesized via click reaction of compound 5 and freshly prepared azide derivatives in the presence of the catalytic amount of triethylamine (Et₃N) in H₂O and t-BuOH (1:1) at RT [34–36].

**In vitro α-glycosidase enzymatic assay**

The fourteen derivatives prepared herein (9a-n) were subjected to in vitro α-glycosidase inhibition. According to the results reported in Table 1, all compounds showed exceptionally high potency against α-glycosidase with an IC₅₀ value ranging from 6.31 to 49.89 μM which is significantly lower than that of acarbose as the positive control (IC₅₀ = 750.0 ± 10.0 μM). Compound 9g (IC₅₀ = 6.31 μM;...
R₁ = H,  R₂ = H,  R₃ = OCH₃), (IC₅₀ = 8.30 µM;  R₁ = 4CH₃, R₂ = CH₃,  R₃ = H), and (IC₅₀ = 8.88 µM;  R₁ = 4Br,  R₂ = H,  R₃ = H) showed the highest activity among this series of compounds. To better understand the SAR, synthetic compounds were divided into six groups.

Evaluating the effect of R₁ moiety on phenoxymethybenzoimidazole derivatives (R₂ = H and  R₃ = H)

According to the obtained results, it can be seen that 9a as an unsubstituted compound (R₁ = H,  R₂ = H,  R₃ = H) demonstrated an IC₅₀ value of 19.12 µM with around 39 times improvement in potency compared to that of acarbose as a positive control. Substitution of fluorine as a small electron-withdrawing group at R₁ (9b) decreased the inhibitory potency compared to 9a. However, the replacement of fluorine (9c) with bromine (9d) as more lipophile and bulkier halogen group significantly improved the α-glycosidase inhibition with around twofold increase in the inhibitory potency compared to 9a. Considering the substitution of electron-donating moieties, it can be seen that the presence of a moderate electron-donating group at the para position led to the relatively strong inhibitory activity (9d; R₁ = 4CH₃,  R₂ = H,  R₃ = H; IC₅₀ = 9.53 µM). Replacement of the methyl group with a strong electron-donating group (MeO) on the benzoimidazole ring significantly reduced the α-glycosidase inhibition. This trend can be seen in 9e (R₁ = 4OCH₃,  R₂ = H,  R₃ = H; IC₅₀ = 35.11 µM) and 9f (R₁ = 3OCH₃,  R₂ = H,  R₃ = H; IC₅₀ = 15.01 µM).

Evaluating the effect of R₁ moiety on phenoxymethybenzoimidazole derivatives while  R₂ = H and  R₃ = OCH₃

In cases of 9g-j, it can be seen that the 9g (R₁ = H,  R₂ = H,  R₃ = OCH₃) recorded the best inhibitory activity among all derivatives with an IC₅₀ value of 6.31 µM. As can be understood in 9h (R₁ = 4Br,  R₂ = H and  R₃ = OCH₃; IC₅₀ = 26.97 µM), 9i (R₁ = 4CH₃,  R₂ = H and  R₃ = OCH₃; IC₅₀ = 49.89 µM), and 9j (R₁ = 3OCH₃,  R₂ = H and  R₃ = OCH₃; IC₅₀ = 11.25 µM), any substitution in this set dramatically reduced the α-glycosidase inhibitory activity. The least potent derivatives in this set were 9i possessing para-CH₃ at R₁ with IC₅₀ value of 49.89 µM still demonstrating 15-fold increasing in potency comparing with acarbose.
Evaluating the effect of $R^1$ moiety on phenoxymethybenzoimidazole derivatives while $R^2 = CH_3$ and $R^3 = H$

In this set of compounds (9k-n), the most active compound was $9m$ ($R^1 = 4CH_3$, $R^2 = CH_3$ and $R^3 = H$) with an $IC_{50}$ value of 8.30 µM. Disappointingly, replacement of 4CH$_3$ in $9m$ with 4OCH$_3$ ($9n$) moiety significantly lessened the inhibitory activity. Although the substitution of para-bromine as an electron-withdrawing group ($9l$, $IC_{50} = 14.2 ± 0.21$ µM) led to around twofold improvement of α-glycosidase inhibitory activity compared with $9n$, the inhibitory potency did not improve compared with 4CH$_3$ ($9m$) counterpart.

