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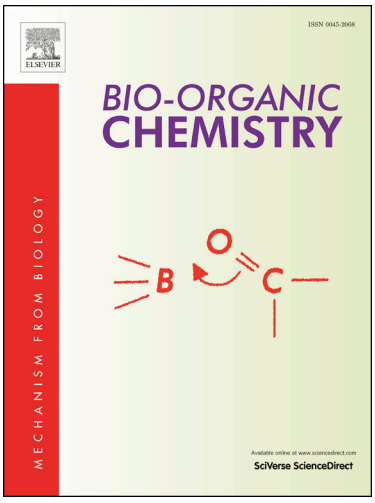

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Nafise Asemanipoor, Maryam Mohammadi-Khanaposhtani, Shahram Moradi, Mahbobeh Vahidi, Mehdi Asadi, Mohammad Ali Faramarzi, Mohammad Mahdavi, Mahmood Biglar, Bagher Larijani, Haleh Hamedifar, Mir Hamed Hajimiri

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Synthesis and biological evaluation of new benzimidazole-1,2,3-triazole hybrids as potential α-glucosidase inhibitors

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Abstract

In this study, a series of benzimidazole-1,2,3-triazole hybrids **8a-n** as new α-glucosidase inhibitors were designed and synthesized. *In vitro* α-glucosidase inhibition activity results indicated that all the synthesized compounds (IC_{50} values ranging from 25.2 ± 0.9 to 176.5 ± 6.7 μM) exhibited more inhibitory activity in comparison to standard drug acarbose (IC_{50} = 750.0 ± 12.5 μM). Enzyme kinetic study on the most potent compound **8c** revealed that this compound was a competitive inhibitor into α-glucosidase. Moreover, the docking study was performed in order to evaluation of interaction modes of the synthesized compounds in the active site of α-glucosidase and to explain structure-activity relationships of the most potent compounds and their corresponding analogs.

Keywords: α-Glucosidase inhibitor, Molecular docking, Benzimidazole, 1,2,3-Triazole

1. Introduction

Diabetes mellitus (DM) is a metabolic disorder which has two main type 1 and type 2: in the type 1 of DM, the body does not produce enough insulin and in the type 2 of this disease, insulin is sufficient, but the cells cannot use it efficiently [1]. The common treatment for type 1 diabetes is injectable insulin while the main medications for type 2 diabetes are oral blood glucose-lowering drugs that acted with various mechanisms such as enhances the effect of insulin, reduce intestinal glucose absorption, increased glucosuria through the inhibition of sodium/glucose cotransporter 2 (SGLT2) in the kidney, and reduce insulin resistance through the stimulation of peroxisome

proliferator-activated receptors (PPARs) [2]. As was mentioned above, one of the most important of these mechanisms is reduce intestinal glucose absorption that occurs through inhibition of the carbohydrate-hydrolysing enzymes such as α-glucosidase and α-amylase [3]. Blocking the activity of the latter enzymes led to a decrease in the decomposition of carbohydrates to glucose and reduces level of this metabolite in the blood. Today, α-glucosidase inhibitors such as acarbose, miglitol, and voglibose have been developed to treat of type 2 diabetes. Although these agents have certain therapeutic effect on type 2 diabetes, taking them is associated with gastrointestinal adverse reactions such as bloating, diarrhea, abdominal pain, and etc [4]. Therefore, it is urgent to develop new efficient and potent α-glucosidase inhibitors with low side effects for treatment of the type 2 diabetes.

Benzimidazole ring is an attractive pharmacophore for the medicinal chemists that widely used for design and development of new biological active compounds [5]. Several benzimidazole derivatives with α-glucosidase inhibitory activity have been reported (Fig. 1, **A**) [6-8]. Another one of the useful pharmacophores for design new potent α-glucosidase inhibitors is 1,2,3-triazole ring [9-11]. In this regard, recently, Wang et al. have been reported xanthone-triazole hybrids **B** with high anti-α-glucosidase activities (Fig. 1) [12].

Keeping in view of the above mentioned importance of benzimidazole and 1,2,3-triazole moieties in the design of new α-glucosidase inhibitors, herein, we designed, synthesized, and screened novel benzimidazole-1,2,3-triazole hybrids **8a-n** for their α-glucosidase inhibitory activity (Fig. 1). Kinetic and docking studies of these compounds in order to evaluation of their interactions with α-glucosidase were performed.

