Molecular Diversity
https://doi.org/10.1007/s11030-020-10072-8

ORIGINAL ARTICLE

Design and synthesis of 4,5-diphenyl-imidazol-1,2,3-triazole hybrids as new anti-diabetic agents: in vitro *α*-glucosidase inhibition, kinetic and docking studies

Mohammad Sadegh Asgari[1] · Maryam Mohammadi-Khanaposhtani[2] · Zeinab Sharafi[3] · Mohammad Ali Faramarzi[4] · Hossein Rastegar[5] · Ensieh Nasli Esfahani[6] · Fatemeh Bandarian[6] · Parviz Ranjbar Rashidi[1] · Rahmatollah Rahimi[7] · Mahmood Biglar[8] · Mohammad Mahdavi[8] · Bagher Larijani[8]

Received: 24 April 2019 / Accepted: 9 March 2020

Abstract

Fourteen novel 4,5-diphenyl-imidazol-1,2,3-triazole hybrids **8a**–**n** were synthesized with good yields by performing click reaction between the 4,5-diphenyl-2-(prop-2-yn-1-ylthio)-1H-imidazole and various benzyl azides. The synthesized compounds **8a**–**n** were evaluated against yeast α-glucosidase, and all these compounds exhibited excellent inhibitory activity (IC_{50} values in the range of 85.6 ± 0.4–231.4 ± 1.0 μM), even much more potent than standard drug acarbose (IC_{50} = 750.0 μM). Among them, 4,5-diphenyl-imidazol-1,2,3-triazoles possessing 2-chloro and 2-bromo-benzyl moieties (compounds **8g** and **8i**) demonstrated the most potent inhibitory activities toward α-glucosidase. The kinetic study of the compound **8g** revealed that this compound inhibited α-glucosidase in a competitive mode. Furthermore, docking calculations of these compounds were performed to predict the interaction mode of the synthesized compounds in the active site of α-glucosidase.

Graphic abstract

A novel series of 4,5-diphenyl-imidazol-1,2,3-triazole hybrids **8a**–**n** was synthesized with goodyields by performing click reaction between the 4,5-diphenyl-2-(prop-2-yn-1-ylthio)-1Himidazoleand various benzyl azides. The synthesized compounds

Mohammad Sadegh Asgari and Maryam Mohammadi-Khanaposhtani contributed equally to this work.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11030-020-10072-8) contains supplementary material, which is available to authorized users.

✉ Mohammad Mahdavi
Mahdavi_chem@yahoo.com

✉ Bagher Larijani
emrc@tums.ac.ir

1 School of Chemistry, College of Science, University of Tehran, Tehran, Iran

2 Cellular and Molecular Biology Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran

3 Razi Herbal Medicines Research Center, Lorestan University of Medical Sciences, Khorramabad, Iran

4 Department of Pharmaceutical Biotechnology, Faculty of Pharmacy and Biotechnology Research Center, Tehran University of Medical Sciences, Tehran, Iran

5 Food and Drug Research Institute, Food and Drug Administration, MOHE, Tehran, Iran

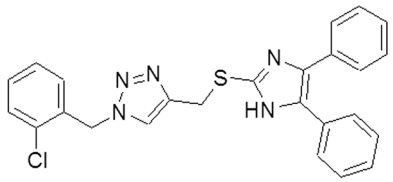
6 Diabetes Research Center, Endocrinology and Metabolism Clinical Sciences Institute, University of Medical Sciences, Tehran, Iran

7 Department of Chemistry, Iran University of Science and Technology, Tehran, Iran

8 Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

Published online: 18 March 2020

8a–**n** were evaluated againstyeast α-glucosidase and all these compounds exhibited excellent inhibitory activity (IC50 valuesin the range of 85.6 ± 0.4-231.4 ± 1.0 µM), even much more potent than standard drug acarbose(IC50 = 750.0 µM).

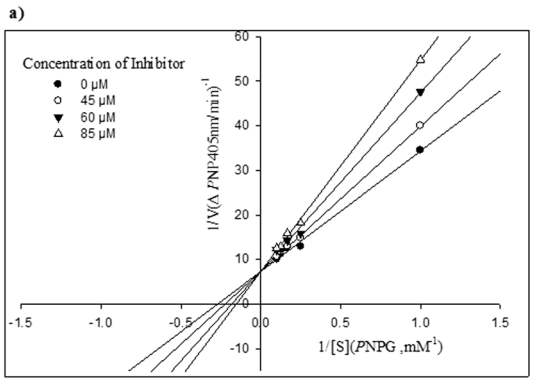


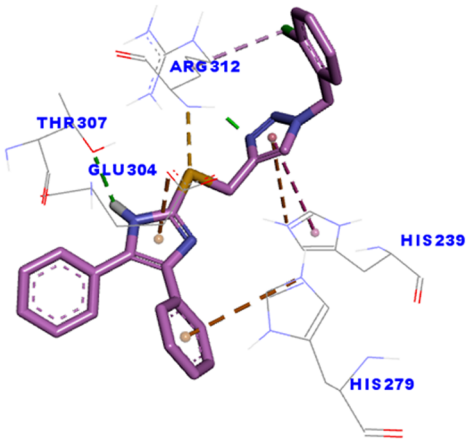
Compound **8g**

IC_{50} (α-glucosidase) = 85.6± 0.4 µM

Competitive inhibition

Docking pose





Keywords Anti-diabetic agents · Kinetic study · α-Glucosidase · Molecular docking · 4,5-Diphenyl-imidazol,1,2,3-triazole

Introduction

α-Glucosidase (EC 3.2.1.20) is a carbohydrate-hydrolyzing enzyme that catalytic activity of it resulted in cleavage of poly- and disaccharides to glucose. Therefore, inhibition of this enzyme decreases postprandial blood glucose level. Several effective glucosidic-based α-glucosidase inhibitors such as acarbose [1], voglibose [2], miglitol [3], and nojirimycin, [4] are clinically used for the treatment of type 2 diabetes. These agents suffer from side effects such as flatulence, meteorism, abdominal distension, and diarrhea [5]. Recently, the design and development of non-glucosidic-based α-glucosidase inhibitors have received attention in order to achieve more effective and safer α-glucosidase inhibitors [6, 7].

1,2,3-Triazole ring has a undeniable importance in medicinal chemistry due to having unique features such as metabolic stability, high dipole moment, and capability to form hydrogen bonds [8, 9]. The construction of this ring by click chemistry as an efficient method has led to increasing the development of biological active compounds containing 1,2,3-triazole ring [10]. The antibacterial, anticancer, antifungal, antitubercular, anti-acetylcholinesterase, and anti-HIV activities of 1,2,3-triazole derivatives have been well documented [10–16]. Furthermore, several hybrid scaffolds containing 1,2,3-triazole ring with high inhibitory activity against α-glucosidase have been reported (Fig. 1a, b) [17, 18]. In this regard, recently, we reported the synthesis and α-glucosidase inhibitory activity of 1,2,3-triazole-quinazolinone hybrids **C** (Fig. 1) [19]. On the other hand, several derivatives of imidazole with excellent α-glucosidase

