



# Synthesis, in vitro and in silico enzymatic inhibition assays, and toxicity evaluations of new 4,5-diphenylimidazole-*N*-phenylacetamide derivatives as potent $\alpha$ -glucosidase inhibitors

Maryam Mohammadi-Khanaposhtani<sup>1</sup> · Atefeh Nikraftar<sup>2</sup> · Mohammad Sadegh Asgari<sup>3</sup> · Mehdi Emadi<sup>4</sup> · Somayeh Mojtavavi<sup>5</sup> · Mohammad Ali Faramarzi<sup>5</sup> · Hossein Rastegar<sup>6</sup> · Bagher Larijani<sup>7</sup> · Mohammad Mahdavi<sup>7</sup>

Received: 16 December 2020 / Accepted: 28 April 2021 / Published online: 15 May 2021

© The Author(s), under exclusive licence to Springer Science+Business Media, LLC, part of Springer Nature 2021

## Abstract

$\alpha$ -Glucosidase is responsible for glucose release of oligosaccharides and disaccharides in the intestine and increase postprandial hyperglycemia. Inhibition of this enzyme is a beneficial therapeutic method for glycemic control in diabetes. This study deals with the design and synthesis of 4,5-diphenylimidazole-*N*-phenylacetamide derivatives **7a–l** and the screen of these compounds for their potential for  $\alpha$ -glucosidase inhibition. All the synthesized compounds exhibited superior  $\alpha$ -glucosidase inhibition ( $IC_{50} = 90.0–598.5 \mu M$ ) as compared to standard inhibitor acarbose ( $IC_{50} = 750.0 \mu M$ ). In contrast, these compounds were inactive against  $\alpha$ -amylase. Among the synthesized compounds, compound **7h** was the most potent inhibitor of this library and was a competitive inhibitor into  $\alpha$ -glucosidase with  $K_i$  value =  $86.3 \mu M$ . Docking study of the most potent compounds was performed to evaluate the binding interactions of these compounds with the active site of enzyme and to determine of binding energies of ligand–enzyme complexes. The results of this in silico study are in complete agreement with the results obtained from in vitro  $\alpha$ -glucosidase inhibition assay. Docking study of the most potent compound demonstrated that it interacted with important residues in the active site of  $\alpha$ -glucosidase. In vitro cytotoxic activity of the most potent compounds and in silico druglikeness/ADME/toxicity study of these compounds were evaluated.

**Keywords**  $\alpha$ -Glucosidase · 4,5-Diphenylimidazole · *N*-Phenylacetamide · Molecular modeling

## Introduction

Diabetes mellitus is a metabolic disorder that affect people of different ages, from children to the elderly [1]. This disease is

classified to two main types: type 1, that is, insulin dependent and due to defects in pancreatic  $\beta$ -cells in insulin secretion and type 2 diabetes, that is, non-insulin dependent and insulin resistance in body cells is usually observed in it [2, 3]. The high prevalence and increasing number of diabetic patients has led to the use of various treatment methods to control blood sugar in these patients. The main treatment for type 1 diabetes is insulin, and the main treatment for type 2 diabetes

**Supplementary information** The online version contains supplementary material available at <https://doi.org/10.1007/s00044-021-02734-5>.

✉ Maryam Mohammadi-Khanaposhtani  
maryammoha@gmail.com

✉ Mohammad Mahdavi  
momahdavi@tums.ac.ir

<sup>1</sup> Cellular and Molecular Biology Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran

<sup>2</sup> Department of Medicinal Chemistry, Faculty of Pharmacy, Islamic Azad University, Ayatollah Amoli Branch, Amol, Iran

<sup>3</sup> School of Chemistry, College of Science, University of Tehran, Tehran, Iran