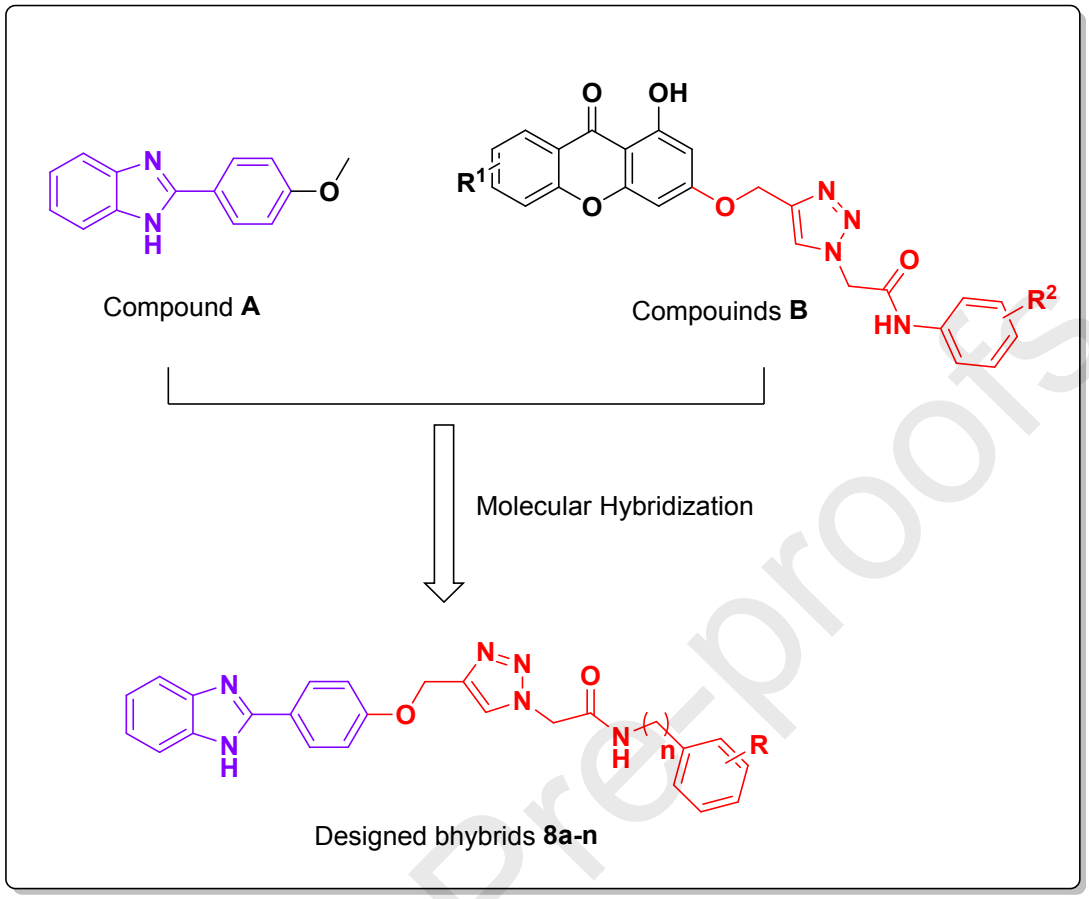


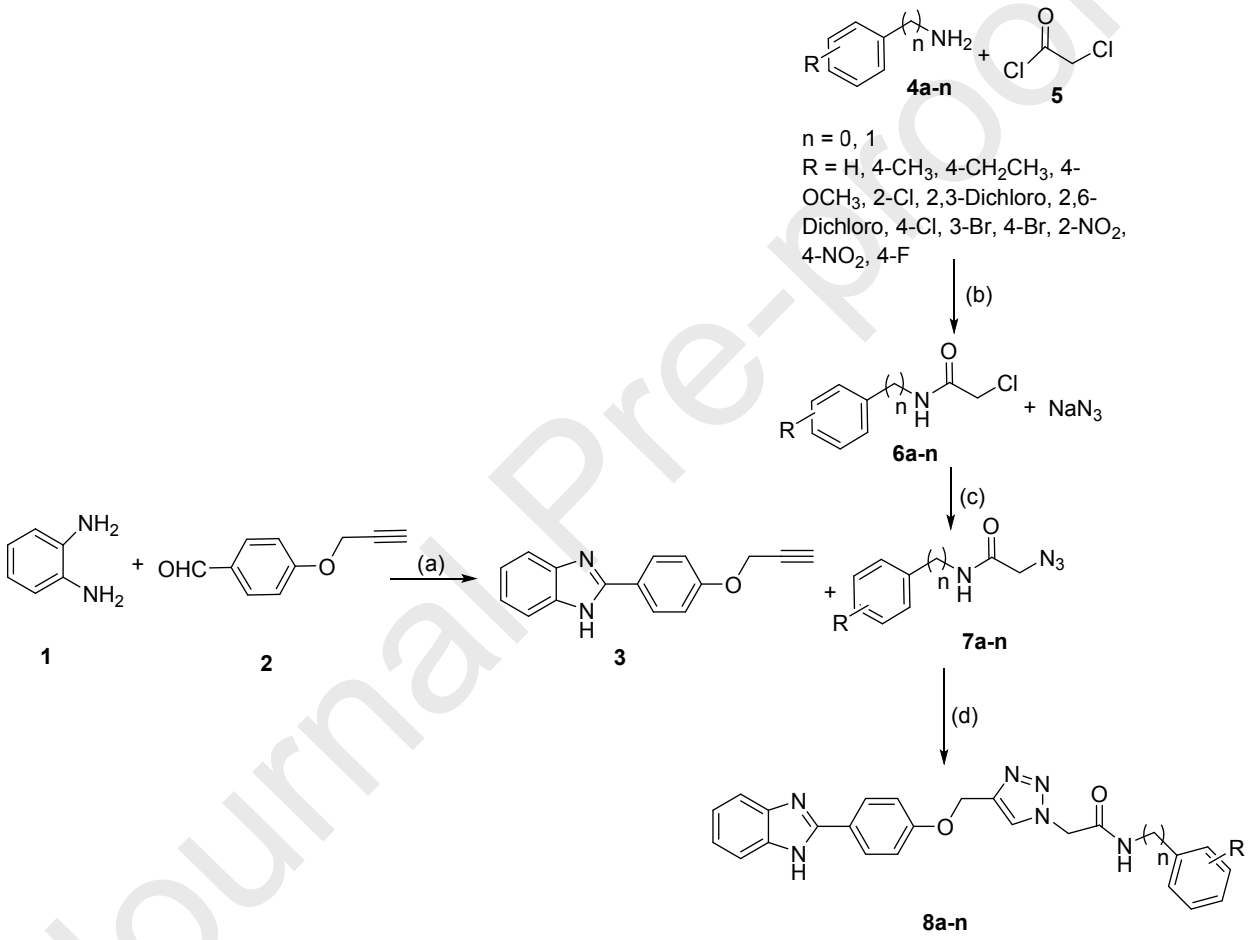
Fig. 1. Design strategy for benzimidazole-1,2,3-triazole hybrids **8a-n** as new α-glucosidase inhibitors.

2. Results and discussion

2.1. Chemistry

The synthetic route for the synthesis of benzimidazole-1,2,3-triazoles **8a-n** has been depicted in Scheme 1. This route was started from the reaction of o-phenylenediamine **1** and 4-(prop-2-ynyloxy)benzaldehyde **2** in the presence of $Na_2S_2O_5$ in DMF at 100 °C to give 2-(4-(prop-2-ynyloxy)phenyl)-1H-benzo[d]imidazole **3**. On the other hand, amines **4a-n** reacted with chloroacetyl chloride **5** in DMF at room temperature (RT), to give *N*-phenyl (or benzyl)-2-chloroacetamides **6**. In order to produce the appropriate molecules to participate in the click

reaction, *N*-phenyl (or benzyl)-2-chloroacetamides **6a-n** and sodium azide reacted in the mixture of H_2O and t-BuOH (1:1) in the presence of triethylamine (Et_3N) at RT [13]. Then, mixture of 2-(4-(prop-2-ynyloxy)phenyl)-1H-benzo[d]imidazole **3**, sodium ascorbate, and copper(II) sulfate ($CuSO_4$) was added to the freshly prepared azide derivatives **7a-n** and the reaction was continued at RT for 24-48 h to give the target compounds **8a-n**.



Scheme 1. Reagents and conditions for the synthesis of benzimidazole-1,2,3-triazoles **8a-n**: (a) DMF, $Na_2S_2O_5$, 100 °C, 2 h; (b) DMF, RT, 30 min; (c) Et_3N, H_2O/t-BuOH, RT, 1 h; (d) $CuSO_4.5H_2O$, sodium ascorbate, RT, 24-48 h.

2.2. In vitro α-glucosidase inhibitory activity

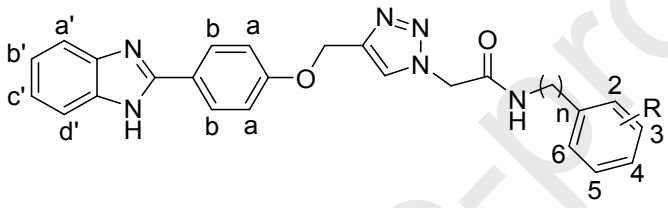
The synthesized compounds **8a–n** were screened for their *in vitro* α-glucosidase inhibition against yeast α-glucosidase. The obtained IC_{50} values of the *N*-phenylacetamide derivatives **8a-l** and *N*-benzylacetamide derivatives **8m-n** showed that all these compounds are more potent than standard drug acarbose (IC_{50} = 750.0 ± 12.5 μM) and among them, the most potent compounds were compounds **8c**, **8k**, **8b**, **8a**, and **8f** with IC_{50} values 25.2 ± 0.9, 35.0 ± 1.0, 43.1 ± 1.5, 51.5 ± 1.8, and 56.6 ± 2.1 μM, respectively. Moreover, the remaining compounds with the IC_{50} values ranging from 63.0 ± 2.5 to 176.5 ± 6.7 μM exhibited α-glucosidase inhibitory activities around 12–4 folds more than acarbose.

In the *N*-phenylacetamide derivatives **8a-l**, the most potent compound was 4-ethyl derivative **8c**. Removing the ethyl substituent or replace it with methyl substituent, led to a slightly decrees in the inhibitory activity as observed in the compounds **8a** and **8b**, respectively. Moreover, replacing of ethyl substituent with methoxy, bromo, or nitro substituents, as in compounds **8d**, **8j**, and **8l**, respectively, caused to a significant decrease in the anti-α-glucosidase activity. Among the halo-substituted derivatives **8e-j**, compound **8f** with 2,3-dichlorophenyl moiety was the most potent compound. Removing the 3-chloro substituent, as in compound **8e**, led to slightly decrease in the activity while movement of 3-chloro to 6-position, as in compound **8g**, led to a significant decrease in the activity. Among the synthesized compounds, the less active compound was *N*-4-bromophenylacetamide **8j**. Replacement of bromo with chloro substituent or changing the position of the bromine atom in the phenyl ring from 4-position to 3-position, producing compound **8h** and **8i**, dramatically increased the inhibitory activity. The second most potent compounds among the synthesized compounds was 2-nitro derivative **8k** while it 4-nitro analog **8l** was one of the weakest compounds synthesized against α-glucosidase. From the activity pattern of *N*-phenylacetamide derivatives **8a-l** it can be ascertain that the position of the substitutions on phenyl ring of *N*-

phenylacetamide moiety as well as their electron property play important role in the obtained anti-α-glucosidase activity.

Inhibitory activity of *N*-benzylacetamide derivative **8m** is 2.3-fold less than that of it corresponding analog **8a** of *N*-phenylacetamide series. The introduction of 4-fluoro substituent on benzyl group improved inhibitory activity against α-glucosidase as observed in compound **8n**.

Table 1. *In vitro* inhibitory activities of compounds **8a-n** against α-glucosidase.



Compound	n	R	IC_{50} (μM)[a]
8a	0	H	51.5 ± 1.8
8b	0	4-CH_3	43.1 ± 1.5
8c	0	4-CH_2CH_3	25.2 ± 0.9
8d	0	4-OCH_3	112.5 ± 5.3
8e	0	2-Cl	70.6 ± 2.6
8f	0	2,3-Dichloro	56.6 ± 2.1
8g	0	2,6-Dichloro	133.7 ± 6.0
8h	0	4-Cl	91.6 ± 3.0
8i	0	3-Br	85.2 ± 2.8
8j	0	4-Br	176.5 ± 6.7
8k	0	2-NO_2	35.0 ± 1.0

8l	0	4-NO_2	107.3 ± 5.1
8m	1	H	121.1 ± 5.5
8n	1	4-F	63.0 ± 2.5
Acarbose	-	-	750.0 ± 12.5

[a] Data are expressed as mean ± S.E. of at least three different experiments.

2.3. Kinetic study

In order to gain the interaction mechanism between the synthesized compounds and α-glucosidase, the most potent compound **8c** was selected to study the inhibition kinetic. As shown in Fig. 2a, it was revealed that compound **8c** is a competitive α-glucosidase inhibitor. Moreover, the inhibitory constant (K_i) of this compound was 23 μM (Fig. 2b).