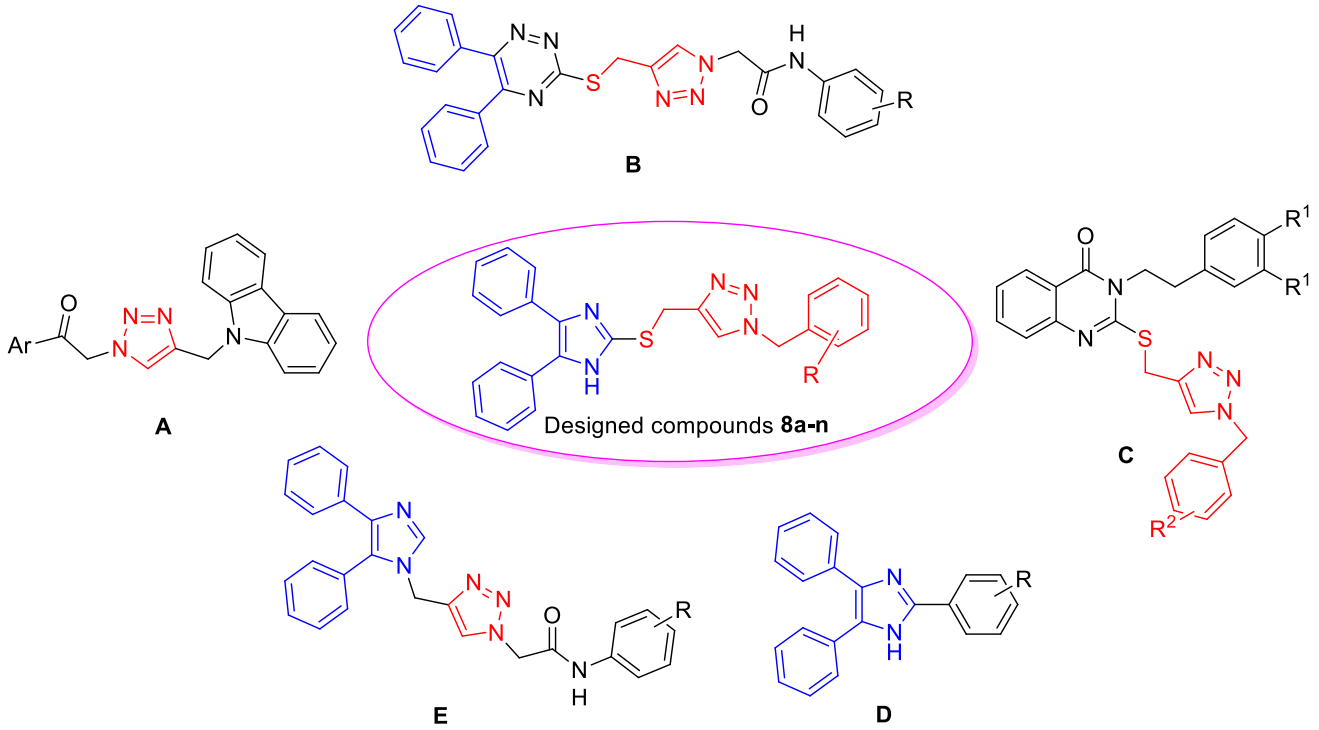


Fig. 1 Several potent α-glucosidase inhibitors containing 1,2,3-triazole (**a**–**c**) or imidazole (**e**–**d**) and designed derivatives **8a**–**n** as new α-glucosidase inhibitors

inhibitory activity have been reported (Fig. 1) [20]. For example, 2,4,5-triarylimidazoles **D** and 2,4,5-triarylimidazole-1,2,3-triazole hybrids **E** are potent inhibitors against α-glucosidase (Fig. 1) [21]. Based on the mentioned points and in continuation of our interest in the synthesis of new α-glucosidase inhibitors, herein, we reported the design of a novel series of 4,5-diarylimidazole-1,2,3-triazole hybrids **8a**–**n** [22–24]. These compounds were synthesized by click reaction and evaluated against α-glucosidase. Furthermore, kinetic and docking studies were also performed to understand the inhibition modes of these compounds against α-glucosidase.

Results and discussion

Chemistry

The synthetic route for the synthesis of 4,5-diphenyl-imidazol-1,2,3-triazole hybrids **8a**–**n** is depicted in Scheme 1. It was started from the reaction between 2-hydroxy-1,2-diphenylethanone **1** and thiourea **2** in DMF at 100 °C for 3 h to give 4,5-diphenyl-1H-imidazole-2-thiol **3**. The latter compound reacted with propargyl bromide **4** in the presence of potassium carbonate in acetone at 0–10 °C for 5 min to give 4,5-diphenyl-2-(prop-2-yn-1-ylthio)-1H-imidazole **5**. On the other hand, different benzyl halides **6** and sodium azide reacted in the presence of Et_3N in the mixture of H_2O/t-BuOH at room temperature for 1 h. Finally, mixture of 4,5-diphenyl-2-(prop-2-yn-1-ylthio)-1H-imidazole **5**, $CuSO_4$, and sodium ascorbate was added to the freshly prepared azide derivatives **7** and the reaction was continued at room temperature for 24 h to give the corresponding compounds **8a**–**n**.

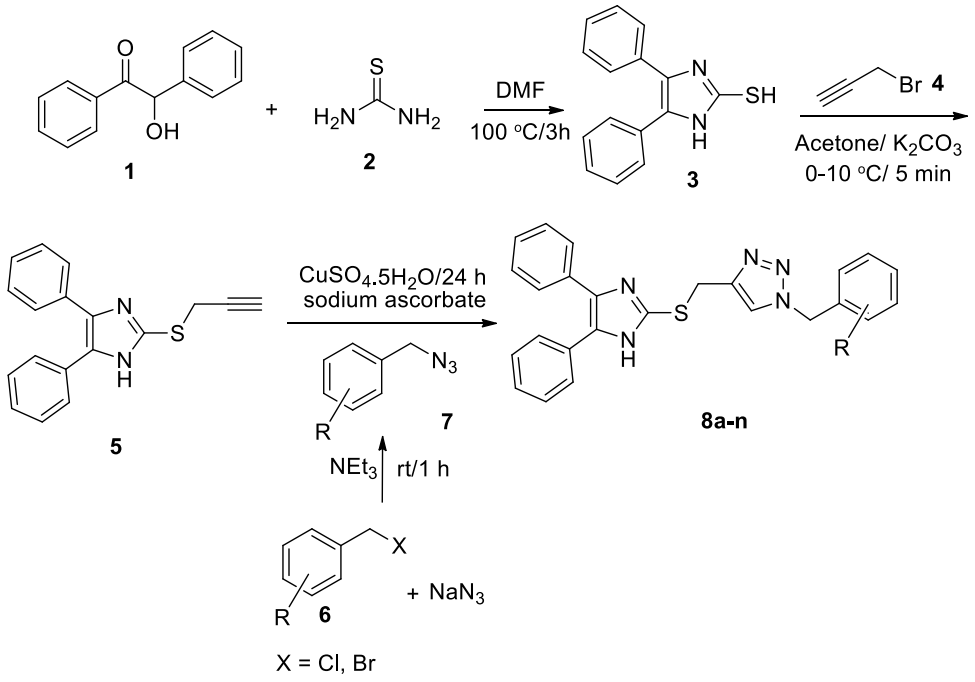
Biological study

In vitro α-glucosidase inhibitory activity

The synthesized compounds **8a**–**n** were screened for their in vitro inhibitory activities against α-glucosidase in comparison with the standard inhibitor acarbose. The obtained results were expressed as mean ± S.E. of three independent experiments. The IC_{50} values of the target compounds demonstrated that all the synthesized compounds showed significant inhibition against α-glucosidase at concentrations less than 231.4 ± 1.0 µM, while acarbose showed IC_{50} = 750.0 ± 1.5.

In order to obtain an optimized α-glucosidase inhibitor, the substituent was altered on the pendant phenyl moiety. The most active compounds were 2-chloro, 2-bromo, 2-fluoro, 2-methyl derivatives (the compounds **8g**, **8i**, **8d**, and **8b**, respectively) with IC_{50} values ≤ 95.2 ± 0.4 µM.

Scheme 1 Synthesis of 4,5-diphenyl-imidazol-1,2,3-triazole hybrids **8a**–**n**



The IC_{50} value of the un-substituted compound **8a** was 173.4 ± 0.7. The introduction of methyl, fluoro, chloro, and bromo substituents on the 2-position of the pendant phenyl group led to around twofold increase in the inhibitory activity, as observed in the compounds **8b**, **8d**, **8g**, and **8i**. Movement of the mentioned substituents to the 3 or 4-position on the pendant phenyl group, as in the compounds **8e**, **8f**, **8h**, **8j**, and **8k,** led to a decrease in the inhibitory activity in comparison with their 2-substituted regioisomers. Interestingly, the inhibitory activities of the 3-substituted compound **8c** with the electron-donating group (methoxy) and **8m** with the electron-withdrawing group (nitro) were more than those of the un-substituted compound **8a**. On the other hand, the weakest compounds among the synthesized compounds were 2-nitro and 4-nitro derivatives **8l** and **8n**. From the obtained results, it can be ascertained that the type and position of the substituents in the pendant phenyl group play a significant role in the inhibitory activity of the synthesized compounds.