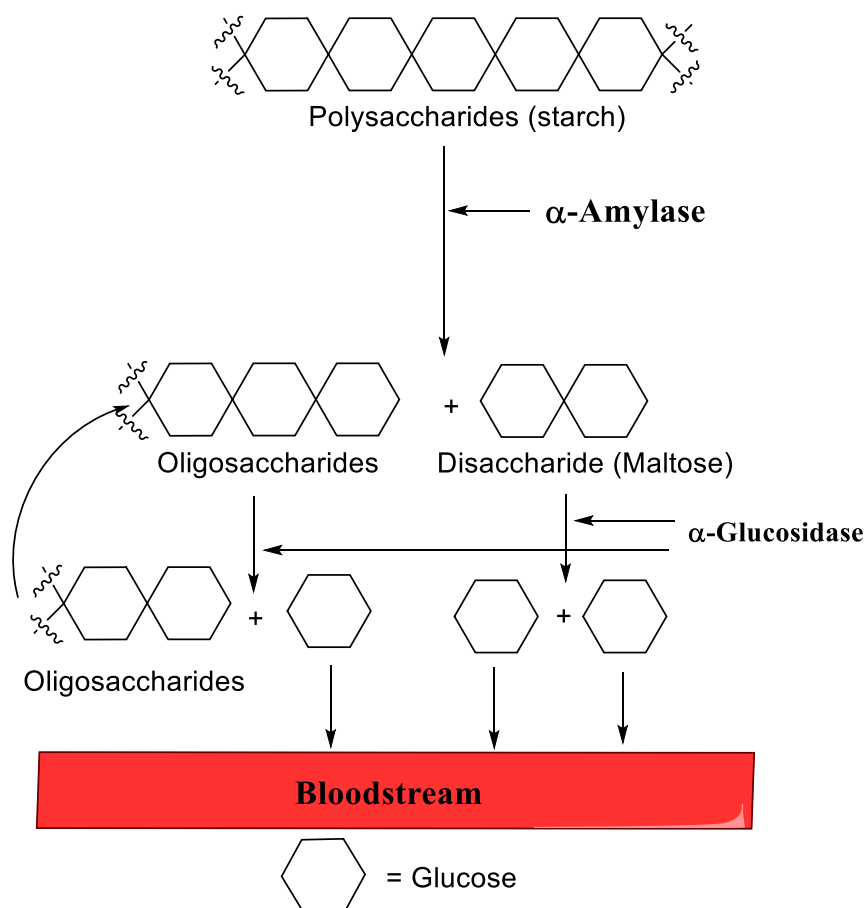
<sup>4</sup> Electrical and Computer Engineering Department, Babol Noshirvani University of Technology, Babol, Iran

<sup>5</sup> Department of Pharmaceutical Biotechnology, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

<sup>6</sup> Cosmetic Products Research Center, Iranian Food and Drug Administration, MOHE, Tehran, Iran

<sup>7</sup> Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

**Fig. 1** Hydrolysis of carbohydrates by  $\alpha$ -amylase and  $\alpha$ -glucosidase



is oral medications that lower postprandial hyperglycemia [4, 5]. One of the important classes of the latter medications are  $\alpha$ -glucosidase inhibitors, such as acarbose, voglibose, and miglitol [6]. These drugs effectively inhibited  $\alpha$ -glucosidase that is responsible for breaking down oligosaccharides and disaccharides to monosaccharides and decreased glucose level in blood [7]. Acarbose showed intestinal complications such as flatulence, bloating, cramping, and abdominal pain that several enzymatic studies have suggested that  $\alpha$ -amylase inhibition is the cause of these side effects [8].  $\alpha$ -Amylase is an important carbohydrate hydrolyzing enzyme that converts polysaccharides to oligosaccharides and disaccharides.  $\alpha$ -Amylase inhibition in addition to helping to lower blood glucose leads to the secretion of undecomposed polysaccharides to long intestine and causes intestinal complications. Mechanism of actions of  $\alpha$ -glucosidase and  $\alpha$ -amylase is schematically shown in Fig. 1.

Nitrogen-containing heterocycles have broad range of biological activities and are important blocks for drug design [9]. One of the most important of these heterocycles is imidazole, which is found broadly in the natural and synthetic molecules with biological properties, such as antifungal, anti-inflammatory, antitubercular, anticancer, and antiviral activities [10–14]. 4,5-Diphenylimidazole as a valuable imidazole