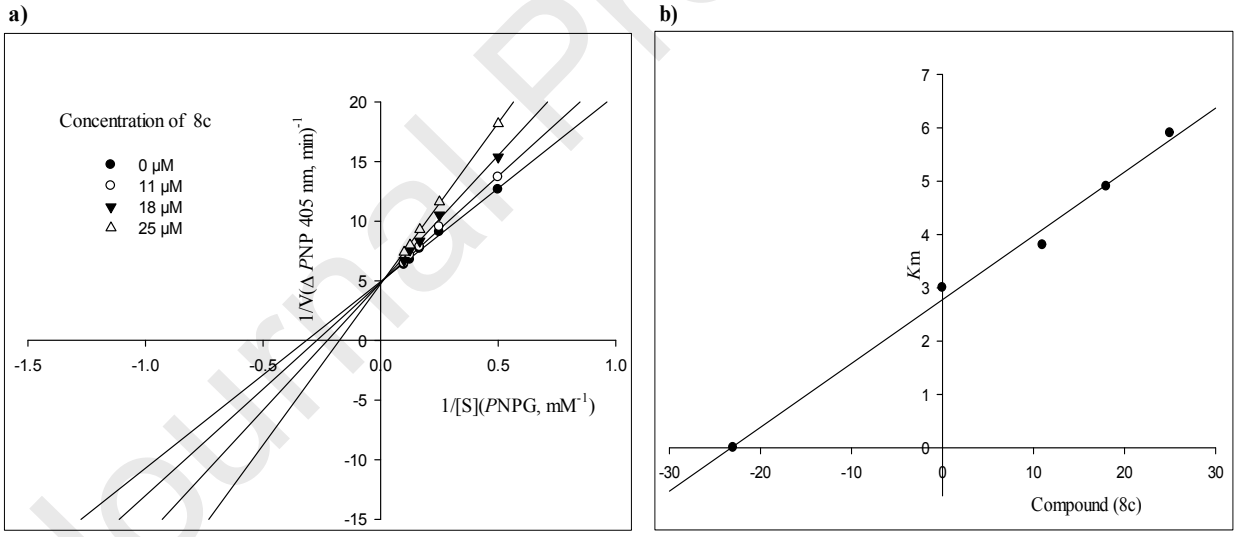


Fig. 2. The inhibition type and K_i of the most potent compound **8c**.

2.4. Molecular docking study

In order to gain an insight of the interaction modes in the active site of α-glucosidase and also explain the different activities of the synthesized compounds, molecular docking studies were

conducted using AutodockTools (version 1.5.6) on modeled α-glucosidase [14]. Interaction modes of the selected analogs **8b-c**, **8k-l**, **8a** and **8m**, and **8e-f** were showed in the Figs. 3-6 and details of their interactions in the active site were listed in Tables 2-5. In each table, green entries showed the same interactions between comparative analogs and the active site.

The comparison of interaction modes of the most potent compound **8c** and it analog **8b** (the third most potent compound) (Fig. 3 and Table 2) showed that *N*-(4-ethylphenyl)acetamide moiety of the compound **8c** formed three interactions with Phe300 and Phe157 by 4-ethyl substituent, pendant phenyl ring, and NH unit of amide moiety and *N*-(4-methylphenyl)acetamide moiety the compound **8b** established three interactions with Phe158, Arg312, Phe311 by 4-methyl substituent, pendant phenyl ring, and carbonyl unit of amide moiety. Furthermore, 1,2,3-triazol ring of the compound **8c** interacted with His239 *via* a π-π interaction and a π-cation interaction while this ring of the compound **8b** showed only a hydrogen bond with His279. Moreover, additional interactions between middle phenyl and benzimidazole moieties of the compound **8c** and Glu304 in comparison to the compound **8b** can be also seen. Other interactions are the same in the both compound **8b** and **8c**.

(**8b**) (**8c**)

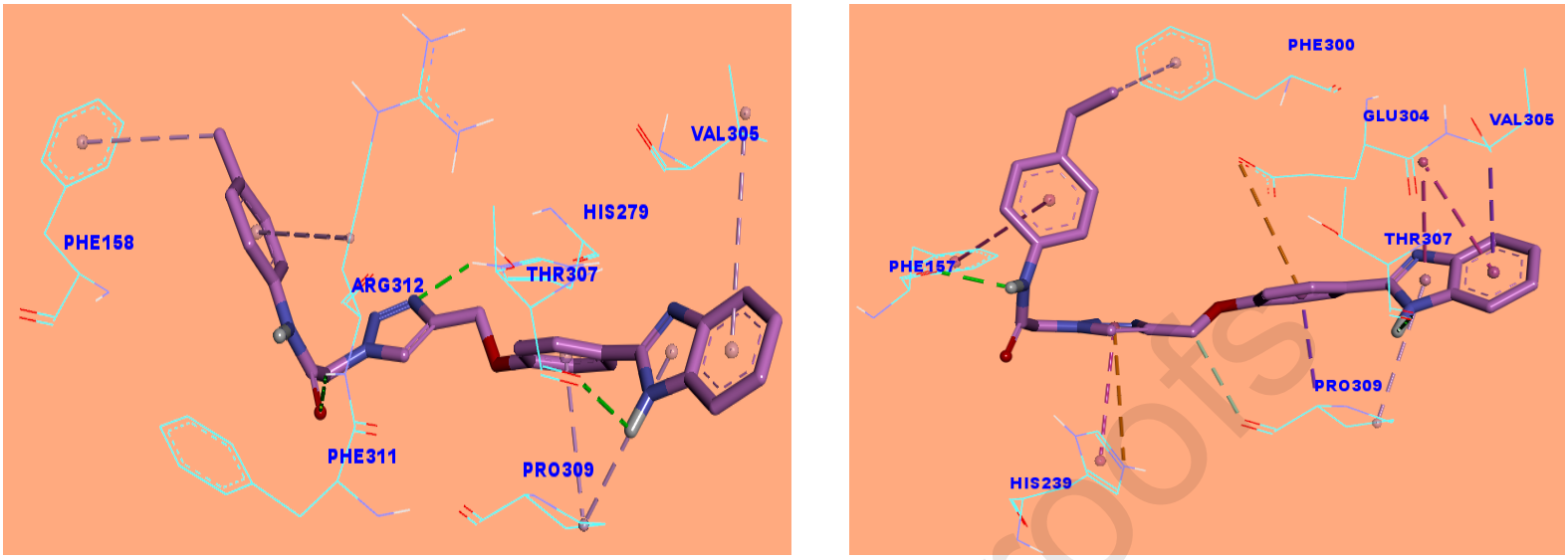


Fig. 3. Interaction modes of compounds **8b** and **8c** in the active site of α-glucosidase.

Table 2. Interaction mode details of the compounds **8b** and **8c**.

Compound	Interaction	Interacting unit of the ligand	Amino acid	Compound	Interaction	Interacting unit of the ligand	Amino acid
8b	Hydrophobic	4-Methyl	Phe158	**8c**	Hydrophobic	4-Ethyl	Phe300
	Hydrophobic	Pendant phenyl	Arg312		π-π	Pendant phenyl	Phe157
	H-bond	NH-CO	Phe311		H-bond	NH-CO	Phe157
	H-bond	1,2,3-triazol	His279		π-π	1,2,3-triazol	His239
	Hydrophobic	Middle phenyl	Pro309		π-cation	1,2,3-triazol	His239
	H-bond	NH unit of benzimidazole	Thr307		π-anion	Middle phenyl	Glu304
	Hydrophobic	Benzimidazole	Val305		Hydrophobic	Middle phenyl	Pro309
	Hydrophobic	Benzimidazole	Pro309		H-bond	NH unit of benzimidazole	Thr307
					Hydrophobic	Benzimidazole	Glu304
					Hydrophobic	Benzimidazole	Glu304
					Hydrophobic	Benzimidazole	Val305
					Hydrophobic	Benzimidazole	Pro309

The second most potent compound **8k** (IC_{50} = 35.0 ± 1.0 µM) with 2-nitro-phenyl group in comparison to it regioisomer **8l** (IC_{50} = 107.3 ± 5.1 µM) with 4-nitro-phenyl group showed additional interactions with Phe157, His239, His279, Pro309 through amide group, 1,2,3-triazol ring, and benzimidazole moiety as can be seen in the Fig.4 and Table 3. Moreover, an additional hydrophobic interaction between benzimidazole moiety of the compound **8k** and Glu304 was observed.