Kinetic study

The kinetic study of the most active compound **8g** against α-glucosidase was performed in order to determine the inhibition mode of the synthesized compounds. As can be observed in Fig. 2a, the Lineweaver–Burk plot showed that

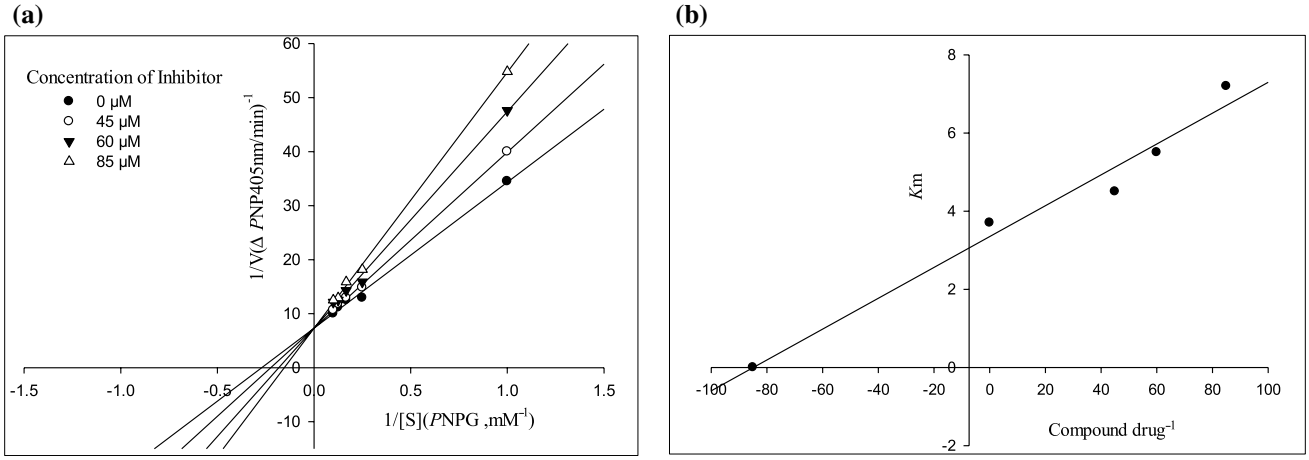


Fig. 2 Kinetic study of compound **8g** against α-glucosidase. **a** The Lineweaver–Burk plot in the absence and presence of different concentrations of compound **8g**; **b** the secondary plot between K_m and various concentrations of compound **8g**

with increase in the concentration of the compound **8g**, the K_m gradually increased, while V_{max} remained unchanged. This finding demonstrated that the compound **8g** was a competitive inhibitor to α-glucosidase. The K_i value of this compound was calculated as 85 μM through the secondary re-plot of the obtained Lineweaver–Burk plots (Fig. 2b).

Molecular modeling study

To clarify the interaction mode of the synthesized compounds in the active site of α-glucosidase and explain the different activities of these compounds, molecular modeling studies were conducted using Auto Dock Tools (version 1.5.6) on the modeled α-glucosidase [25]. Acarbose as a standard inhibitor and compounds **8d**–**e**, and **8g**–**i** were docked in the modeled α-glucosidase. The superposed structure of acarbose and the most potent compound **8g** in the active site of enzyme is shown in Fig. 3. Molecular modeling of the standard inhibitor acarbose predicted that this drug interacted with Asn241, His279, Thr301, Glu304, Thr307, Ser308, Pro309, Arg312, and Gln322 residues (Fig. 4) [25].

The 2-chloro substituent of the most active compound **8g** formed hydrophobic interactions with Phe311, Tyr313, and Arg312 (Fig. 4). The latter residue also created a hydrophobic interaction with pendant phenyl ring, an interaction with sulfur atom, and two interaction with 1,2,3-triazol ring (a hydrogen bond and a hydrophobic interaction). In addition, 1,2,3-triazol also interacted with His239 through a π–π interaction and a π-cation interaction. Imidazole moiety formed a hydrogen bond with Thr307 and a π-anion with Glu304. Moreover, one of the phenyl rings attached to imidazole moiety interacted with residue His279 via a π-cation interaction. Comparison of interaction modes of acarbose and compound **8g** in the active site showed that both compounds interacted with four amino acids Thr307, Arg312, His279, and Glu304. However, there are differences in the interactions of these compounds with active site: (1) acarbose interacted with Thr307 via a hydrogen bond and an unfavorable interaction while compound **8g** interacted with this amino acid via a hydrogen bond, (2) acarbose interacted with His279 via a hydrophobic interaction while compound **8g** interacted with this amino acid via a π-cation interaction, (3) acarbose interacted with Glu304 via a hydrogen bond, while compound **8g** interacted with this amino acid via a π-anion interaction, and (4) acarbose formed a hydrogen bond and an unfavorable interaction with Arg312, while compound **8g**, in addition to forming a hydrogen bond, creates three interactions with this amino acid. Further studies on binding energies of acarbose and compound **8g** revealed that compound **8g** has a lower binding energy (−9.74 kcal/mol) than acarbose (−4.04 kcal/mol) and therefore binds easily to α-glucosidase than does acarbose.

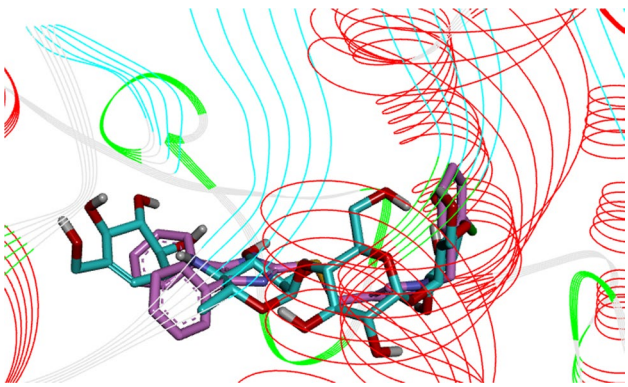


Fig. 3 Acarbose (cyan) and most potent compound **8g** (pink) superimposed in the active site pocket

Movement of the chloro substituent into 4-position, as in the compound **8h**, caused a significant decrease in the potency and number of interactions with the active site in comparison with the 2-substituted compound **8g**. In this regard, as can be observed in Fig. 4, the compound **8h** interacted with two important residues (Arg312 and Glu304), while the compound **8g** interacted with four important residues (His279, Glu304, Thr307, and Arg312). The detailed binding mode of the compound **8h** showed that 4-chloro substituent and phenyl ring of the benzyl moiety formed a hydrophobic interaction with Asp408 and a hydrophobic interaction with Arg312, respectively. 1,2,3-triazole ring of this compound created a hydrogen bond and a hydrophobic interaction with Arg312 and a weak hydrophobic interaction with Pro309. The latter amino acid established two weak hydrophobic interactions with 5-phenyl and imidazole rings. Moreover, the imidazole ring of compound **8h** interacted with Glu304 via a π-anion (Fig. 4). The values of the binding energies of the compounds **8g** and **8h** were −9.74 and −9.19, respectively. This finding showed that the compound **8g** was more stable than the compound **8h** inside the active site.

As can be observed in Table 1, the 2-chloro substituted compound **8g** and 2-bromo substituted compound **8i** showed approximately same inhibitory activity against AChE. 2-Bromo substituent and imidazole moiety of the compound **8i**, like the compound **8g**, interacted with Arg312, Phe311, Tyr313, Thr307, and Glu304 (Fig. 4). The 1,2,3-triazole ring of the compound **8i** interacted with Arg312 and His239, while this moiety in the compound **8i** only interacted with His239. In addition, the sulfur atom and phenyl ring attached to the imidazole ring in the compound **8i**, unlike the compound **8g**, could not interact with the active site. It is worthy to note that the binding energy of the compound **8i** (-10.12 kcal/mol) was better than that of the compound **8g** (−9.74 kcal/mol).

The interaction mode of the third most potent compound **8d** showed that the pendant 2-fluoro phenyl ring of this