### Table 1 In vitro α-glycosidase inhibitory activity of novel phenoxymethybenzoimidazo coupled different aryl thiazole-triazole acetamide derivatives ($9a$–$n$)

| Compounds | $R^1$ | $R^2$ | $R^3$ | $IC_{50}$ (µM)[a] | Concentrations of Precipitation (µM) |
|-----------|-------|-------|-------|----------------|----------------------------------|
| Acarbose  |       |       |       | 750.0 ± 10.0   | -                                |
| $9a$      | H     | H     | H     | 19.12 ± 0.08  | 750, 300, 150, 100               |
| $9b$      | 4F    | H     | H     | 31.56 ± 0.12  | 750, 300, 150, 100               |
| $9c$      | 4Br   | H     | H     | 8.88 ± 0.07   | 750, 300, 150, 100               |
| $9d$      | 4CH$_3$ | H  | H     | 9.53 ± 0.12   | 750, 300, 150, 100               |
| $9e$      | 4OCH$_3$ | H | H     | 35.11 ± 0.07  | 750, 300, 150, 100               |
| $9f$      | 3OCH$_3$ | H | H     | 15.01 ± 0.18  | 750, 300, 150, 100               |
| $9g$      | H     | H     | OCH$_3$ | 6.31 ± 0.03   | 750, 300, 150, 100               |
| $9h$      | 4Br   | H     | OCH$_3$ | 26.97 ± 0.25  | 750, 300, 150, 100               |
| $9i$      | 4CH$_3$ | H  | OCH$_3$ | 49.89 ± 0.09  | 750, 300, 150, 100               |
| $9j$      | 4OCH$_3$ | H | OCH$_3$ | 11.25 ± 0.15  | 750, 300, 150, 100               |
| $9k$      | H     | CH$_3$ | H     | 12.67 ± 0.05  | 750, 300, 150, 100               |
| $9l$      | 4Br   | CH$_3$ | H     | 14.20 ± 0.21  | 750, 300, 150, 100               |
| $9m$      | 4CH$_3$ | CH$_3$ | H     | 8.30 ± 0.16   | 750, 300, 150, 100               |
| $9n$      | 4OCH$_3$ | CH$_3$ | H     | 24.19 ± 0.1   | 750, 300, 150, 100               |

[a] Data represented in terms of mean ± SD.

Evaluating the inhibitory effect on phenoxymethybenzoimidazole while $R^1 = 4CH_3$ moiety.

On the other hand, the potency of $9d$, $9i$, $9m$ bearing methyl group at $R^1$ indicated the following order of potency so that $9m$ ($IC_{50} = 8.30$ µM, $R^1 = 4CH_3$, $R^2 = CH_3$, $R^3 = H$) > $9d$ ($IC_{50} = 9.53$ µM, $R^1 = 4CH_3$, $R^2 = H$, $R^3 = H$) > $9i$ ($IC_{50} = 49.89 ± 0.09$ µM, $R^1 = 4CH_3$, $R^2 = H$, $R^3 = 2OCH_3$). It seems that substitution of OCH$_3$ at $R^3$ position in compounds bearing 4CH$_3$ at $R^1$ deteriorated the inhibitory potency.

Evaluating the inhibitory effect on phenoxymethybenzoimidazole while $R^1 = 4Br$ moiety

Comparison of the bromine derivatives at $R^1$ ($9c$, $9h$, $9l$) highlighted this trend that the presence of OCH$_3$ pendant with strick hindrance at $R^3$ had a negative effect on α-glycosidase inhibition compared to the unsubstituted one.
Furthermore, the power and the position of substitution significantly affect the potency. This pattern can be seen in compounds \(9c\) (IC\(_{50}\) = 8.88 µM; \(R^1 = 4Br, R^2 = H, R^3 = H\)) > \(9l\) (IC\(_{50}\) = 14.20 µM, \(R^1 = 4Br, R^2 = CH_3, R^3 = H\)) > \(9h\) (IC\(_{50}\) = 26.97 µM; \(R^1 = 4Br, R^2 = H, R^3 = OCH_3\)).