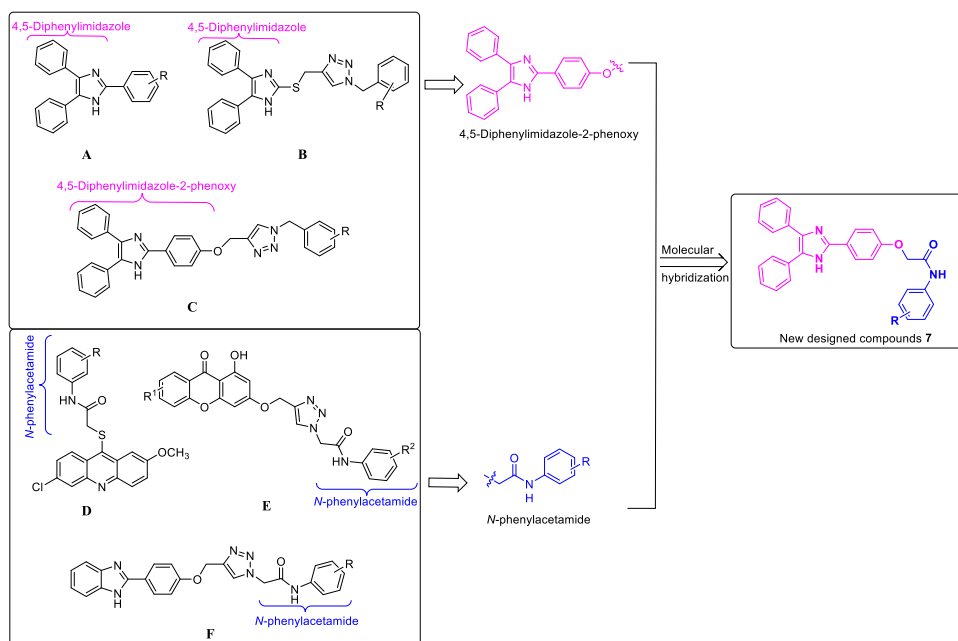
derivative also exhibited various biological activities [11]. This moiety is found in the several potent  $\alpha$ -glucosidase inhibitors, such as compounds **A** and **B** (Fig. 2) [15, 16]. Furthermore, 4,5-diphenylimidazole-2-phenoxy derivatives **C** also exhibited high inhibitory activity against  $\alpha$ -glucosidase [17]. On the other hand, *N*-phenylacetamid moiety is found in the several series of new potent  $\alpha$ -glucosidase inhibitors such as compounds **D–F** (Fig. 2) [18–20]. Therefore, herein, novel structures **7** by connecting 4,5-diphenylimidazole-2-phenoxy to *N*-phenylacetamid were designed, synthesized, and evaluated as new  $\alpha$ -glucosidase inhibitors.

## Material and methods

### General chemistry

Melting points of 4,5-diphenylimidazole-*N*-phenylacetamide derivatives **7a–I** were carried out on a Kofler hot stage apparatus and are uncorrected. Infrared spectra were recorded using KBr disks for solid materials on a Nicolet Magna FTIR 550 instrument. The  $^1\text{H}$  nuclear magnetic resonance (NMR) and  $^{13}\text{C}$  NMR spectra were run on a Bruker FT-500. Compounds were dissolved in dimethyl sulfoxide (DMSO)- $d_6$ , and

**Fig. 2** Design strategy for 4,5-diphenylimidazole-*N*-phenylacetamide derivatives **7** as new  $\alpha$ -glucosidase inhibitors



chemical shifts were referenced to tetramethylsilane. Mass spectra were obtained on an Agilent Technology (HP; MS Model: 5973 Network Mass Selective Detector) analysis system. Elemental analyses were performed on an Elementar Analysensysteme GmbH Vario EL CHNS mode instrument.

### General procedure for the synthesis of 2-chloro-*N*-phenylacetamide derivatives (**3a–l**)

A mixture of aniline derivatives **1a–l** (1 mmol) and chloroacetyl chloride **2** (1.2 mmol) in acetone (15 mL) was stirred at room temperature for 30 min. Then the reaction mixture was poured in water and the obtained precipitate was filtered and washed with water to obtain pure 2-chloro-*N*-phenylacetamide derivatives **3a–l**.

### General procedure for the synthesis of 2-(4-formylphenoxy)-*N*-phenylacetamides (**5a–l**)

A suspension of 2-chloro-*N*-phenylacetamide derivatives **3a–l** (1 mmol), 4-hydroxybenzaldehyde **4** (1 mmol), KI (1 mmol), and  $K_2CO_3$  (2 mmol) in acetone (15 mL) was stirred at 80 °C for 4 h. Similar to previous step, the reaction mixture was poured in water and residue was filtered and washed with water to obtain pure 2-(4-formylphenoxy)-*N*-phenylacetamides **5a–l**.