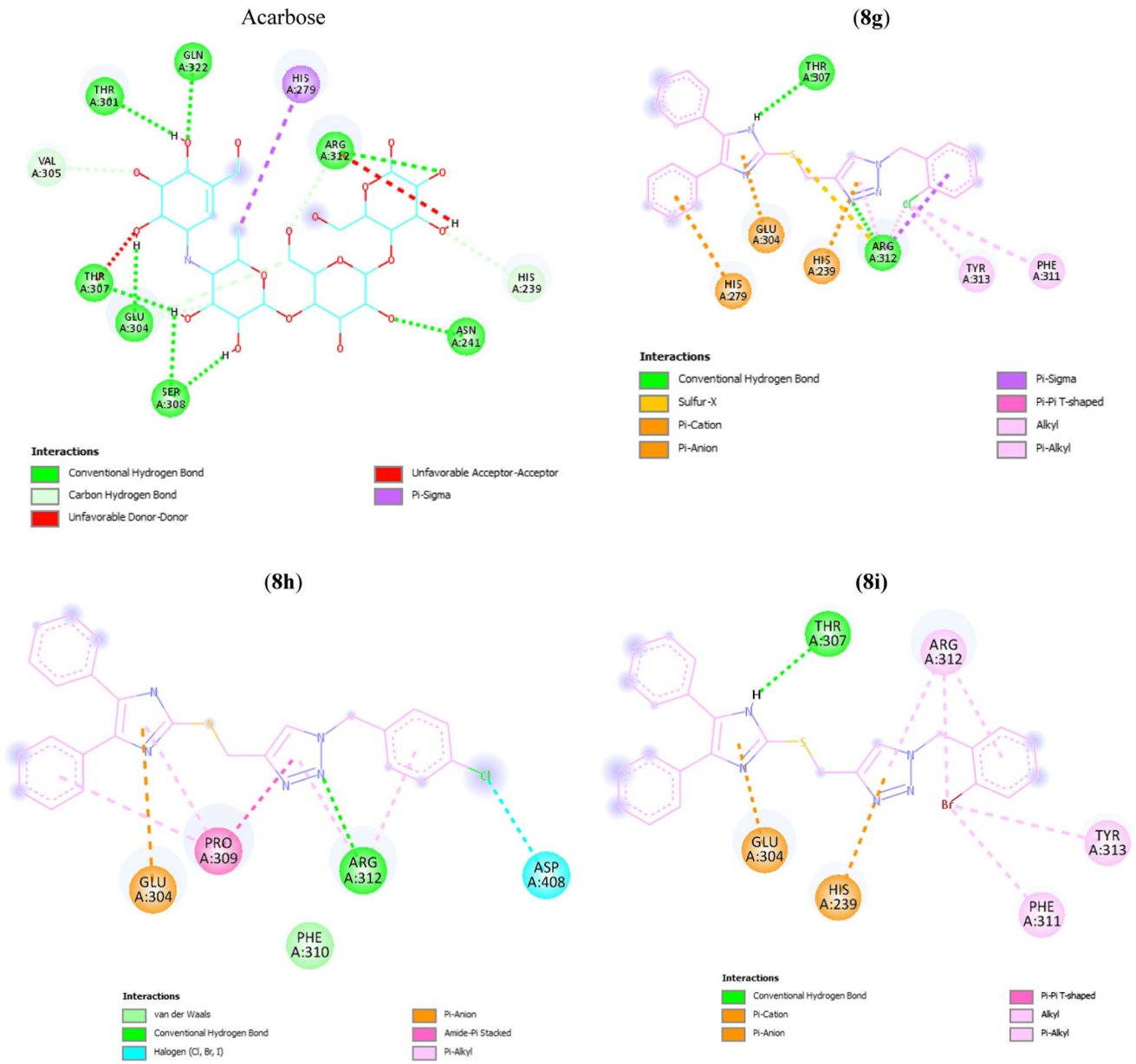


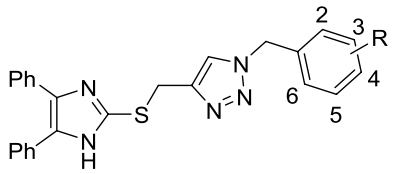
Fig. 4 Interactions of the standard inhibitor acarbose and compounds **8g**, **8h**, and **8i** in the active site amino acid residues of the modeled α-glucosidase

compound formed a π-anion interaction with Asp408 and a hydrophobic interaction with Arg312 (Fig. 5). Interactions of the 1,2,3-triazole and imidazole rings of the compound **8d** were similar to those of the compound **8i**. Changing the position of the fluorine atom on the pendant phenyl ring from 2-position to 3-position led to a slight decrease in the inhibitory activity and minor changes in interaction mode (Table 1 and Fig. 5). The pendant 3-fluorophenyl ring of the compound **8e**, unlike the compound **8d**, could not interact with the active site. Interactions of the imidazole ring of the compound **8e** were similar to those of the compound **8d**. 1,2,3-Triazole ring of compound **8e** only formed a π-cation interaction with His239. The values for the binding energies of the compounds **8d** and **8e** were −9.49 and −9.43 kcal/mol, respectively.

ADME and toxicity studies

ADME/T properties of the most potent compounds **8b**, **8d**, **8g**, and **8i** were calculated using PreADMET as an online software, and the results are presented in Table 2 [26]. As can be seen in this Table, the most potent compounds have good Caco-2 cell permeability, human oral absorption (HIA), and skin permeability. On the other hand, blood

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



Compound	R	IC_{50} (μM)	Compound	R	IC_{50} (μM)
8a	H	173.4 ± 0.7	**8h**	4-Cl	159.8 ± 0.9
8b	2-CH_3	95.2 ± 0.4	**8i**	2-Br	88.0 ± 0.5
8c	3-OCH_3	121.0 ± 0.4	**8j**	3-Br	168.1 ± 0.7
8d	2-F	93.3 ± 0.6	**8k**	4-Br	128.1 ± 0.9
8e	3-F	103.3 ± 0.9	**8l**	2-NO_2	213.8 ± 1.1
8f	4-F	125.2 ± 1.3	**8m**	3-NO_2	136.9 ± 1.0
8g	2-Cl	85.6 ± 0.4	**8n**	4-NO_2	231.4 ± 1.0
Acarbose	–	750.0 ± 1.5	Acarbose	–	750.0 ± 1.5

brain permeability (BBB) of these compounds was not in the acceptable range. Predicting the toxicity of the most potent compounds **8b**, **8d**, **8g**, and **8i** by PreADMET Toxicity server demonstrated that these compounds were non-mutagenic (Ames_test) and medium cardiotoxic (hERG_inhibition). All test compounds, with the exception of compound **8i** which may have a carcinogenic effect in rat, carcinogenic effect had not on mouse and rat.

Conclusion

We synthesized a new series of 4,5-diphenyl-imidazol-1,2,3-triazole hybrids **8a–n** in good yields with the use of the click reaction by coupling an 4,5-diphenyl–1H-imidazole containing a terminal alkyne with various benzyl azides. These molecules were screened in vitro for their α-glucosidase inhibition. In general, the synthesized compounds showed excellent α-glucosidase inhibitory activities in comparison with acarbose as the standard drug. Among the synthesized compounds, the 2-chloro and 2-bromo derivatives **8g** and **8i** showed the highest α-glucosidase inhibitory activity. The compound **8g** could inhibit α-glucosidase in a competitive mode. The docking study of these compounds confirmed that they were well fitted in the active site of α-glucosidase.

Experimental

Chemistry

The melting points of 4,5-diphenyl-imidazol-1,2,3-triazole hybrids **8a–n** were determined on a Kofler hot-stage apparatus. The ^{1}H and ^{13}C NMR spectra of the title compounds were determined on a Bruker FT-500 using TMS as an internal standard. The IR spectra were recoded using KBr disks on a Nicolet Magna FTIR 550 spectrophotometer. Elemental analysis was carried out with an Elementar Analysen system GmbH VarioEL CHN mode.

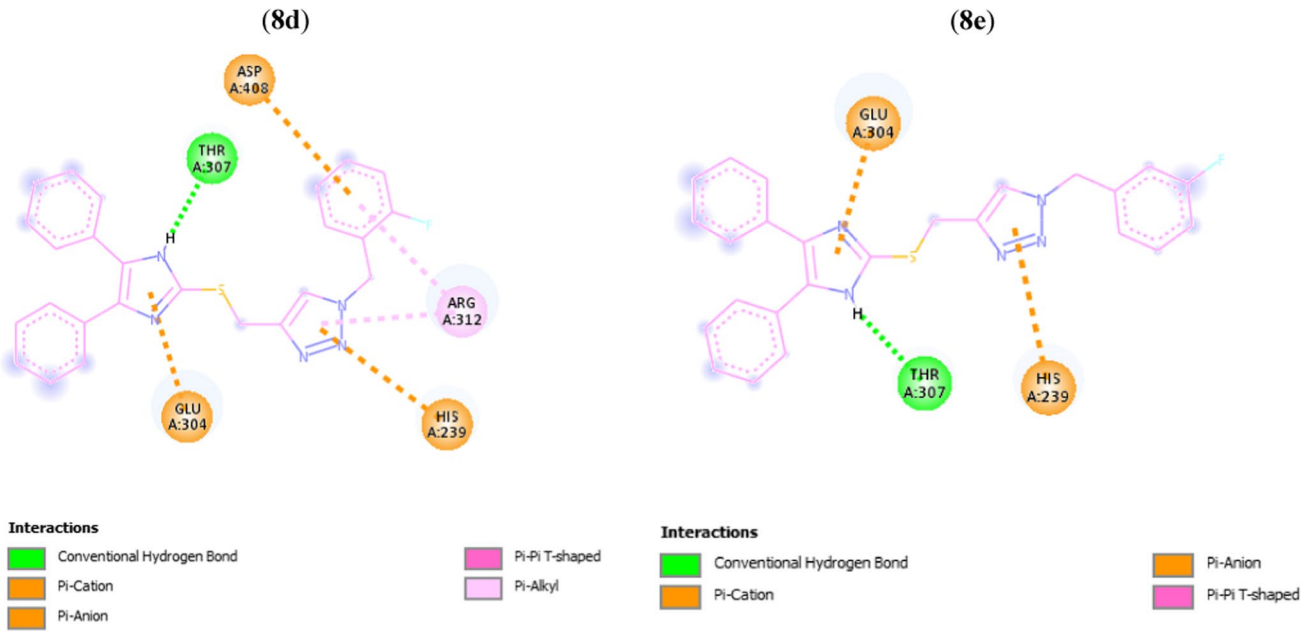


Fig. 5 Interaction modes of compounds **8d** and **8e** with the active site residues of modeled α-glucosidase