Evaluating the inhibitory effect on phenoxymethybenzimidazole while \(R^1 = methoxy\) moiety

From the screening data of \(9e, 9f, 9j,\) and \(9n\), it was revealed that \(9j\) having \(4OCH_3\) moiety at \(R^1\) (IC\(_{50}\) = 11.25 µM; \(R^1 = 4OCH_3, R^2 = H, R^3 = OCH_3\)) had superior inhibitory activity toward α-glycosidase in this analog followed by \(9f\) (IC\(_{50}\) = 15.01 µM; \(R^1 = 3OCH_3, R^2 = H, R^3 = H\)), \(9n\) (IC\(_{50}\) = 24.19 µM; \(R^1 = 4OCH_3, R^2 = CH_3, R^3 = H\)), \(9e\) (IC\(_{50}\) = 35.11 µM; \(R^1 = 4OCH_3, R^2 = H, R^3 = H\)). It seems that the presence of MeO as a strong and bulk electron-donating group at \(R^1\) and \(R^3\) in this set can improve anti-α-glycosidase activity.

Overall, it can be understood that phenoxymethybenzimidazole bearing thiazole-triazole acetamide as the basic skeleton was responsible for this outstanding α-glycosidase inhibition.

![Fig. 2](image1.png)  
**Fig. 2** Kinetics of α-glycosidase inhibition by \(9c\). \(a\) The Lineweaver–Burk plot in the absence and presence of different concentrations of \(9c\); \(b\) the secondary plot between \(1/V_{max}\) and various concentrations of \(9c\)

![Fig. 3](image2.png)  
**Fig. 3** Kinetics of α-glycosidase inhibition by \(9g\). \(a\) The Lineweaver–Burk plot in the absence and presence of different concentrations of \(9g\); \(b\) the secondary plot between \(1/V_{max}\) and various concentrations of \(9g\)
**Enzyme kinetic studies**

According to Figs. 2, 3, and S1, the Lineweaver–Burk plot showed that the $K_m$ gradually increased and $V_{max}$ remained unchanged with increasing inhibitor concentration indicating an uncompetitive inhibition. The results showed $9c$, $9g$, and $9m$ bind to ES and had no binding with the free active site. Furthermore, the plots of the $1/V_{max}$ versus different concentrations of $9c$, $9g$, and $9m$ gave an estimate of the inhibition constant, $K_i$ of 8.5, 6.3, and 8.3 µM, respectively (Figs. 2b, 3b, and Fig. S1b).

**Docking analyses**

Docking studies were carried out to understand the interaction modes of the most potent derivatives ($9c$, $9g$, and $9m$) in the α-glycosidase active site. First, the validation process was performed and resulted in an RMSD value of 3.41 Å. The top-scoring pose of acarbose as a crystallographic ligand (PDB ID: 5NN8) is shown in Fig. 4. Acarbose demonstrated seven H-bound interactions with Asp282, Arg600, Asp616, and His674, two Van der Waals with Trp376 and Asp404 plus one π-alkyl interaction with Trp376.

The gold score value of $9c$, $9g$, $9m$ plus their interactions with amino acid residues in the α-glycosidase active site is shown in Table 2. As can be seen, the order of in vitro inhibitory potency recorded well correlation with gold score values. This trend can easily be seen in $9g$ as the most potent compound with an IC$_{50}$ value of 6.31 µM, generated the highest gold score value (70.16).

3D interaction patterns of compounds $9c$, $9g$, $9m$ as the best α-glycosidase inhibitors are shown in Figs. 5, 6, 7. Overall it can be seen that benzimidazole and triazole rings can be considered as critical moieties to develop anti-α-glycosidase agents. Meanwhile, phenoxyethyl and thiazoleacetamide linkers can provide optimum length and bulkiness to properly occupy the α-glycosidase active site.

Interestingly, amino-4-(hydroxymethyl)cyclohexene-triol group of acarbose was well aligned on the benzimidazole moiety of $9c$ and $9g$, while methylphenyl group ($R^1$) of $9m$ was aligned on glucopyranose of acarbose. According to docking studies, it was clear that substituted moiety at $R^1$ and $R^2$ effectively determined the conformation and pose of each ligand in the binding site as well as provided additional interactions with the active site. Although these compounds were unable to exhibit the same binding pose, they were properly fitted into the binding site and demonstrated interactions with the critical residues of the α-glycosidase active site.

**Conclusion**

A novel series of phenoxyethylbenzimidazole incorporating different aryl thiazole-triazole acetamide derivatives ($9a-n$) were rationally designed, synthesized, and evaluated for their α-glycosidase inhibitory activity. All tested derivatives demonstrated better α-glucosidase inhibitory potential with an IC$_{50}$ value ranging from 6.31 to 49.89 µM compared to acarbose.