### General procedure for the synthesis of 4,5-diphenylimidazole-*N*-phenylacetamide derivatives (**7a–l**)

2-(4-Formylphenoxy)-*N*-phenylacetamides **5a–l** (1 mmol), benzil **6** (1 mmol), ammonium acetate (10 mmol), and

dimethylformamide (DMF) were stirred at 100 °C for 8 h. Then the reaction mixture was poured into cold water, the precipitate was filtered off, and washed with water to afford 4,5-diphenylimidazole-*N*-phenylacetamide derivatives **7a–l**.

### 2-(4-(4,5-diphenyl-1H-imidazol-2-yl)phenoxy)-*N*-phenylacetamide (**7a**)

White solid; isolated yield: 82%, mp 179–181 °C. Infrared (IR) (KBr,  $\nu$ ): 3289, 3052, 2935, 1637  $cm^{-1}$ .  $^1H$  NMR (500 MHz,  $DMSO-d_6$ )  $\delta$  12.54 (s, 1H), 8.03 (d,  $J = 8.5$  Hz, 2H), 7.73 (d,  $J = 7.6$  Hz, 2H), 7.59–7.56 (m, 3H), 7.54–7.52 (m, 4H), 7.45–7.42 (m, 2H), 7.41–7.32 (m, 5H), 7.08 (d,  $J = 8.6$  Hz, 2H), 4.51 (s, 2H, O- $CH_2$ ).  $^{13}C$  NMR (126 MHz,  $DMSO-d_6$ )  $\delta$  170.27, 164.37, 158.38, 145.97, 139.69, 132.89, 130.98, 130.84, 130.58, 129.53, 129.40, 129.25, 129.14, 129.00, 128.95, 128.73, 127.10, 125.66, 124.15, 115.36, 67.25. MS (70 eV,  $m/z$  [ $M^+$ ]) = 445. Anal Calcd for  $C_{29}H_{23}N_3O_2$ , C, 78.18, H, 5.20, N, 9.43. Found C, 78.16, H, 5.27, N, 9.41.

### 2-(4-(4,5-diphenyl-1H-imidazol-2-yl)phenoxy)-*N*-(*p*-tolyl)acetamide (**7b**)

White solid; isolated yield: 84%, mp 204–206 °C. IR (KBr,  $\nu$ ): 3277, 3069, 2921, 1655  $cm^{-1}$ .  $^1H$  NMR (500 MHz, Chloroform- $d$ )  $\delta$  12.84 (s, 1H), 7.99 (d,  $J = 8.7$  Hz, 2H), 7.88 (d,  $J = 7.4$  Hz, 4H), 7.78–7.68 (m, 1H), 7.58–7.55 (m, 1H), 7.49–7.44 (m, 4H), 7.44–7.38 (m, 3H), 7.35 (d,  $J = 8.8$  Hz, 2H), 7.30–7.27 (m, 1H), 7.16–7.08 (m, 1H), 5.25 (s, 2H, O- $CH_2$ ), 2.17 (s, 3H,  $CH_3$ ).  $^{13}C$  NMR (126 MHz,  $DMSO-d_6$ )  $\delta$  170.58, 158.40, 145.97, 138.41, 136.47,

134.01, 132.59, 131.43, 128.86, 128.19, 127.51, 127.14, 125.34, 124.03, 122.20, 120.94, 119.65, 118.15, 115.36, 115.12, 115.12, 65.02, 19.10. MS (70 eV,  $m/z$  [ $M^+$ ]) = 459. Anal Calcd for  $C_{30}H_{25}N_3O_2$ , C, 78.41, H, 5.48, N, 9.14. Found C, 78.44, H, 5.41, N, 9.13.