(8k) **(8l)**

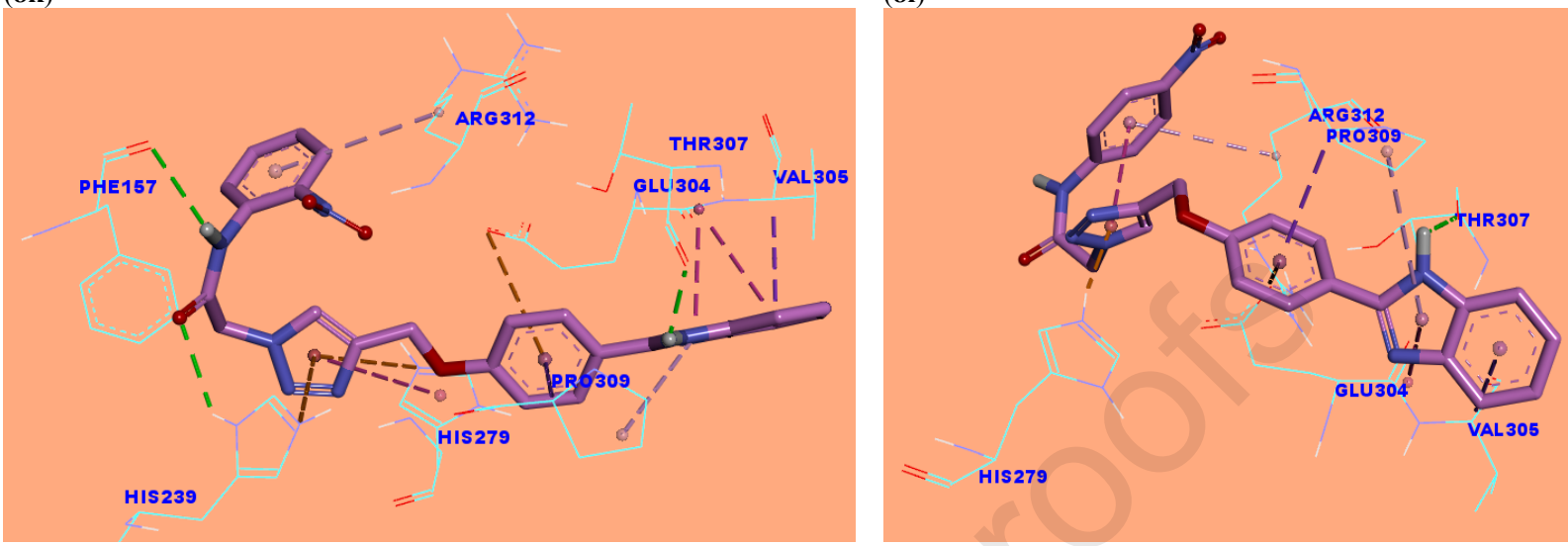


Fig. 4. Interaction modes of compounds **8k** and **8l** in the active site of α-glucosidase.

Table 3. Interaction mode details of the compounds **8k** and **8l**.

Compound	Interaction	Interacting unit of the ligand	Amino acid	Compound	Interaction	Interacting unit of the ligand	Amino acid
8k	Hydrophobic	Pendant phenyl	Arg312	**8l**	Hydrophobic	Pendant phenyl	Arg312
	H-bond	NH-CO	Phe157		π-cation	1,2,3-triazol	His279
	H-bond	NH-CO	His239		π-anion	Middle phenyl	Glu304
	π-cation	1,2,3-triazol	His239		Hydrophobic	Middle phenyl	Pro309
	π-π	1,2,3-triazol	His279		H-bond	NH unit of benzimidazole	Thr307
	π-cation	1,2,3-triazol	His279		Hydrophobic	Benzimidazole	Glu304
	π-anion	Middle phenyl	Glu304		Hydrophobic	Benzimidazole	Val305
	Hydrophobic	Middle phenyl	Pro309		Hydrophobic	Benzimidazole	Pro309
	H-bond	NH unit of benzimidazole	Thr307				
	Hydrophobic	Benzimidazole	Glu304				
	Hydrophobic	Benzimidazole	Glu304				
	Hydrophobic	Benzimidazole	Val305				
	Hydrophobic	Benzimidazole	Pro309				

As can be seen in the Fig. 5 and Tables 1 and 4, insertion of a methylene unit between amid group and pendant phenyl ring in the compound **8a** (IC_{50} = 51.5 ± 1.8 µM), as in compound **8m** (IC_{50} = 121.1 ± 5.5 µM), led to a significant decrease in the inhibitory activity and changes in interaction of amide group with the active site. Amide group of the compound **8a** formed two hydrogen bonds with Asp408 (NH

unit) and Asn412 (carbonyl unit) while this moiety of the compound **8m** established only a hydrogen bond with Phe157 (NH unit). Other interactions are the same in the both compound **8a** and **8m**.

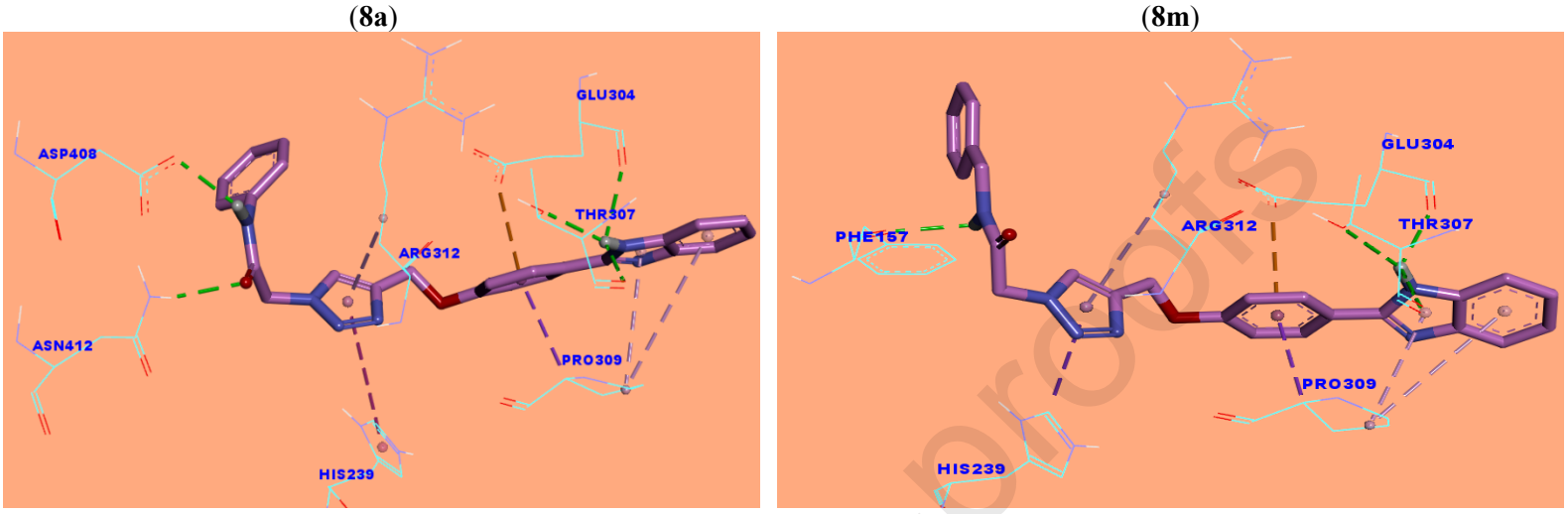


Fig. 5. Interaction modes of compounds **8k** and **8l** in the active site of α-glucosidase.

Table 4. Interaction mode details of the compounds **8a** and **8m** in the active site of α-glucosidase.

Compound	Interaction	Interacting unit of the ligand	Amino acid	Compound	Interaction	Interacting unit of the ligand	Amino acid
8a	H-bond	NH-CO	Asp408	**8m**	H-bond	NH-CO	Phe157
	H-bond	NH-CO	Asn412		π-π	1,2,3-triazol	His239
	π-π	1,2,3-triazol	His239		Hydrophobic	1,2,3-triazol	Arg312
	Hydrophobic	1,2,3-triazol	Arg312		π-anion	Middle phenyl	Glu304
	π-anion	Middle phenyl	Glu304		Hydrophobic	Middle phenyl	Pro309
	Hydrophobic	Middle phenyl	Pro309		H-bond	NH unit of benzimidazole	Thr307
	H-bond	NH unit of benzimidazole	Thr307		H-bond	NH unit of benzimidazole	Glu304
	H-bond	NH unit of benzimidazole	Glu304		Hydrophobic	Benzimidazole	Pro309
	Hydrophobic	Benzimidazole	Pro309		Hydrophobic	Benzimidazole	Pro309
	Hydrophobic	Benzimidazole	Pro309				

N-(2,3-dichlorophenyl)acetamide moiety of the most potent halogenated compound **8f** (IC_{50} = 56.6 ± 2.1 μM) showed hydrophobic interactions with Tyr313 and Arg312 through chloro substituents and pendant phenyl ring and a hydrogen bond with Phe157 through NH unit of amide group while it 2-chlorophenyl analog **8e** (IC_{50} = 70.6 ± 2.6 μM) as the second most potent halogenated derivative formed a hydrophobic interaction with Tyr313 through 2-chloro substituent and two hydrogen bonds with Asp408 and Asn412

through amide group (Fig. 6 and Table 5). Moreover, 1,2,3-triazole ring of the compound **8f** interacted with residues His239 and His279 *via* π-interactions while this ring of the compound **8e** only formed a hydrophobic interaction with Arg312. Middle phenyl moieties of these compounds showed the same interactions with the active site. On the other hand, NH unit of benzimidazole moiety of compound **8e** formed two additional hydrogen bonds with Glu304 and Thr307 in comparison with the compound **8f**. Finally, benzimidazole moiety of the compound **8f** formed four hydrophobic interactions with Glu304 (two interactions), Val305, and Pro309 while this moiety of the compound **8e** only two hydrophobic interactions established with Pro309.