Table 2 ADME/T profile of the most potent compounds **8b**, **8d**, **8g**, and **8i**

ADME/T properties[a]	Compound			
	8b	**8d**	**8g**	**8i**
Caco2	36.2378	52.9295	56.1878	53.5177
HIA	96.022248	95.942170	96.265681	96.410695
BBB	2.9484	2.41331	3.53386	3.75894
Skin_Permeability	− 2.14579	− 2.42795	− 2.31292	− 2.33852
Ames_test	Non-mutagen	Non-mutagen	Non-mutagen	Non-mutagen
hERG_inhibition	Medium risk	Medium risk	Medium risk	Medium risk
Carcino_Mouse	Negative	Negative	Negative	Negative
Carcino_Rat	Negative	Negative	Negative	Positive

[a]The recommended ranges for Caco2: < 25 poor, > 500 great, HIA: > 80% is high < 25% is poor, BBB = − 3.0 to 1.2, and Skin_Permeability = − 8.0 to 1.0

General procedure for the preparation of 4,5-diphenyl-1H-imidazole-2-thiol 3

A mixture of 2-hydroxy-1,2-diphenylethanone **1** (1 mmol, 0.2 g) and thiourea **2** (1 mmol, 0.07 g) in DMF (15 mL) was heated at 100 °C for 3 h. Then, the mixture was poured into ice-cold water and the obtained precipitate was filtered off and recrystallized in ethanol to obtain 4,5-diphenyl-1H-imidazole-2-thiol **3** [27].

General procedure for the preparation of 4,5-diphenyl-2-(prop-2-yn-1-ylthio)-1H-imidazole 5

A mixture of 4,5-diphenyl-1H-imidazole-2-thiol **3** (1 mmol, 0.25 g), propargyl bromide **4** (1.2 mmol, 0.15 mL), and potassium hydroxide (1.2 mmol, 0.06 g) in acetone (10 mL) was stirred at 0–10 °C for 5 min. After completion of the reaction (checked by TLC), the reaction mixture was cooled down to room temperature and poured into cold water. Subsequently, the precipitated product was filtered off to give pure 4,5-diphenyl-2-(prop-2-yn-1-ylthio)-1H-imidazole **5** [28].

General procedure for the synthesis of 4,5-diphenyl-imidazol-1,2,3-triazole hybrids 8a–n

At first, benzyl azide derivatives **7** were prepared in situ. For this purpose, the mixture of benzyl halides **6** (1.1 mmol) and sodium azide (0.9 mmol) in the presence of Et_3N (1.3 mmol) and the mixture of water/t-BuOH (8 mL, 1:1) was stirred at room temperature for 1 h [19]. Subsequently, the mixture of 4,5-diphenyl-2-(prop-2-yn-1-ylthio)-1H-imidazole **5** (1 mmol, 0.3 g), $CuSO_4$.$5H_2O$ (7 mol%, 0.3 g), and sodium ascorbate (15 mol%, 0.13 g) was added to the freshly prepared benzyl azide derivative **7** and stirred at room temperature for 24-48 h. Upon completion of the reaction (monitored by TLC), the reaction mixture was poured into crushed ice. Then, the precipitated product was filtered off, washed with cold water, and purified by recrystallization in ethanol to give the corresponding derivatives **8a**–**n**.

1-Benzyl-4-(4,5-diphenyl-1H-imidazol-2-ylsulfanylmethyl) -1H-[1,2,3]triazole (8a)

Cream powder; yield: 87% (0.37 g), mp 158–160; IR (KBr, υ): 3373, 1463, 771 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 12.62 (s, 1H, NH), 8.01 (s, 1H, Triazole), 7.46 (d, $J = 7.7$ Hz, 1H, Ph), 7.43–7.36 (m, 4H, Ph), 7.35–7.32 (m, 2H, Ph), 7.32–7.25 (m, 6H, Ph), 7.23 (s, 1H, Ph), 5.57 (s, 2H, CH_2), 4.41 (s, 2H, S-CH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 144.20, 139.61, 137.75, 136.40, 131.12, 129.14, 129.11, 128.62, 128.51, 128.30, 128.24, 128.10, 127.48, 127.02, 123.94, 53.22 (S-CH_2), 28.14 (CH_2). Anal. Calcd for $C_{25}H_{21}N_5S$: C, 70.90; H, 5.00; N, 16.54. Found: C, 71.05; H, 5.16; N, 16.68.

4-(4,5-Diphenyl-1H-imidazol-2-ylsulfanylmethyl)-1-(2-methyl-benzyl)-1H-[1,2,3]triazole (8b)

Cream powder; isolated yield: 94% (0.41 g), mp 167–169; IR (KBr, υ): 3375, 1460, 778 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 12.65 (s, 1H, NH), 7.85 (s, 1H, Triazole), 7.43 (d, $J = 7.6$ Hz, 2H, Ph-H), 7.39 (d, $J = 7.8$ Hz, 1H, H3), 7.38–7.35 (m, 3H, Ph), 7.33 (d, $J = 6.7$ Hz, 1H, Ph), 7.27 (d, $J = 7.5$ Hz, 2H, Ph), 7.22 (d, $J = 7.3$ Hz, 1H, Ph), 7.19 (dd, $J = 7.3$, 1.4 Hz, 1H, H6), 7.15 (d, $J = 7.3$ Hz, 1H, H5), 7.09 (dd, $J = 7.3$, 1.5 Hz, 1H, H4), 7.06–7.01 (m, 1H, H3), 5.56 (s, 2H, CH_2), 4.41 (s, 2H, S-CH_2), 2.22 (s, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 143.59, 139.04, 137.18, 136.14, 134.65, 133.77, 130.49, 130.24, 128.55, 128.50, 128.16, 128.01, 127.60, 127.50, 126.91, 126.45, 126.05, 123.30, 50.84 (S-CH_2), 27.47 (CH_2), 18.38 (CH_3). Anal. Calcd for $C_{26}H_{23}N_5S$: C, 71.37; H, 5.30; N, 16.01. Found: C, 71.51; H, 5.45; N, 16.19.

4-(4,5-Diphenyl-1H-imidazol-2-ylsulfanylmethyl)-1-(3-methoxy-benzyl)-1H-[1,2,3]triazole (8c)

Cream powder; isolated yield: 92% (0.42 g), mp 172–174; IR (KBr, υ): 3379, 1466, 762 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 12.66 (s, 1H, NH), 8.02 (s, 1H, Triazole), 7.49–7.43 (m, 2H, Ph), 7.41–7.35 (m, 4H, Ph), 7.32–7.25 (m, 3H, Ph), 7.24–7.17 (m, 2H,Ph, H5), 6.90–6.84 (m, 2H, H2,6), 6.80 (s, 1H, H4), 5.54 (s, 2H, CH_2), 4.44 (s, 2H, S-CH_2), 3.69 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.40, 143.78, 139.26, 137.36, 134.84, 130.71, 129.91, 129.86, 128.63, 128.17, 127.76, 127.60, 127.06, 126.73, 126.57, 123.50, 119.93, 113.68, 113.45, 55.04 (OCH_3), 52.72 (S-CH_2), 27.64 (CH_2). Anal. Calcd for $C_{26}H_{23}N_5S$: C, 68.85; H, 5.11; N, 15.44. Found: C, 68.91; H, 5.25; N, 15.59.