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Fig. 4 The 3D and 2D interaction of the top-scoring pose of acarbose within the α-glycosidase active site
| Compound | Gold score | Category (type) | Ligand involved moiety | Receptor involved part |
|----------|------------|----------------|------------------------|-----------------------|
| 9c       | 66.30      | Hydrogen Bond  | NH of benzimidazole    | Asp616                |
|          |            | Pi-Pi-Stacked  | Benzimidazole          | Phe649                |
|          |            | Pi-Pi-Stacked  | Benzimidazole          | Phe649                |
|          |            | Pi-Anion      | Benzimidazole          | Asp518                |
|          |            | Pi-Anion      | Benzimidazole          | Asp518                |
|          |            | Pi-Cation     | Benzimidazole          | Arg600                |
|          |            | Pi-Alkyl      | Benzimidazole          | Met519                |
|          |            | Pi-Sulfur     | Phenoxymethyl          | Met519                |
|          |            | Pi-Anion      | Phenoxymethyl          | Asp282                |
| Van der Waals |            | Van der Waals | Phenoxymethyl          | Asp282                |
| Hydrogen Bond |            | Triazole      | Ala284                 | Ala284                |
| Pi-Alkyl |            | Triazole      | Ala284                 | Ala284                |
| Van der Waals |            | Triazole      | Leu283                 | Leu283                |
| Pi-Alkyl |            | Triazole      | Leu283                 | Leu283                |
| Pi-Sigma |            | Triazole      | Leu650                 | Leu650                |
| Amide-Pi-Stacked |      | Triazole      | Leu678                 | Leu678                |
| Pi-Alkyl |            | Triazole      | Leu678                 | Leu678                |
| 9g       | 70.16      | Hydrogen Bond  | NH of benzimidazole    | Asp616                |
|          |            | Pi-Pi-Stacked  | Benzimidazole          | Phe649                |
|          |            | Pi-Anion      | Benzimidazole          | Asp518                |
|          |            | Pi-Anion      | Benzimidazole          | Asp518                |
|          |            | Pi-Cation     | Benzimidazole          | Arg600                |
|          |            | Pi-Sulfur     | Methoxyphenoxymethyl   | Arg600                |
|          |            | Pi-Anion      | Methoxyphenoxymethyl   | Asp282                |
| Hydrogen Bond |            | Methoxyphenoxymethyl | Asp616               |
| Hydrogen Bond |            | Methoxyphenoxymethyl | Asp282               |
| Van der Waals |            | Triazole      | Arg281                 | Arg281                |
| Pi-Alkyl |            | Triazole      | Leu283                 | Leu283                |
| Hydrogen Bond |            | Acetamide     | Ala284                 | Ala284                |
| Pi-Sulfur |            | Thiazole      | Trp618                 | Trp618                |
| Pi-Alkyl |            | Thiazole      | Leu283                 | Leu283                |
| Pi-Sigma |            | Thiazole      | Ala284                 | Ala284                |
| Hydrogen Bond |            | Thiazole      | Ala284                 | Ala284                |
to standard drug acarbose (IC$_{50}$ = 750.0 ± 10.0 µM). Among the series, compound 9g (IC$_{50}$ = 6.31 µM; R$^1$ = H, R$^2$ = H, R$^3$ = OCH$_3$), 9m (IC$_{50}$ = 8.30 µM; R$^1$ = 4CH$_3$, R$^2$ = CH$_3$, R$^3$ = H), and 9c (IC$_{50}$ = 8.88 µM; R$^1$ = 4Br, R$^2$ = H, R$^3$ = H) were found to be the most potent α-glycosidase inhibitors. According to SAR analysis, it was found that the phenoxy-methybenzoimidazole bearing thiazole-triazole acetamide as the basic skeleton of compounds was responsible for this promising α-glycosidase inhibition. The obtained SAR profile found that in the case of benzoimidazole core (9a-j), 2OCH$_3$-substituted on phenoxy (R$^3$), while R$^1$ = H contributed to the improved inhibitory activity. Additionally, in the other set bearing methyl-benzoimidazole (9k-n) small and moderate electron-donating group at R$^1$ is more favorable.