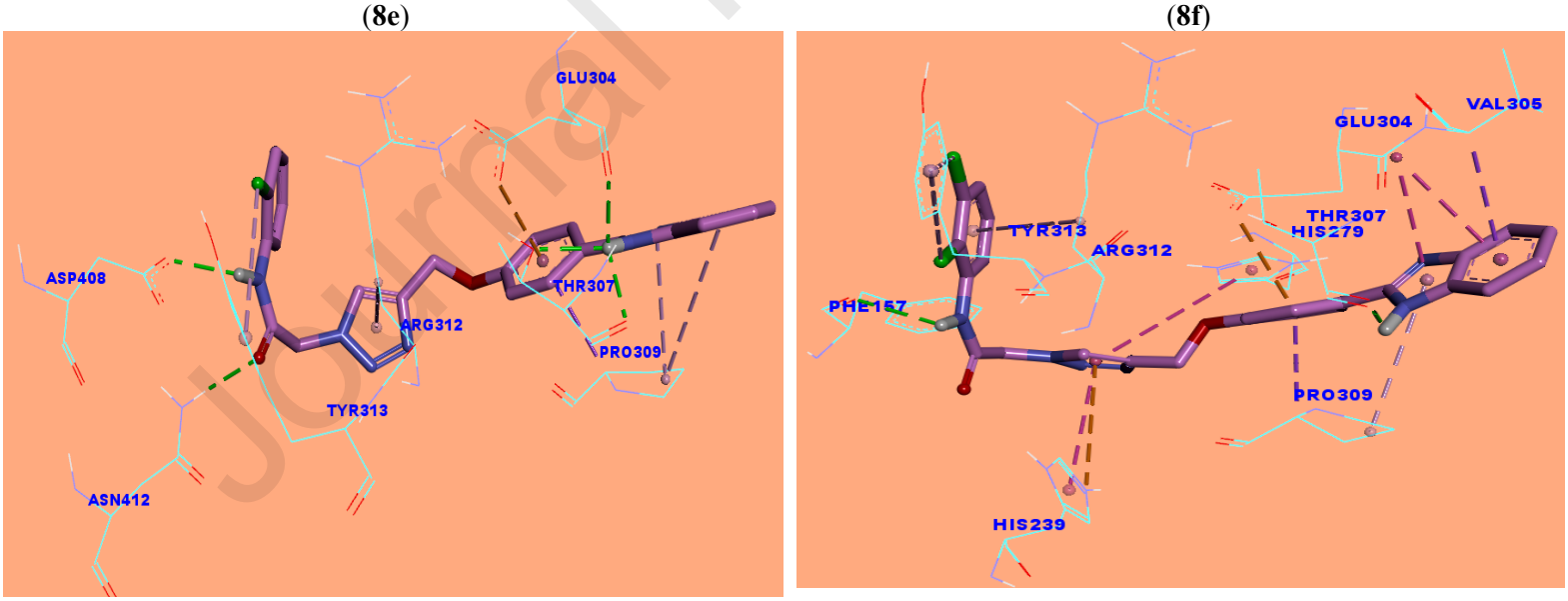


Fig. 6. Interaction modes of the compounds **8e** and **8f** in the active site of α-glucosidase.

Table 5. Interaction mode details of the compounds **8e** and **8f** in the active site of α-glucosidase.

Compound	Interaction	Interacting unit of the ligand	Amino acid	Compound	Interaction	Interacting unit of the ligand	Amino acid
8e	Hydrophobic	2-Cl	Tyr313	**8f**	Hydrophobic	2-Cl	Tyr313
	H-bond	NH-CO	Asp408		Hydrophobic	3-Cl	Tyr313
	H-bond	NH-CO	Asn412		Hydrophobic	Pendant phenyl	Arg312
	Hydrophobic	1,2,3-triazol	Arg312		H-bond	NH-CO	Phe157
	π-anion	Middle phenyl	Glu304		π-π	1,2,3-triazol	His279
	Hydrophobic	Middle phenyl	Pro309		π-π	1,2,3-triazol	His239
	H-bond	NH unit of benzimidazole	Thr307		π-cation	1,2,3-triazol	His239
	H-bond	NH unit of benzimidazole	Thr307		π-anion	Middle phenyl	Glu304
	H-bond	NH unit of benzimidazole	Glu304		Hydrophobic	Middle phenyl	Pro309
	Hydrophobic	Benzimidazole	Pro309		H-bond	NH unit of benzimidazole	Glu304
	Hydrophobic	Benzimidazole	Pro309		H-bond	NH unit of benzimidazole	Thr307
					Hydrophobic	Benzimidazole	Glu304
					Hydrophobic	Benzimidazole	Glu304
					Hydrophobic	Benzimidazole	Val305
					Hydrophobic	Benzimidazole	Pro309

2.5. α-Amylas inhibition assay

Another strategy for the reduction of released glucose from carbohydrates is inhibition of α-amylase [15]. In this regard, anti-α-amylase activity (against porcine pancreatic α-amylase) of the most active α-glucosidase inhibitors **8c**, **8k**, and **8a** was evaluated. Obtained results revealed that the latter compounds were inactive against α-amylase (at 300 μM) when compared with acarbose as a standard α-amylase inhibitor (IC_{50} =108 ± 0.71 μM).

3. Conclusion

In conclusion, a series of novel benzimidazole-1,2,3-triazole hybrids **8a-n** were designed and synthesized *via* click reaction. *In vitro* anti-α-glucosidase activity evaluation of title compounds revealed that all the synthesized derivatives exhibited excellent inhibitory potency compared with acarbose. The evaluation of inhibition mechanism revealed that the most active compound **8c** inhibited α-glucosidase in a competitive mode. Moreover, docking studies of the most potent compounds and their corresponding analogs in the active site of modeled α-glucosidase were also performed in order to evaluate of interaction modes and structure-activity relationships. α-Amylas

inhibition assay of the most potent compounds demonstrated that these compounds at 300 μM do not exhibit activity.

4. Experimental

The melting points of benzimidazole-1,2,3-triazoles **8a-n** were determined on a Kofler hot stage apparatus and uncorrected. ^{1}H and ^{13}C NMR spectra of these derivatives were recorded on a Bruker FT-500 in DMSO-d_6 with tetramethylsilane as an internal standard. Nicolet Magna FTIR 550 spectrophotometer was used to record IR spectra of the synthesized compounds by using KBr disks. Elemental analysis of title compounds **8a-n** was performed on an Elementar Analysen system GmbH VarioEL CHNS mode.

*4.1. General Procedure for the Synthesis of 2-(4-(prop-2-ynyloxy)phenyl)-1H-benzo[d]imidazole **3***

A mixture of o-phenylenediamine **1** (1 mmol), 4-(prop-2-ynyloxy)benzaldehyde **2** (1 mmol), and $Na_2S_2O_5$ (1.1 mmol) in DMF (15 mL) was stirred at 100 °C for 2 h. Then, the reaction mixture was poured in the water and obtained product **3** was filtered off.

*4.2. General Procedure for the Synthesis of N-phenyl (or benzyl)-2-chloroacetamides **6a-n***

A solution of amines **4a-n** (1mmol) and chloroacetyl chloride **5** (1.1 mmol) in DMF (15 mL) was stirred at RT for 30 min. Then, the mixture was diluted with cold water, poured into ice, and the obtained precipitates were filtered off. The residue was washed with water to obtain pure *N*-phenyl (or benzyl)-2-chloroacetamide **6a-n**.

*4.3. General Procedure for the Synthesis of azide derivatives **7a-n***

In order to do a click reaction, azide derivatives **7a-n** were prepared in situ of reaction between *N*-phenyl (or benzyl)-2-chloroacetamide **6a-n** (1.1 mmol), sodium azide (0.9 mmol), and Et_3N (1.3 mmol) in the mixture of H_2O and t-BuOH(10 mL, 1:1) at RT for 1 h.