4-(4,5-Diphenyl-1H-imidazol-2-ylsulfanylmethyl)-1-(2-fluoro-benzyl)-1H-[1,2,3]triazole (8d)

Cream powder; isolated yield: 90% (0.40 g), mp 159–161; IR (KBr, υ): 3365, 1467, 777 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 12.67 (s, 1H, NH), 8.02 (s, 1H, Triazole), 7.96 (d, J = 19.9 Hz, 1H, H3), 7.55 (d, J = 7.2 Hz, 1H, H4), 7.45–7.35 (m, 7H, Ph), 7.30–7.25 (m, 3H, Ph), 7.19 (t, J = 9.6 Hz, 2H, H6), 7.12 (t, J = 7.6 Hz, 1H, H5), 5.61 (s, 2H, CH_2), 4.41 (s, 2H, S-CH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.99, 159.03, 148.25, 143.84, 139.26, 137.99, 137.37, 134.73, 130.69, 130.62, 130.60, 130.57, 129.55, 128.70, 128.61, 128.23, 128.12, 127.71, 127.08, 126.59, 124.75, 124.72, 123.55, 122.73, 122.62, 115.61, 115.44, 46.84 (S-CH_2), 27.62 (CH_2). Anal. Calcd for $C_{25}H_{20}FN_5S$: C, 68.01; H, 4.57; N, 15.86. Found: C, 68.16; H, 4.37; N, 15.71.

4-(4,5-Diphenyl-1H-imidazol-2-ylsulfanylmethyl)-1-(3-fluoro-benzyl)-1H-[1,2,3]triazole (8e)

Cream powder; isolated yield: 97% (0.43 g), mp 163–165; IR (KBr, υ): 3375, 1455, 776 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 12.66 (s, 1H, NH), 8.06 (s, 1H, Triazole), 7.54–7.45 (m, 2H, Ph), 7.44–7.41 (m, 1H, H5), 7.41–7.35 (m, 3H, Ph), 7.33 (d, J = 7.6 Hz, 2H, Ph), 7.30–7.24 (m, 2H, Ph), 7.24–7.20 (m, 1H, Ph), 7.14 (t, J = 10.0 Hz, 2H, H2, H6), 7.09 (d, J = 8.0 Hz, 1H, H4), 5.59 (s, 2H, CH_2), 4.44 (s, 2H, S-CH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.06, 161.12, 143.92, 139.23, 138.60, 138.54, 137.34, 134.78, 130.76, 130.70, 130.64, 128.61, 128.12, 127.74, 127.61, 127.08, 126.57, 123.90, 123.88, 123.64, 115.01, 114.84, 114.67, 52.10 (SCH_2), 27.69 (CH_2). Anal. Calcd for $C_{25}H_{20}FN_5S$: C, 68.01; H, 4.57; N, 15.86. Found: C, 68.14; H, 4.32; N, 15.78.

4-(4,5-Diphenyl-1H-imidazol-2-ylsulfanylmethyl)-1-(4-fluoro-benzyl)-1H-[1,2,3]triazole (8f)

Cream powder; isolated yield: 85% (0.37 g), mp 169-171; IR (KBr, υ): 3370, 1466, 769 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 12.67 (s, 1H, NH), 7.99 (s, 1H, Triazole), 7.46 (d, J = 7.7 Hz, 2H, H3, H5), 7.38 (d, J = 5.3 Hz, 4H, Ph), 7.33 (dt, J = 8.4, 3.6 Hz, 3H, Ph), 7.27 (d, J = 7.5 Hz, 2H, Ph), 7.22 (t, J = 7.1 Hz, 1H, Ph), 7.09 (t, J = 8.8 Hz, 2H, H2, H6), 5.56 (s, 2H, CH_2), 4.43 (s, 2H, S-CH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.83, 160.88, 143.91, 139.21, 137.39, 134.86, 132.18, 130.69, 130.24, 130.18, 128.70, 128.22, 127.81, 127.71, 127.10, 126.66, 123.46, 115.64, 115.47, 52.02 (SCH_2), 27.77 (CH_2). Anal. Calcd for $C_{25}H_{20}FN_5S$: C, 68.01; H, 4.57; N, 15.86. Found: C, 67.94; H, 4.69; N, 15.94.

1-(2-Chloro-benzyl)-4-(4,5-diphenyl-1H-imidazol-2-ylsulfanylmethyl)-1H-[1,2,3]triazole (8g)

Cream powder; isolated yield: 89% (0.41 g), mp 162–164; IR (KBr, υ): 3378, 1462, 779 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 12.66 (s, 1H, NH), 7.97 (s, 1H, Triazole), 7.49–7.15 (m, 14H, Ph, H3, H4, H5, H6), 5.67 (s, 2H, CH_2), 4.43 (s, 2H, S-CH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 143.77, 139.15, 137.33, 134.86, 133.16, 132.58, 130.68, 130.39, 130.15, 129.55, 128.62, 128.15, 127.76, 127.62, 127.05, 126.56, 123.81, 50.57 (SCH_2), 27.61 (CH_2). Anal. Calcd for $C_{25}H_{20}ClN_5S$: C, 65.56; H, 4.40; N, 15.29. Found: C, 65.38; H, 4.53; N, 15.12.

1-(4-Chloro-benzyl)-4-(4,5-diphenyl-1H-imidazol-2-ylsulfanylmethyl)-1H-[1,2,3]triazole (8h)

Cream powder; isolated yield: 88% (0.40 g), mp 193–195; IR (KBr, υ): 3371, 1462, 776 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 12.62 (s, 1H, NH), 7.98 (s, 1H, Triazole), 7.44 (d, J = 7.7 Hz, 2H, H3, H5), 7.41–7.35 (m, 4H, Ph), 7.33–7.20 (m, 8H, Ph, H2, H6), 5.57 (s, 2H, CH_2), 4.41 (s, 2H, S-CH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 144.32, 139.52, 137.77, 135.42, 135.29, 133.24, 131.12, 130.20, 130.18, 129.13, 129.13, 128.64, 128.24, 128.13, 128.12, 127.49, 127.07, 127.04, 124.02, 123.98, 52.39 (SCH_2), 28.18 (CH_2). Anal. Calcd for $C_{25}H_{20}ClN_5S$: C, 65.56; H, 4.40; N, 15.29. Found: C, 65.64; H, 4.27; N, 15.16.

1-(2-Bromo-benzyl)-4-(4,5-diphenyl-1H-imidazol-2-ylsulfanylmethyl)-1H-[1,2,3]triazole (8i)

Cream powder; isolated yield: 93% (0.47 g), mp 180–182; IR (KBr, υ): 3379, 1468, 773 cm^{-1}; ^1H NMR (500 MHz,

DMSO-d_6) δ 12.65 (s, 1H, NH), 7.94 (s, 1H, Triazole), 7.64 (dd, J = 11.5, 9.8 Hz, 1H, H3), 7.47–7.21 (m, 12H, Ph, H4, H5), 7.11 (d, J = 6.9 Hz, 1H, H6), 5.62 (s, 2H, CH_2), 4.42 (s, 2H, S-CH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 143.75, 139.15, 137.33, 135.04, 134.77, 132.84, 130.63, 130.38, 130.34, 128.64, 128.18, 128.16, 127.76, 127.64, 127.06, 126.59, 123.87, 122.83, 52.90 (SCH_2), 27.60 (CH_2). Anal. Calcd for $C_{25}H_{20}BrN_5S$: C, 59.76; H, 4.01; N, 13.94. Found: C, 59.53; H, 4.13; N, 14.05.

1-(3-Bromo-benzyl)-4-(4,5-diphenyl-1H-imidazol-2-ylsulfanylmethyl)-1H-[1,2,3]triazole (8j)

Cream powder; isolated yield: 94% (0.47 g), mp 174-176; IR (KBr, υ): 3379, 1468, 770 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.64 (s, 1H, NH), 8.06 (s, 1H, Triazole), 7.54 (d, J = 1.9 Hz, 1H, H4), 7.52–7.49 (m, 1H, H2), 7.46 (d, J = 7.3 Hz, 2H, Ph), 7.41–7.35 (m, 5H, Ph), 7.34–7.31 (m, 1H, Ph), 7.30–7.26 (m, 2H, Ph), 7.24 (d, J = 5.1 Hz, 2H, H5, H6), 5.59 (s, 2H, CH_2), 4.44 (s, 2H, S-CH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 148.27, 143.88, 139.17, 138.56, 137.27, 134.82, 130.97, 130.88, 130.71, 129.57, 128.89, 128.73, 128.64, 128.26, 128.17, 127.96, 127.76, 127.63, 127.04, 126.93, 126.57, 123.64, 121.81, 51.92 (SCH_2), 27.63 (CH_2). Anal. Calcd for $C_{25}H_{20}BrN_5S$: C, 59.76; H, 4.01; N, 13.94. Found: C, 59.83; H, 4.11; N, 13.84.