### Table 2 (continued)

| Compound | Gold score | Category (type) | Ligand involved moiety | Receptor involved part |
|----------|------------|-----------------|------------------------|------------------------|
| 9m       | 68.53      | Hydrogen Bond   | NH of benzimidazole    | Asn524                 |
|          |            | Hydrogen Bond   | N of benzimidazole     | Arg281                 |
|          |            | Alkyl-Alkyl     | Methyl Benzimidazole   | Ala554                 |
|          |            | Pi-Alkyl        | Benzimidazole          | Ala554                 |
|          |            | Pi-Alkyl        | Benzimidazole          | Arg527                 |
|          |            | Pi-Alkyl        | Benzimidazole          | Ala555                 |
|          |            | Pi-Sigma        | Benzimidazole          | Ala555                 |
|          |            | Pi-Alkyl        | Phenoxymethyl          | Ala555                 |
|          |            | Hydrogen Bond   | Triazole               | Arg600                 |
|          |            | Pi-Alkyl        | Triazole               | Met519                 |
|          |            | Sulfur-Alkyl    | Triazole               | Met519                 |
|          |            | Sulfur-Alkyl    | Triazole               | Met519                 |
|          |            | Pi-Pi T-shaped  | Triazole               | Trp481                 |
|          |            | Pi-Anion        | Triazole               | Asp616                 |
|          |            | Pi-Anion        | Thiazole               | Phe649                 |
|          |            | Pi-Sigma        | Methylphenyl           | Leu650                 |
|          |            | Pi-Alkyl        | Methylphenyl           | Tro618                 |
|          |            | Pi-Alkyl        | Methylphenyl           | Leu678                 |

**Fig. 5.** 3D and 2D interaction patterns of compounds 9c in the active site of α-glycosidase
The in vitro kinetic assay of 9g, 9m, and 9c presented the uncompetitive type of inhibition against α-glycosidase. Docking studies showed the critical role of benzoimidazole and triazole moieties of the synthesized compounds to fit properly into the active site and occupy the binding site of α-glycosidase. Even though the inhibitory activities of compounds 9g, 9m, and 9c were considered quite good, due to the presence of benzoimidazole and phenoxymethyltriazole moieties which effectively participated in interactions with the critical residues of the α-glycosidase active site, the important role of aryl-substituted at R1 should not be neglected. The substituted groups at R1 rather than providing additional hydrophobic interactions, played the dominant role in the conformation of these derivatives in the α-glycosidase active site.

**Experimental section**

**Chemistry**

All reagents of this protocol were purchased from chemical suppliers and used without further purification. The purity of synthesized analogs was checked through TLC (aluminum plates precoated with silica gel, Kieselgel 60, 254, E. Merck, Germany). The melting points of 9a-n were determined on a Kofler hot stage apparatus. Nicolet Magna FTIR 550 spectrophotometer was used to record IR spectra of the synthesized compounds by using KBr disks. 1H-NMR and 13C-NMR were carried out on Avance Bruker 500 MHz.

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**Fig. 6.** 3D and 2D interaction patterns of compounds 9g in the active site of α-glycosidase

**Fig. 7.** 3D and 2D interaction patterns of compounds 9m in the active site of α-glycosidase
2-(4-(Prop-2-yn-1-yloxy)phenyl)-1H-benzo[d]imidazole (8a)

In a round-bottom flask, 10 mmol benzene-1,2-diamine (6a) and 10 mmol 4-(prop-2-yn-1-yloxy)benzaldehyde (7a) were dissolved in DMF in the presence of Na₂S₂O₅. The reaction mixture was then stirred at 100 °C for 4 h and then the crude product was extracted and recrystallized in EtOH. ¹H NMR (400 MHz, DMSO-d₆) δ 9.9 (s, 1H, NH), 8.17 (d, J = 8.9 Hz, 2H), 7.67–7.62 (m, 2H, H₂, H4, 7), 7.28–7.24 (m, 2H, H5, 6), 7.12 (d, J = 8.9 Hz, 2H, H3,5 Ph), 4.92 (s, 2H, CH₂). 

C₂₇H₂₁N₇O₂S: C, 63.89; H, 4.17; N, 19.32; found: C, 63.86; H, 4.20; N, 19.37.