*4.4. General Procedure for the Synthesis of benzimidazole-1,2,3-triazole-acetamides **8a-n***

A mixture of 2-(4-(prop-2-ynyloxy)phenyl)-1H-benzo[d]imidazole **3** (1 mmol), sodium ascorbate, and $CuSO_4.5H_2O$ (7 mol %) was added to the azide derivatives **7a-n**, and obtained mixture was stirred at RT for 18-24 h. After that, reaction mixture was poured into crushed ice and precipitated products **8a-n** were filtered off, washed with water, and purified by recrystallization in ethyl acetate.

*4.4.1. 2-(4-((4-(1H-benzo[d]imidazol-2-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-phenylacetamide **8a***

White powder; Yield: 77%; mp =166–168 °C. IR (KBr): 3698, 1702, 1602 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): 5.28 (2H, s, CH_2-O), 5.37 (2H, s,CH_2), 7.15-7.19 (3H, m, Hα, H4), 7.24 (2H, d, *J* = 8.5Hz, H3, H5), 7.34 (2H, dd, *J* = 7.5, 6 Hz, Hb', Hc'), 7.58 (2H, d, *J* = 7.5 Hz, H2, H6), 7.62 (2H, d, *J* = 6 Hz, Ha', Hd'), 8.12 (2H, d, *J* = 8 Hz, Hβ), 8.31 (1H, s, H-triazole), 10.49 (1H, s, NH), 12.75 (1H, s, NH). ^{13}C NMR (125 MHz, DMSO-d_6): 58.2, 66.7, 111.3, 1116.7, 121.6, 126.3, 127.6, 128.5, 128.7, 129.1, 130.3, 130.4, 131.0, 132.5, 135.2, 135.7, 142.9, 150.8, 157.3, 163.5. Anal. Calcd for $C_{24}H_{20}N_6O_2$: C, 67.91; H, 4.75; N, 19.80. Found: C, 67.83; H, 4.68; N, 19.92.

*4.4.2. 2-(4-((4-(1H-benzo[d]imidazol-2-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(p-tolyl)acetamide **8b***

White powder; yield: 80%; mp =164–166 °C. IR (KBr): 3398, 3766, 1709, 1605 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): 2.59 (3H, s, CH_3), 5.28 (2H, s, CH_2-O), 5.38 (2H, s, CH_2), 7.13 (2H, d, *J*

= 8.5 Hz, Hα), 7.18 (2H, m, , Hb', Hc'), 7.25 (2H, d, *J* = 7 Hz, H3, H5), 7.47 (2H, d, *J* = 8 Hz, H2, H6), 7.57 (2H, m, Ha', Hd'), 8.13 (2H, d, *J* = 8Hz, Hβ), 8.30 (1H, s, H-triazole), 10.4 (1H, s, NH), 10.64 (1H, s, NH). ^{13}C NMR (125 MHz, DMSO-d_6): 20.0, 58.1, 65.5, 113.5, 114.9, 116.1, 118.7, 124.5, 126.3, 127.5, 128.1, 128.2, 129.4, 131.8, 134.2, 136.9, 143.1, 150.7, 157.1, 165.0. Anal. Calcd for $C_{25}H_{22}N_6O_2$: C, 68.48; H, 5.06; N, 19.17. Found: C, 68.57; H, 7.92; N, 19.27.

4.4.3. 2-(4-((4-(1H-benzo[d]imidazol-2-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(4-ethylphenyl)acetamide ***8c***

Cream powder; yield: 75%; mp =151–153 °C. IR (KBr): 3298, 38764, 1702, 1562 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): 1.15 (3H, t, *J* = 6 Hz, CH_3), 2.56 (2H, m, CH_2), 5.28 (2H, s, CH_2-O), 5.35 (2H, s, CH_2), 7.17 (4H, m, Hα, H3, H5), 7.24 (2H, d, *J* = 7 Hz, Hb', Hc'), 7.48 (3H, m, H2, H6, Hd' or Ha'), 7.62 (1H, d, *J* = 7 Hz, Ha' or Hd'), 8.12 (2H, d, *J* = 7Hz, Hβ), 8.30 (1H, s, H-triazole), 10.42 (1H, s, NH), 12.77 (1H, s, NH). ^{13}C NMR (125 MHz, DMSO-d_6): 16.4, 28.6, 56.3, 63.2, 115.4, 116.7, 118.8, 122.4, 122.8, 124.3, 125.3, 126.6, 128.5, 129.4, 132.0, 133.0, 139.7, 141.6, 149.4, 157.8, 166.4. Anal. Calcd for $C_{26}H_{24}N_6O_2$: C, 69.01; H, 5.35; N, 18.57. Found: C, 68.89; H, 5.43; N, 18.71.

4.4.4. 2-(4-((4-(1H-benzo[d]imidazol-2-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(4-methoxyphenyl)acetamide ***8d***

White powder; yield: 83%; mp =170–172 °C. IR (KBr): 3198, 3866, 1708, 1602 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): 3.74 (3H,s, -OCH_3), 5.28 (2H, s, CH_2-O), 5.38 (2H, s, CH_2), 7.18 (2H, bs, Hα), 7.25 (2H, d, *J* = 7.5 Hz, H3, H5), 7.50 (2H, d, *J* = 8 Hz, H2, H6), 7.57 (2H, bs, Ha', Hd'), 8.13 (2H, d, *J* = 7.5Hz, Hβ), 8.30 (1H, s, H-triazole), 10.87 (1H, s, NH), 10.64 (1H, s, NH). ^{13}C

NMR (125 MHz, DMSO-d_6): 55.2, 56.2, 65.4, 111.4, 116.3, 118.7, 120.7, 122.6, 125.8, 126.3, 126.6, 127.6, 128.2, 128.8, 129.3, 129.6, 134.3, 139.9, 141.8, 150.9, 157.0, 158.5, 164.8. Anal. Calcd for $C_{25}H_{22}N_6O_3$: C, 66.07; H, 4.88; N, 18.49. Found: C, 66.16; H, 4.72; N, 18.63.

4.4.5. 2-(4-((4-(1H-benzo[d]imidazol-2-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(2-chlorophenyl)acetamide ***8e***

Pale yellow powder; yield: 72%; mp =190–192 °C. IR (KBr): 3392, 3566, 1708, 1602 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): 5.28 (2H, s, CH_2-O), 5.48 (2H, s, CH_2-), 7.18 (3H, m, Hα, H6), 7.23 (3H, m, Hb', Hc', H4), 7.35 (1H, dd, J = 8, 6 Hz, H5), 7.53 (2H, d, J = 8 Hz, Ha', Hd'), 7.74 (1H, d, J = 8.5 Hz, H6), 8.12 (2H, d, J = 9Hz, Hβ), 8.31(1H, s, H-triazole), 10.11 (1H, s, NH), 12.73 (1H, s, NH). ^{13}C NMR (125 MHz, DMSO-d_6): 56.3, 65.9, 111.6, 112.6, 117.1, 119.2, 122.9, 126.6, 127.1, 128.9, 129.5, 129.9, 132.2, 135.4, 135.8, 139.1, 143.1, 149.7, 157.4, 165.5. Anal. Calcd for $C_{24}H_{19}ClN_6O_2$: C, 62.81; H, 4.17; N, 18.31. Found: C, 62.98; H, 4.23; N, 18.52.

4.4.6. 2-(4-((4-(1H-benzo[d]imidazol-2-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(2,3-dichlorophenyl)acetamide ***8f***

White powder; yield: 75%; mp =150–152 °C. IR (KBr): 3776, 1701, 1630 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): 5.29 (2H, s, CH_2-O), 5.50 (2H, s,CH_2), 7.18 (2H, m, Hα), 7.25 (2H, d, J = 8 Hz, Hb', Hc',), 7.38 (1H, dd, J = 8.5, 8 Hz, H3), 7.50 (1H, d, J = 7.5 Hz, H4), 7.56 (2H, m, Ha', Hd'), 7.74 (1H, d, J = 8 Hz, H2), 8.13 (2H, d, J = 8.5 Hz, Hβ), 8.31 (1H, s, H-triazole), 10.27 (1H, s, NH), 12.69 (1H, s, NH). ^{13}C NMR (125 MHz, DMSO-d_6): 55.6, 64.9, 111.4, 116.8, 118.8, 121.5, 122.3, 123.3, 124.6, 126.5, 126.6, 128.1, 128.6, 129.0, 129.4, 131.5, 132.0, 133.2, 139.7, 142.5, 149.5, 157.2, 164.2. Anal. Calcd for $C_{24}H_{18}Cl_2N_6O_2$: C, 58.43; H, 3.68; N, 17.03. Found: C, 58.32; H, 3.51; N, 17.11.