1-(4-Bromo-benzyl)-4-(4,5-diphenyl-1H-imidazol-2-ylsulfanylmethyl)-1H-[1,2,3]triazole (8k)

Cream powder; isolated yield: 92% (0.46 g), mp 197–199; IR (KBr, υ): 3379, 1462, 774 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.64 (s, 1H, NH), 7.99 (s, 1H, Triazole), 7.45 (t, J = 7.5 Hz, 4H, Ph, H2, H6), 7.41–7.35 (m, 4H, Ph), 7.33 (d, J = 6.5 Hz, 1H, Ph), 7.29 (t, J = 7.4 Hz, 2H, Ph), 7.23 (d, J = 7.1 Hz, 1H, Ph), 7.19 (d, J = 8.2 Hz, 2H, H2, H6), 5.55 (s, 2H, CH_2), 4.42 (s, 2H, S-CH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 148.28, 143.87, 139.06, 138.01, 137.32, 135.36, 134.83, 131.60, 130.66, 130.02, 129.59, 128.66, 128.28, 128.18, 127.78, 127.67, 127.03, 126.60, 123.56, 121.34, 52.00 (S-CH_2), 27.74 (CH_2). Anal. Calcd for $C_{25}H_{20}BrN_5S$: C, 59.76; H, 4.01; N, 13.94. Found: C, 59.62; H, 3.96; N, 14.08.

4-(4,5-Diphenyl-1H-imidazol-2-ylsulfanylmethyl)-1-(2-nitro-benzyl)-1H-[1,2,3]triazole (8l)

Cream powder; isolated yield: 86% (0.40 g), mp 175–177; IR (KBr, υ): 3378, 1462, 776 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.65 (s, 1H, NH), 8.11 (s, 1H, Triazole), 8.02 (s, 1H, H3), 7.64–7.51 (m, 2H, H4, H5), 7.48–7.20 (m, 10H, Ph), 7.01–6.88 (m, 1H, H6), 5.95 (s, 2H, CH_2), 4.49 (s, 2H, S-CH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 147.43, 143.94, 139.04, 134.22, 130.87, 129.79, 129.49, 128.61, 128.16, 127.74, 127.01, 126.52, 124.97, 124.23, 49.89 (S-CH_2), 27.67 (CH_2). Anal. Calcd for $C_{25}H_{20}N_6O_2S$: C, 64.09; H, 4.30; N, 17.94. Found: C, 64.17; H, 4.51; N, 17.87.

4-(4,5-Diphenyl-1H-imidazol-2-ylsulfanylmethyl)-1-(3-nitro-benzyl)-1H-[1,2,3]triazole (8m)

Cream powder; isolated yield: 95% (0.44 g), mp 168-170; IR (KBr, υ): 3378, 1462, 771 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.63 (s, 1H, NH), 8.23 (s, 1H, H2), 8.15 (d, J = 8.1, 2.3 Hz, 1H, H4), 8.11 (s, 1H, Triazole), 7.69 (d, J = 7.7 Hz, 1H, H6), 7.57 (t, J = 8.0, 2.1 Hz, 1H, H5), 7.47–7.20 (m, 10H, Ph), 5.76 (s, 2H, CH_2), 4.46 (s, 2H, S-CH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 147.80, 144.01, 139.15, 138.04, 137.32, 134.83, 134.57, 130.66, 130.29, 128.63, 128.14, 127.74, 127.62, 127.01, 126.72, 126.56, 123.77, 123.05, 122.80, 51.73 (S-CH_2), 27.64 (CH_2). Anal. Calcd for $C_{25}H_{20}N_6O_2S$: C, 64.09; H, 4.30; N, 17.94. Found: C, 63.92; H, 4.22; N, 17.85.

4-(4,5-Diphenyl-1H-imidazol-2-ylsulfanylmethyl)-1-(4-nitro-benzyl)-1H-[1,2,3]triazole (8n)

Cream powder; isolated yield: 89% (0.42 g), mp 189–191; IR (KBr, υ): 3375, 1461, 775 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.63 (s, 1H, NH), 8.10 (d, J = 8.7 Hz, 2H, H5, H3), 8.04 (s, 1H, Triazole), 7.43 (dt, J = 8.7, 2.7 Hz, 4H, Ph), 7.39–7.29 (m, 5H, Ph), 7.27 (t, J = 7.5 Hz, 2H, H2, H6), 7.23–7.17 (m, 1H, Ph), 5.75 (s, 2H, CH_2), 4.43 (s, 2H, S-CH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 147.57, 144.50, 143.90, 139.41, 137.79, 135.25, 131.09, 129.26, 129.18, 129.10, 128.62, 128.22, 128.14, 127.45, 127.06, 124.39, 124.26, 52.28 (S-CH_2), 28.21 (CH_2). Anal. Calcd for $C_{25}H_{20}N_6O_2S$: C, 64.09; H, 4.30; N, 17.94. Found: C, 63.95; H, 4.43; N, 17.81.

Biological assays

In vitro α-glucosidase inhibition assay

Enzyme (α-glucosidase from Saccharomyces cerevisiae, EC3.2.1.20, 20 U/mg) and substrate (*p*-nitrophenyl glucopyranoside) were prepared from Sigma-Aldrich. An appropriate concentration of enzyme was prepared by potassium phosphate buffer (pH 6.8, 50 mM), and the 4,5-diarylimidazole-1,2,3-triazole hybrids **8a**–**n** were dissolved in DMSO (10% final concentration). The enzyme (20 µL), different concentrations of the title compounds (20 µL), and potassium phosphate buffer (135 µL) were added to a 96-well plate and incubated at 37 °C for 10 min [17–25]. Then, a substrate (25 µL, 4 mM) was added to each well of the plate and allowed to be incubated at 37 °C for 20 min.

Finally, the change in the absorbance was measured at 405 nm by using the Gen5 spectrophotometer (Power wave xs2, BioTek, America). DMSO as control and acarbose as the standard inhibitor were used. The percentage of inhibition for the synthesized compounds **8a**–**n**, control, and acarbose was calculated by using the following formula:

$$\%\text{Inhibition} = \left[(\text{Abs control} - \text{Abs sample})/\text{Abs control}\right] \times 100$$

The IC_{50} values of the tested agents were determined from the nonlinear regression curve using the Logit method.

Kinetic study

The α-glucosidase solution (1 U/mL, 20 µL) was incubated with different concentrations of the compound **8g** (0, 45, 60, and 85 µM) for 15 min at 30 °C. The enzymatic reaction was initiated by adding various concentrations of p-nitrophenyl glucopyranoside as substrate (1–10 mM). Then, change in the absorbance was determined for 20 min at 405 nm by using the spectrophotometer (Gen5, Power wave xs2, BioTek, America).

Docking study

Building the homology model of α-glucosidase and docking studies of the selected compounds **8d**–**e** and **8g**–**i** in the active site of this enzyme were conducted using the previously described method [25].

In silico ADME/T study

In silico ADME-Tox study of the most potent compounds **8b**, **8d**, **8g**, and **8i** was performed using the PreADMET online server (http://preadmet.bmdrc.org/) [26].

Acknowledgements This project was financially supported by the National Institute for Medical Research Development (NIMAD) (the Grant Number: 977073).