2 - { 4 - [ 4 - ( 1 H - 1 , 3 - b e n z o d i a z o l - 2 - y l ) p h e n o x y m e t h y l ] - 1 H - 1 , 2 , 3 - t r i a z o l - 1 - y l } - N - [ 2 - ( 4 - b r o m o p h e n y l ) - 1 , 3 - t h i a z o l - 5 - y l ] a c e t a m i d e (9a)

White solid; isolated yield: 89%; mp 170–172 °C; IR (KBr, ν): 3354, 2921, 1673 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆) δ 10.04–10.22 (m, 2H, 2x NH), 8.42 (s, 1H), 8.21 (d, J = 8.3 Hz, 2H), 7.94–7.89 (m, 2H), 7.81 (s, 1H), 7.71–7.68 (m, 2H), 7.65–7.61 (m, H 5, 6), 7.35–7.18 (m, 6H), 5.62 (s, 2H, H-23), 5.36 (s, 2H, H-17); ¹³C NMR (101 MHz, DMSO-d₆) δ 164.99, 162.26, 159.36, 159.24, 158.87, 157.50, 147.78, 143.03, 142.38, 133.25, 131.69, 127.98, 127.66, 126.49, 123.10, 122.99, 120.97, 115.30, 115.10, 115.06, 109.37, 61.10 (C-17), 51.48 (C-23); Anal Calcd for C₂₇H₂₁BrN₂O₂S: C, 63.89; H, 4.17; N, 19.32; found: C, 63.86; H, 4.20; N, 19.37.

Fig. 8 Representation of the docking poses of compounds over the active site. Acarbose was presented in yellow in stick mode, while 9c, 9g, and 9m are shown in purple, cyan, and red color in line mode.

2-[(4-[1H-1,3-benzodiazo-2-yl]phenoxymethyl)-1H-1,2,3-triazol-1-yl]-N-[2-(4-formylphenyl)-1,3-thiazol-5-yl]acetamide (9c)

White solid; isolated yield: 92%; mp 212–214 °C; IR (KBr, ν): 3351, 2925, 1678 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆) δ 13.24–13.33 (m, 2H, 2x NH), 8.43 (s, 1H), 8.22 (d, J = 8.1 Hz, 2H), 7.98 (d, J = 7.2 Hz, 1H), 7.75 (s, 1H), 7.66–7.63 (m, 2H), 7.50 (t, J = 7.5 Hz, 2H), 7.42–7.38 (m, 1H), 7.32 (d, J = 8.2 Hz, 2H), 7.25–7.23 (m, 2H), 5.63 (s, 2H, H-23), 5.36 (s, 2H, H-17); ¹³C NMR (101 MHz, DMSO-d₆) δ 164.92, 162.26, 159.40, 159.31, 159.27, 158.89, 157.29, 148.97, 142.36, 137.91, 134.04, 128.76, 128.01, 127.89, 126.50, 125.64, 122.99, 122.89, 121.81, 115.11, 115.07, 61.09 (C-17), 51.48 (C-23); Anal Calcd for C₂₇H₂₁BrN₂O₂S: C, 61.70; H, 3.84; N, 18.66; found: C, 61.77; H, 3.80; N, 18.65.

2-[(4-[1H-1,3-benzodiazo-2-yl]phenoxymethyl)-1H-1,2,3-triazol-1-yl]-N-[2-(4-bromophenyl)-1,3-thiazol-5-yl]acetamide (9d)

White solid; isolated yield: 90%; mp 197–199 °C; IR (KBr, ν): 3353, 2925, 1679 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆) δ 13.91 (s, 1H, NH), 8.42 (s, 1H), 8.30–8.15 (m, 2H), 7.85 (d, J = 8.1 Hz, 2H), 7.68–7.58 (m, 3H), 7.35–7.16 (m, 7H), 5.61 (s, 2H, H-23), 5.35 (s, 2H, H-17), 2.36 (s, 3H, CH₃); ¹³C NMR (101 MHz, DMSO-d₆) δ 164.84, 159.44, 157.18, 151.61, 151.47, 149.07, 142.38, 139.50, 139.08, 137.22, 131.40, 129.30, 128.02, 126.50, 125.59, 122.85, 121.87, 115.09, 114.76, 114.66, 107.65, 61.12 (C-17), 51.49 (C-23), 20.77 (CH₃); Anal Calcd for C₂₇H₂₁Br₂N₂O₂S: C, 64.48; H, 4.44; N, 18.80; found: C, 64.44; H, 4.50; N, 18.87.