4.4.7. 2-(4-((4-(1H-benzo[d]imidazol-2-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(2,6-dichlorophenyl)acetamide ***8g***

Cream powder; yield: 74%; mp =199–201 °C. IR (KBr): 3744, 1680 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): 5.28 (2H, s, CH_2-O), 5.41 (2H, s, CH_2), 7.17 (2H, m, Hα), 7.24 (2H, d, J = 8.5 Hz, Hb', Hc'), 7.34 (1H, m, H4), 7.57 (2H, m, H3, H5), 7.64 (2H, m, Ha', Hd'), 8.13 (2H, d, J = 8.5 Hz, Hβ), 8.31 (1H, s, H-triazole), 10.86 (1H, s, NH), 12.77 (1H, s, NH). ^{13}C NMR (125 MHz, DMSO-d_6): 58.9, 65.8, 111.3, 116.5, 116.9, 124.0, 126.2, 127.6, 128.4, 128.6, 129.2, 130.9, 133.1, 135.1, 135.2, 135.7, 137.1, 143.2, 151.3, 158.8, 163.4. Anal. Calcd for $C_{24}H_{18}Cl_2N_6O_2$: C, 58.43; H, 3.68; N, 17.03. Found: C, 58.54; H, 3.73; N, 16.91.

4.4.8. 2-(4-((4-(1H-benzo[d]imidazol-2-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(4-chlorophenyl)acetamide ***8h***

White powder; yield: 69%; mp =176–178 °C. IR (KBr): 3398, 3766, 1718, 1610 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): 5.28 (2H, s, CH_2-O), 5.38 (2H, s,CH_2), 7.19 (2H, m, H α), 7.24 (2H, d, J = 7 Hz, Hb', Hc'), 7.40 (2H, d, J = 8 Hz, H3, H5), 7.56 (2H, m, H2, H6), 7.61 (2H, d, J = 7.5 Hz, Ha', Hd'), 8.13 (2H, d, J = 8 Hz, Hβ), 8.31(1H, s, H-triazole), 9.95 (1H, s, NH), 10.64 (1H, s, NH). ^{13}C NMR (125 MHz, DMSO-d_6): 58.5, 64.5, 113.9, 114.9, 115.6, 118.8, 122.4, 125.0, 126.6, 127.2, 128.4, 128.9, 129.4, 131.2, 131.9, 133.0, 137.1, 139.7, 143.0, 149.5, 157.2, 164.8. Anal. Calcd for $C_{24}H_{19}ClN_6O_2$: C, 62.81; H, 4.17; N, 18.31. Found: C, 62.72; H, 4.05; N, 18.22.

4.4.9. 2-(4-((4-(1H-benzo[d]imidazol-2-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(3-bromophenyl)acetamide ***8i***

Yellow powder; yield: 74%; mp =182–184 °C. IR (KBr): 3198, 3866, 1708, 1600 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): 5.28 (2H, s, CH_2-O), 5.39 (2H, s,CH_2), 7.17 (2H, m, Hα), 7.24 (2H,d, J =

7.5 Hz, H5, H6), 7.30 (3H, m, Hb', Hc'), 7.49 (2H, m, H4, Ha' or Hd'), 7.62 (1H, d, *J* = 7 Hz, Ha' or Hd'),7.93 (1H, s, H2), 8.12 (2H, d, *J* = 8.5 Hz, Hβ), 8.3 (1H, s, H-triazole), 10.68 (1H, s, NH), 12.73 (1H, s, NH). ^{13}C NMR (125 MHz, DMSO-d_6): 56.1, 65.5, 111.4, 116.3, 116.7, 118.7, 122.8, 123.9, 125.2, 126.4, 127.6, 128.0, 128.3, 128.9, 129.4, 130.0, 130.8, 134.2, 139.8, 141.7, 150.4, 166.3. Anal. Calcd for $C_{24}H_{19}BrN_6O_2$: C, 57.27; H, 3.80; N, 16.70. Found: C, 57.15; H, 3.68; N, 16.84.

4.4.10. 2-(4-((4-(1H-benzo[d]imidazol-2-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(4-bromophenyl)acetamide ***8j***

White powder; yield: 75%; mp =194–196 °C. IR (KBr): 3760, 3292, 1717, 1560 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): 5.28 (2H, s, CH_2-O), 5.38 (2H, s,CH_2), 7.17 (2H, m, Hα), 7.24 (2H, d, *J* = 8.5 Hz, Hb', Hc'), 7.52-7.57 (6H, m, H2, H3, H5, H6, Ha', Hd'), 8.12 (2H, d, *J* = 8Hz, Hβ), 8.33 (1H, s, H-triazole), 10.61(1H, s, NH), 12.78 (1H, s, NH). ^{13}C NMR (125 MHz, DMSO-d_6): 55.5, 64.6, 111.3, 116.9, 118.8, 121.6, 123.2, 124.6, 126.3, 127.5, 128.2, 128.3, 129.0, 129.4, 134.4, 139.9, 142.5, 150.7, 156.2, 166.6. Anal. Calcd for $C_{24}H_{19}BrN_6O_2$: C, 57.27; H, 3.80; N, 16.70. Found: C, 57.33; H, 3.96; N, 16.57.

4.4.11. 2-(4-((4-(1H-benzo[d]imidazol-2-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(2-nitrophenyl)acetamide ***8k***

Pale yellow powder; yield: 88%; mp =187–189 °C. IR (KBr): 3766, 1704, 1562 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): 5.28 (2H, s, CH_2-O), 5.476 (2H, s,CH_2), 7.17 (2H, m, Hα), 7.23 (2H, d, *J* = 9 Hz, Hb', Hc'), 7.33 (2H, dd, *J* = 9, 7.5 Hz, H4, H5), 7.50 (1H, m, Ha' or Hd'), 7.69 (1H, d, *J* = 7.5 Hz, Ha' or Hd'), 7.75 (1H, dd, *J* = 7.5, 6 Hz, H3), 8.00 (1H, d, *J* = 8 Hz, H6), 8.12 (2H, d, *J* = 8 Hz, Hβ), 8.28 (1H, s, H-triazole), 10.78 (1H, s, NH), 12.76 (1H, s, NH). ^{13}C NMR (125 MHz,

DMSO-d_6): 55.8, 64.1, 111.3, 113.4, 116.8, 116.9, 118.7, 122.3, 123.6, 124.2, 126.5, 128.2, 129.01, 132.0, 132.2, 133.2, 139.7, 142.3, 149.4, 158.3, 165.5. Anal. Calcd for $C_{24}H_{19}N_7O_4$: C, 61.40; H, 4.08; N, 20.89. Found: C, 61.57; H, 4.17; N, 20.78.

4.4.12. 2-(4-((4-(1H-benzo[d]imidazol-2-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(4-nitrophenyl)acetamide ***8l***

Yellow powder; yield: 90%; mp =156–158 °C. IR (KBr): 3746, 1702 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): 5.29 (2H, s, CH_2-O), 5.47 (2H, s, CH_2), 7.18 (2H, bs, Hα), 7.25 (2H, d, J = 8.5 Hz, Hb', Hc'), 7.57 (2H, m, Ha', Hd'), 7.83 (2H, d, J = 8.5 Hz, H2, H6), 8.13 (2H, d, J = 8 Hz, Hβ), 8.26 (2H, d, J = 9 Hz, H3, H5), 8.33 (1H, s, H-triazole), 11.1 (1H, s, NH), 12.80 (1H, s, NH). ^{13}C NMR (125 MHz, DMSO-d_6): 55.6, 65.4, 111.3, 116.5, 116.7, 118.7, 123.6, 124.1, 124.4, 126.3, 127.5, 128.2, 129.0, 129.3, 134.4, 139.8, 142.2, 150.6, 157.3, 164.7. Anal. Calcd for $C_{24}H_{19}N_7O_4$: C, 61.40; H, 4.08; N, 20.89. Found: C, 61.29; H, 3.94; N, 20.97.

4.4.13. 2-(4-((4-(1H-benzo[d]imidazol-2-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-benzylacetamide ***8m***

Cream powder; yield: 83%; mp =155–158 °C. IR (KBr): 3396, 3566, 1700, 1607 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): 4.32 (2H, s, CH_2), 5.20 (2H, s, CH_2-O), 5.25 (2H, s, CH_2-), 7.16 (2H, m, Hα), 7.22 (2H, d, J = 8 Hz, H2, H6), 7.26-7.29 (3H, m, Hb', Hc',H4), 7.33 (2H, m, H3, H5), 7.48 (1H, bs, Ha' or Hd'), 7.61 (1H, bs, Ha' or Hd'), 8.11 (2H, d, J = 8 Hz, Hβ), 8.25 (1H, s, H-triazole), 8.89 (1H, s, NH), 12.7 (1H, s, NH), 10.64 (1H, s, NH). ^{13}C NMR (125 MHz, DMSO-d_6): 400, 56.3, 65.5, 111.6, 115.9, 118.8, 120.7, 122.2, 122.9, 125.9, 126.5, 126.7, 128.4, 129.1, 129.3, 131.8,

133.0, 139.8, 142.1, 149.4, 157.7, 165.0. Anal. Calcd for $C_{25}H_{22}N_6O_2$: C, 68.48; H, 5.06; N, 19.17. Found: C, 68.56; H, 5.17; N, 19.31.