References

1. Schmidt DD, Frommer W, Junge B, Müller L, Wingender W, Truscheit E, Schäfer D (1997) α-Glucosidase inhibitors. Naturwissenschaften 64:535–536. https://doi.org/10.1007/BF00483561
2. Matsuo T, Odaka H, Ikeda H (1992) Effect of an intestinal disaccharidase inhibitor (AO-128) on obesity and diabetes. Am J Clin Nutr 55:314S–317S. https://doi.org/10.1093/ajcn/55.1.314s
3. Scott LJ, Spencer CM (2000) Miglitol Drugs 59:521–549. https://doi.org/10.2165/00003495-200059030-00012
4. Asano N, Oseki K, Tomioka E, Kizu H, Matsui K (1994) *N*-containing sugars from Morus alba and their glycosidase inhibitory activities. Carbohydr Res 259:243–255. https://doi.org/10.1016/0008-6215(94)84060-1
5. Hollander P (1992) Safety profile of acarbose, an α-glucosidase inhibitor. Drugs 44:47–53. https://doi.org/10.2165/00003495-199200443-00007
6. Adisakwattana S, Sookkongwaree K, Roengsumran S, Petsom A, Ngamrojnavanich N, Chavasiri W, Deesamer S, Yibchok-anun S (2004) Structure–activity relationships of trans-cinnamic acid derivatives on α-glucosidase inhibition. Bioorg Med Chem Lett 14:2893–2896. https://doi.org/10.1016/j.bmcl.2004.03.037
7. Sou S, Mayumi S, Takahashi H, Yamasaki R, Kadoya S, Sodeoka M, Hashimoto Y (2000) Novel α-glucosidase inhibitors with a tetrachlorophthalimide skeleton. Bioorg Med Chem Lett 10:1081–1084. https://doi.org/10.1016/S0960-894X(00)00161-X
8. Abboud JL, Foces-Foces C, Notario R, Trifonov RE, Volovodenko AP, Ostrovskii VA, Alkorta I, Elguero J (2001) Basicity of *N*-H- and *N*-methyl-1,2,3-triazoles in the gas phase, in solution, and in the solid state—an experimental and theoretical study. Eur J Org Chem 16:3013–3024. https://doi.org/10.1002/1099-0690(200108)2001:16%3c3013:AID-EJOC3013%3e3.0.CO;2-Y
9. Vatmurge NS, Hazra BG, Pore VS, Shirazi F, Chavan PS, Deshpande MV (2008) Synthesis and antimicrobial activity of β-lactam–bile acid conjugates linked via triazole. Bioorg Med Chem Lett 18:2043–2047. https://doi.org/10.1016/j.bmcl.2008.01.102
10. Thirumurugan P, Matosiuk D, Jozwiak K (2013) Click chemistry for drug development and diverse chemical–biology applications. Chem Rev 113:4905–4979. https://doi.org/10.1021/cr200409f
11. Aufort M, Herscovici J, Bouhours P, Moreau N, Girard C (2008) Synthesis and antibiotic activity of a small molecules library of 1,2,3-triazole derivatives. Bioorg Med Chem Lett 18:1195–1198. https://doi.org/10.1016/j.bmcl.2007.11.111
12. Kumar A, Ahmad I, Chhikara BS, Tiwari R, Mandal D, Parang K (2011) Synthesis of 3-phenylpyrazolopyrimidine-1,2,3-triazole conjugates and evaluation of their Src kinase inhibitory and anticancer activities. Bioorg Med Chem Lett 21:1342–1346. https://doi.org/10.1016/j.bmcl.2011.01.047
13. Lima-Neto RG, Cavalcante NN, Srivastava RM, Mendonça Junior FJ, Wanderley AG, Neves RP, dos Anjos JV (2012) Synthesis of 1, 2, 3-triazole derivatives and in vitro antifungal evaluation on Candida strains. Molecules 17:5882–5892. https://doi.org/10.3390/molecules17055882
14. Shanmugavelan P, Nagarajan S, Sathishkumar M, Ponnuswamy A, Yogeeswari P, Sriram D (2011) Efficient synthesis and in vitro antitubercular activity of 1,2,3-triazoles as inhibitors of Mycobacterium tuberculosis. Bioorg Med Chem Lett 21:7273–7276. https://doi.org/10.1016/j.bmcl.2011.10.048
15. Mohammadi-Khanaposhtani M, Mahdavi M, Saeedi M, Sabourian R, Safavi M, Khanavi M, Foroumadi A, Shafiee A, Akbarzadeh T (2015) Design, synthesis, biological evaluation, and docking study of acetylcholinesterase inhibitors: new acridone-1,2,4-oxadiazole-1,2,3-triazole hybrids. Chem Biol Drug Des 86:1425–1432. https://doi.org/10.1111/cbdd.12609
16. Brik A, Alexandratos J, Lin YC, Elder JH, Olson AJ, Wlodawer A, Goodsell DS, Wong CH (2005) 1,2,3-Triazole as a peptide surrogate in the rapid synthesis of HIV-1 protease inhibitors. ChemBioChem 6:1167–1169. https://doi.org/10.1002/cbic.200500101
17. Iqbal S, Khan MA, Javaid K, Sadiq R, Fazal-ur-Rehman S, Choudhary MI, Basha FZ (2017) New carbazole linked 1,2,3-triazoles as highly potent non-sugar α-glucosidase inhibitors. Bioorg Chem 74:72–81. https://doi.org/10.1016/j.bioorg.2017.07.006
18. Wang G, Peng Z, Wang J, Li X, Li J (2017) Synthesis, in vitro evaluation and molecular docking studies of novel triazine-triazole derivatives as potential α-glucosidase inhibitors. Eur J Med Chem 125:423–429. https://doi.org/10.1016/j.ejmech.2016.09.067
19. Saeedi M, Mohammadi-Khanaposhtani M, Pourrabia P, Razzaghi N, Ghadimi R, Imanparast S, Faramarzi MA, Bandarian F, Esfahani EN, Safavi M, Rastegar H (2019) Design and synthesis of

novel quinazolinone-1,2,3-triazole hybrids as new anti-diabetic agents: in vitro α-glucosidase inhibition, kinetic, and docking study. Bioorg Chem 83:161–169. https://doi.org/10.1016/j.bioorg.2018.10.023
20. Yar M, Bajda M, Shahzad S, Ullah N, Gilani MA, Ashraf M, Rauf A, Shaukat A (2015) Organocatalyzed solvent free an efficient novel synthesis of 2,4,5-trisubstituted imidazoles for α-glucosidase inhibition to treat diabetes. Bioorg Chem 58:65–71. https://doi.org/10.1016/j.bioorg.2014.11.006
21. Wang G, Peng Z, Wang J, Li J, Li X (2016) Synthesis and biological evaluation of novel 2,4,5-triarylimidazole-1,2,3-triazole derivatives via click chemistry as α-glucosidase inhibitors. Bioorg Med Chem Lett 26:5719–5723. https://doi.org/10.1016/j.bmcl.2016.10.057
22. Adib M, Peytam F, Shourgeshty R, Mohammadi-Khanaposhtani M, Jahani M, Imanparast S, Faramarzi MA, Larijani B, Moghadamnia AA, Esfahani EN, Bandarian F (2019) Design and synthesis of new fused carbazole-imidazole derivatives as anti-diabetic agents: in vitro α-glucosidase inhibition, kinetic, and in silico studies. Bioorg Med Chem Lett 29:713–718. https://doi.org/10.1016/j.bmcl.2019.01.012
23. Mohammadi-Khanaposhtani M, Yahyavi H, Barzegaric E, Imanparast S, Heravi MM, Ali Faramarzi M, Foroumadi A, Adibi H, Larijani B, Mahdavi M (2018) New biscoumarin derivatives as potent α-glucosidase inhibitors: synthesis, biological evaluation, kinetic analysis, and docking study. Polycycl Aromat Comp 5:1–2. https://doi.org/10.1080/10406638.2018.1509359
24. Adib M, Peytam F, Rahmanian-Jazi M, Mohammadi-Khanaposhtani M, Mahernia S, Bijanzadeh HR, Jahani M, Imanparast S, Faramarzi MA, Mahdavi M, Larijani B (2018) Design, synthesis and in vitro α-glucosidase inhibition of novel coumarin-pyridines as potent antidiabetic agents. New J Chem 42:17268–17278. https://doi.org/10.1039/C8NJ02495B
25. Adib M, Peytam F, Rahmanian-Jazi M, Mahernia S, Bijanzadeh HR, Jahani M, Mohammadi-Khanaposhtani M, Imanparast S, Faramarzi MA, Mahdavi M, Larijani B (2018) New 6-amino-pyrido [2,3-d] pyrimidine-2,4-diones as novel agents to treat type 2 diabetes: a simple and efficient synthesis, α-glucosidase inhibition, molecular modeling and kinetic study. Eur J Med Chem 155:353–363. https://doi.org/10.1016/j.ejmech.2018.05.046
26. Seul, South Corea: Bioinformatics and Molecular Design Research Center; 2004. PreADMET program. http://preadmet.bmdrc.org
27. Maduskuie TP, Wilde RG, Billheimer JT, Cromley DA, Germain S, Gillies PJ, Higley CA, Johnson AL, Pennev P, Shimshick EJ, Wexler RR (1995) Design, synthesis, and structure-activity relationship studies for a new imidazole series of J774 macrophage specific acyl-CoA: cholesterol acyltransferase (ACAT) inhibitors. J Med Chem 38:1067–1083. https://doi.org/10.1021/jm00007a004
28. Veltri L, Mancuso R, Altomare A, Gabriele B (2015) Divergent multicomponent tandem palladium-catalyzed aminocarbonylation-cyclization approaches to functionalized imidazothiazinones and imidazothiazoles. ChemCatChem 7:2206–2213. https://doi.org/10.1002/cctc.201500213