2-[(4-[1H-1,3-benzodiazo-2-yl]phenoxymethyl)-1H-1,2,3-triazol-1-yl]-N-[2-(4-methoxyphenyl)-1,3-thiazol-5-yl]acetamide (9e)

White solid; isolated yield: 87%; mp 245–247 °C; IR (KBr, ν): 3356, 2921, 1680 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆) δ 12.95–12.87 (m, 2H, 2x NH), 8.46 (s, 1H), 8.24 (d, J = 8.6 Hz, 2H), 7.94 (d, J = 8.8 Hz, 1H), 7.83–7.47 (m, 4H), 7.35 (d, J = 8.6 Hz, 2H), 7.30–7.26 (m, 2H), 7.10 (d, J = 8.9 Hz, 2H), 5.64 (s, 2H, H-23), 5.39 (s, 2H, H-17), 3.89 (s, 3H, OCH₃); ¹³C NMR (101 MHz, DMSO-d₆) δ 164.81, 162.26, 159.36, 159.00, 157.31, 157.13, 155.01, 151.25, 148.85, 147.26, 142.35, 130.05, 127.97, 126.99.
2-H), 7.22–7.18 (m, 2H), 5.60 (s, 2H, H-23), 5.29 (s, 2H, \( J = 7.8 \) Hz, 1H), 7.31 (d, \( J = 8.0 \) Hz, 2H), 7.25–7.19 (m, 2H), 6.96 (d, \( J = 8.0 \) Hz, 1H), 5.60 (s, 2H, H-23), 5.35 (s, 2H, H-17), 3.86 (s, 3H, OCH3); \(^{13}\)C NMR (101 MHz, DMSO-\( d_6 \)) \( \delta \) 164.92, 159.23, 157.30, 153.73, 142.36, 139.41, 137.33, 134.04, 128.75, 127.89, 126.63, 125.64, 123.15, 121.79, 119.11, 113.38, 113.17, 109.84, 108.54, 61.48 (C-17), 55.49 (OCH3), 51.49 (C-23); Anal Caled for C\(_{28}\)H\(_{23}\)N\(_7\)O\(_3\)S: C, 62.56; H, 4.31; N, 18.24; found: C, 62.55; H, 4.35; N, 18.20.

2-[4-[4-(1H-1,3-benzodiazol-2-yl)-2-methoxyphenoxymethyl]-1H-1,2,3-triazol-1-yl]-N-[2-(4-methylphenyl)-1,3-thiazol-5-yl]acetamide (9g)

White solid; isolated yield: 91%; mp 238–240 °C; IR (KBr, \( \nu \)): 3357, 2924, 1670 cm\(^{-1}\); \(^{1}\)H NMR (400 MHz, DMSO-\( d_6 \)) \( \delta \) 13.31–12.51 (m, 2H, 2\( \times \)NH), 8.39 (s, 1H), 7.96–7.92 (m, 2H), 7.87–7.81 (m, 2H), 7.69 (s, 1H), 7.63–7.59 (m, 2H), 7.45 (t, \( J = 7.7 \) Hz, 2H), 7.40–7.33 (m, 2H), 7.22–7.18 (m, 2H), 5.60 (s, 2H, H-23), 5.29 (s, 2H, H-17), 3.91 (s, 3H, OCH\(_3\)); \(^{13}\)C NMR (101 MHz, DMSO-\( d_6 \)) \( \delta \) 164.96, 162.26, 157.30, 151.40, 151.30, 149.04, 148.97, 148.91, 142.36, 139.41, 137.33, 134.04, 128.75, 127.89, 126.63, 125.64, 123.15, 121.79, 119.11, 113.38, 113.17, 109.84, 108.54, 61.48 (C-17), 55.49 (OCH3), 51.49 (C-23); Anal Caled for C\(_{28}\)H\(_{23}\)N\(_7\)O\(_2\)S: C, 64.48; H, 4.44; N, 18.24; found: C, 62.55; H, 4.36; N, 18.20.