4.4.14. 2-(4-((4-(1H-benzo[d]imidazol-2-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(4-fluorobenzyl)acetamide ***8n***

White powder; yield: 74%; mp =175–177 °C. IR (KBr): 3700, 1703, 1562 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): 4.32 (2H,s, CH_2), 5.20 (2H, s, CH_2-O), 5.26 (2H, s, CH_2), 7.15-7.18 (4H, m, H α, H3, H4), 7.23 (2H, d, J = 8 Hz, Hb', Hc') 7.32-7.34 (2H, m, H2, H6), 7.49 (1H, d, J = 6.5 Hz , Ha' or Hd'), 7.62 (1H, d, J = 8.5 Hz, Ha' or Hd'), 8.12 (2H, d, J = 8 Hz, Hβ),8.25 (1H, s, triazole), 8.85 (1H, s, H-triazole), 12.75 (1H, s, NH). ^{13}C NMR (125 MHz, DMSO-d_6): 42.0, 52.1, 61.4, 1111.4, 113.4, 115.4, 115.5, 115.6, 118.9, 121.8, 122.5, 123.4, 126.6, 128.4, 129.8, 129.9, 135.1, 135.3, 142.4, 144.3, 151.6, 159.8, 160.5, 162.5, 165.8. Anal. Calcd for $C_{25}H_{21}FN_6O_2$: C, 65.78; H, 4.64; N, 18.41. Found: C, 65.66; H, 4.51; N, 18.62.

4.5. α-Glucosidase inhibition assay

The anti-α-glucosidase effects of benzimidazole-1,2,3-triazoles **8a-n** were screened according to the previously reported method [12]. Firstly, 135 μL of potassium phosphate buffer, 20 μL of target compounds **8a-n** with various concentrations, and 20 μL of α-glucosidase solution were added and incubated in the 96-well microtiter plate for 10 min at 37 °C. Then, p-nitrophenyl glucopyranoside as substrate (25 μL, 4 mM) was added to the incubated mixture and incubation was continued at 37 °C for 20 min. Finally, absorbance was measured at 405 nm by spectrophotometer (Gen5, Power wave xs2, BioTek, USA), and IC_{50} values of target compounds were calculated using the nonlinear regression curve (logit method).

4.6. Kinetics of enzyme inhibition

A kinetic analysis was conducted to determine the type of inhibition of the most potent compound **8c**. To this end, 20 µL of the α-glucosidase solution (1 U/mL) was incubated with concentrations 0, 11, 18, and 25 µM of inhibitor **8c** for 10 min at 37 °C. After that, the enzymatic reaction was initiated by adding concentrations 1–4 mM of the substrate. Changes in absorbance were measured at 405 nm for 20 min on a microtiter plate reader (Gen5, Power wave xs2, BioTek, USA).

4.7. Docking study

The docking study of the selected compounds **8b-c**, **8k-l**, **8a** and **8m**, and **8e-f** in the active site of modeled α-glucosidase was performed by AutoDock Tools, according to previously described method [14]. For this propose, modeled α-glucosidase was constructed based on SWISS-MODEL. After that, the PDBQT coordinate of the modeled α-glucosidase, acarbose, and the selected compounds (as input files for the AutoGrid program) were produced using the AutoDock Tools. In AutoGrid program for each atom type of the inhibitors, maps were determined with 0.375 Å spacing between grid box with center box: x = 12.5825, y = 7.8955, z = 12.519 and the dimensions: 40 × 40 × 40 Å. Flexible ligand dockings for the each of selected inhibitor were accomplished. Each docked system was carried out by 50 runs, and the best pose of each inhibitor was selected for analyzing the interactions in the active site. The obtained results were visualized using Discovery Studio 4.0 Client.

4.8. In vitro α-amylase inhibition assay

The anti-α-amylase activity of the compounds **8c**, **8k**, and **8a** was determined based on the colorimetric method, according to described method by Taha et al. [16].

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Dear Editor

There is no conflict of interest in this research article

Graphical abstract

Synthesis and biological evaluation of new benzimidazole-1,2,3-triazole hybrids as potential α-glucosidase inhibitors

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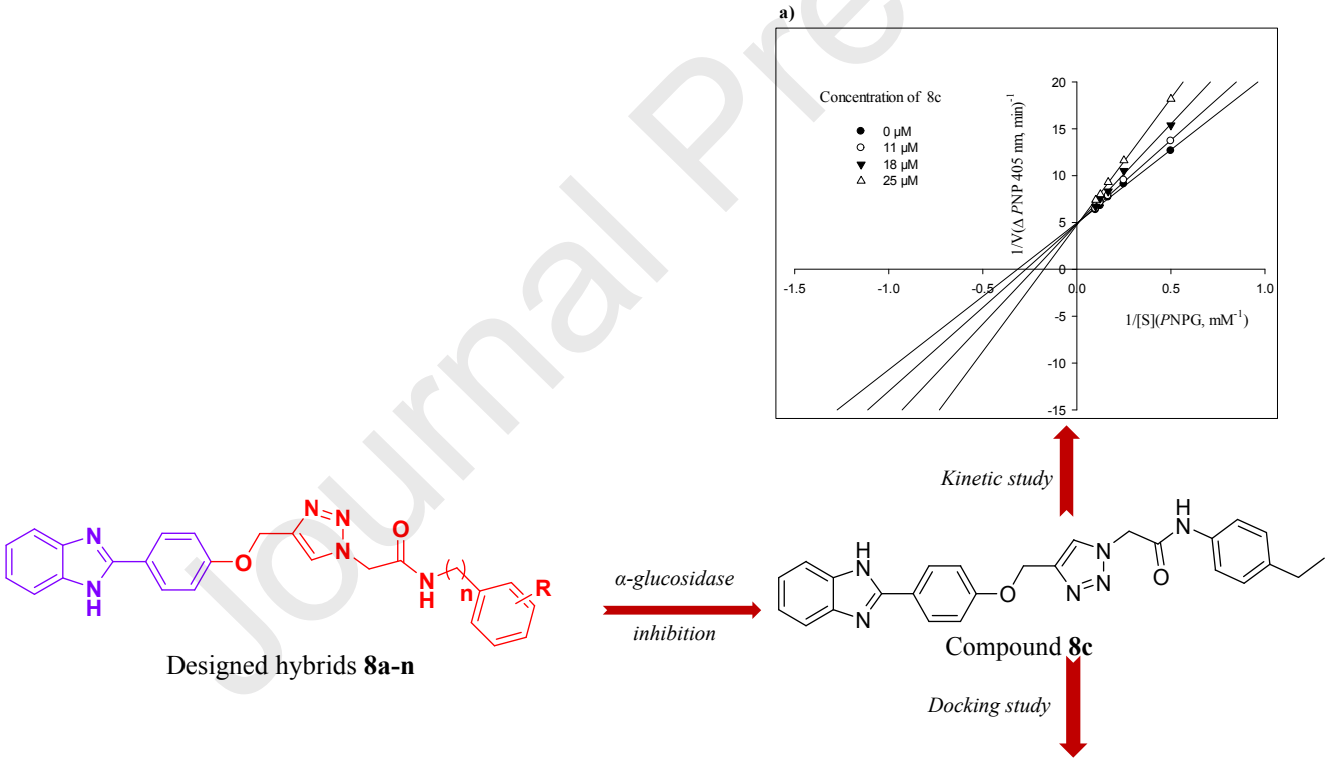

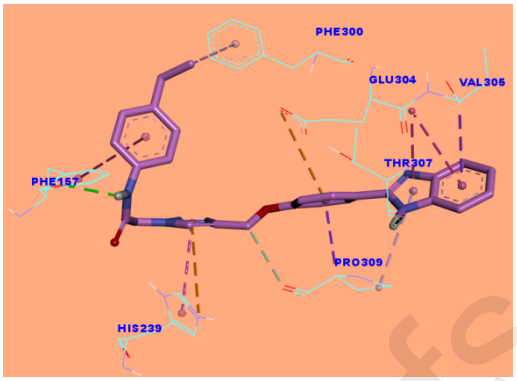

A novel series of benzimidazole-1,2,3-triazole hybrids **8a-n** was were synthesized by click chemistry and evaluated as potent α-glucosidase inhibitors. All the synthesized compounds showed anti-α-glucosidase activity more than standard inhibitor acarbose.

Highlights

- A novel series of benzimidazole-1,2,3-triazole-acetamide hybrids **8a-n** was synthesized and evaluated as potent α-glucosidase inhibitors.
- These compounds were synthesized by click reaction.
- All the title compounds showed α-glucosidase inhibition superior to standard drug acarbose.
- Compound **8c** with *N*-4-ethylphenylacetamide was the most active compound (IC_{50} = 25.2 ± 0.9).
- This compound was a competitive inhibitor against α-glucosidase (K_i = 23 µM).