White solid; isolated yield: 95%; mp 200–202 °C; IR (KBr, v): 3359, 2926, 1675 cm\(^{-1}\); \(^{1}\)H NMR (400 MHz, DMSO-\( d_6 \)) \( \delta \) 13.26–12.62 (m, 2H, 2\( \times \)NH), 8.43 (s, 1H), 7.93–7.86 (m, 4H), 7.75 (s, 1H), 7.66 (d, \( J = 8.2 \) Hz, 4H), 7.42 (d, \( J = 8.3 \) Hz, 1H), 7.25–7.22 (m, 2H), 5.64 (s, 2H, H-23), 5.33 (s, 2H, H-17), 3.94 (s, 3H, OCH\(_3\)); \(^{13}\)C NMR (101 MHz, DMSO) \( \delta \) 165.07, 162.25, 157.65, 151.45, 149.06, 148.93, 148.90, 148.81, 147.93, 134.19, 133.26, 131.65, 127.63, 126.62, 123.34, 123.18, 121.85, 121.79, 120.97, 119.13, 113.17, 109.84, 109.26, 61.50 (C-17), 55.47 (OCH3), 51.55 (C-23); Anal Caled for C\(_{28}\)H\(_{23}\)BrN\(_2\)O\(_3\): C, 54.55; H, 3.60; N, 15.90; found: C, 54.50; H, 3.67; N, 15.93.
N-[2-(4-bromophenyl)-1,3-thiazol-5-yl]-2-[4-{4-(6-methyl-1H-1,3-benzodiazol-2-yl)phenoxymethyl]-1H-1,2,3-triazol-1-yl}acetamide (9h)

White solid; isolated yield: 89%; mp 208–210 °C; IR (KBr, v): 3351, 2917, 1688 cm−1; 1H NMR (400 MHz, DMSO-d6) δ 12.87 (s, 1H, NH), 12.80–12.52 (m, 1H), 8.40 (s, 1H), 8.16 (d, J = 7.9 Hz, 2H), 7.89 (d, J = 8.8 Hz, 2H), 7.57 (s, 1H), 7.48–7.43 (m, 1H), 7.29 (d, J = 8.8 Hz, 2H), 7.06–7.04 (m, 3H), 5.59 (s, 2H, H-23), 5.33 (s, 2H, H-17), 3.84 (s, 3H, OCH3), 2.47 (s, 3H, CH3); 13C NMR (101 MHz, DMSO-d6) δ 164.80, 159.21, 159.00, 158.72, 150.87, 148.84, 143.03, 142.35, 137.92, 127.82, 126.98, 126.87, 126.48, 123.12, 122.98, 115.25, 115.01, 114.09, 110.54, 106.50, 61.06 (C-37), 51.45 (C-23), 21.50 (CH3); Anal Caled for C29H25N7O3S: C, 65.03; H, 4.70; N, 16.33; found: C, 65.08; H, 4.69; N, 16.38.

Enzyme kinetic study

The mode of inhibition of the most active compound (9c, 9g, and 9m), identified with the lowest IC50 value, was investigated against an α-glycosidase activity with different concentrations of p-nitrophenyl α-D-glucopyranoside (2–10 mM) as substrate in the absence and presence of sample (9c, 9g, and 9m) at different concentrations (0, 1.25, 2.5, 5, and 10 µM). A Lineweaver–Burk plot was generated to identify the type of inhibition, and the Michaelis–Menten constant (1/V´ max) was determined from the plot between reciprocal of the substrate concentration (1/[S]) and reciprocal of enzyme rate (1/V) over various inhibitor concentrations. The experimental inhibitor constant (Ki) value was constructed by secondary plots of the inhibitor concentration [I] versus 1/V´ max.[15, 42, 43].

Molecular docking

The 3D structure of α-glycosidase (PDB entry code: 5NN8) in complex with acarbose was obtained from the protein data bank. After editing the crystallographic structure which contains removing ligand and water molecules and adding hydrogen atoms, the prepared ligands (the ligands were sketched in HyperChem software and energy minimized by the MM1 force field) were docked into the active site of the enzyme. The binding site of the enzyme for the docking was defined automatically using the coordinates of the native ligand acarbose in such a way that 10 Å around the ligand was defined as the binding site. Gold docking program with ChemScore function was used for docking analyses and re-dock acarbose inside the 5NN8. The top-score binding poses were used for further analysis. Protein–ligand interactions were analyzed with Discovery Studio Visualizer [17].

α-Glycosidase inhibition assay

The anti-α-glycosidase effects of synthesized compound 9a–n were screened according to the previously reported method. Briefly, 135 µL of potassium phosphate buffer, 20 µL of target compounds 9a–n with various concentrations, and 20 µL of α-glycosidase solution were added to each well in the 96-well plate and incubated for 10 min at 37 °C. Then, p-nitrophenyl glucopyranoside as substrate (25 µL, 4 mM) was added and incubation was continued at 37 °C for 20 min. Finally, absorbance was measured at 405 nm by a spectrophotometer [37–41].
Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11303-021-10310-7.

Declarations

Conflict of interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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