**2-(4-(4,5-diphenyl-1H-imidazol-2-yl)phenoxy)-N-(4-ethylphenyl)acetamide (7c)**

White solid; isolated yield: 83%, mp 167–169 °C. IR (KBr,  $\nu$ ): 3271, 3073, 2938, 1631  $cm^{-1}$ .  $^1H$  NMR (500 MHz, DMSO- $d_6$ )  $\delta$  12.67 (s, 1H), 8.10–7.95 (m, 3H), 7.58–7.50 (m, 5H), 7.43–7.35 (m, 5H), 7.33–7.24 (m, 3H), 7.11–6.95 (m, 3H), 4.77 (s, 2H, O-CH<sub>2</sub>), 2.69 (q,  $J = 7.0$  Hz, 2H, CH<sub>2</sub>), 1.26 (t,  $J = 7.2$  Hz, 3H, CH<sub>3</sub>).  $^{13}C$  NMR (126 MHz, DMSO- $d_6$ )  $\delta$  170.59, 158.42, 145.98, 138.95, 136.90, 134.85, 133.82, 132.77, 131.52, 129.98, 128.86, 128.19, 127.52, 127.16, 125.62, 124.00, 121.56, 119.57, 117.80, 115.12, 65.02, 56.52, 19.03. MS (70 eV,  $m/z$  [ $M^+$ ]) = 473. Anal Calcd for  $C_{31}H_{27}N_3O_2$ , C, 78.62, H, 5.75, N, 8.87. Found C, 78.58, H, 5.67, N, 8.82.

**2-(4-(4,5-diphenyl-1H-imidazol-2-yl)phenoxy)-N-(4-methoxyphenyl)acetamide (7d)**

White solid; isolated yield: 82%, mp 193–195 °C. IR (KBr,  $\nu$ ): 3279, 3071, 2920, 1644  $cm^{-1}$ .  $^1H$  NMR (500 MHz, DMSO- $d_6$ )  $\delta$  12.56 (s, 1H), 8.02 (d,  $J = 8.4$  Hz, 2H), 7.62–7.17 (m, 15H), 7.04 (d,  $J = 8.4$  Hz, 2H), 4.76 (s, 2H, O-CH<sub>2</sub>), 3.74 (s, 3H, O-CH<sub>3</sub>).  $^{13}C$  NMR (126 MHz, DMSO- $d_6$ )  $\delta$  170.58, 158.39, 145.97, 140.02, 138.08, 136.53, 135.14, 133.49, 132.05, 130.71, 128.86, 128.04, 127.12, 125.64, 124.05, 122.18, 120.99, 119.31, 117.93, 115.11, 65.03, 55.67. MS (70 eV,  $m/z$  [ $M^+$ ]) = 475. Anal Calcd for  $C_{30}H_{25}N_3O_3$ , C, 75.77, H, 5.30, N, 8.84. Found C, 75.83, H, 5.28, N, 8.83.

**N-(4-chlorophenyl)-2-(4-(4,5-diphenyl-1H-imidazol-2-yl)phenoxy)acetamide (7e)**

White solid; isolated yield: 86%, mp 239–241 °C. IR (KBr,  $\nu$ ): 3330, 2905, 1742, 1647  $cm^{-1}$ .  $^1H$  NMR (500 MHz, DMSO- $d_6$ )  $\delta$  13.58 – 12.21 (m, 1H), 8.04 (d,  $J = 8.9$  Hz, 2H), 7.65–7.35 (m, 13H), 7.31 (t,  $J = 7.3$  Hz, 2H), 7.06 (d,  $J = 8.9$  Hz, 2H), 4.77 (s, 2H, O-CH<sub>2</sub>).  $^{13}C$  NMR (126 MHz, DMSO- $d_6$ )  $\delta$  170.54, 158.57, 150.64, 145.87, 138.73, 133.33, 132.69, 130.80, 128.90, 128.25, 127.67, 127.32, 125.72, 124.60, 123.52, 122.03, 120.97, 118.84, 115.39, 115.16, 115.16, 65.01. MS (70 eV,  $m/z$  [ $M^+$ ]) = 479. Anal Calcd for  $C_{29}H_{22}ClN_3O_2$ , C, 72.57, H, 4.62, N, 8.75. Found C, 72.52, H, 4.61, N, 8.69.

**N-(2,6-dichlorophenyl)-2-(4-(4,5-diphenyl-1H-imidazol-2-yl)phenoxy)acetamide (7f)**

White solid; isolated yield: 84%, mp 199–201 °C. IR (KBr,  $\nu$ ): 3336, 2953, 1649  $cm^{-1}$ .  $^1H$  NMR (500 MHz, DMSO- $d_6$ )  $\delta$  12.58 (s, 1H), 8.06 (d,  $J = 8.4$  Hz, 2H), 7.64–7.47 (m, 8H), 7.46–7.32 (m, 6H), 7.17 (d,  $J = 8.9$  Hz, 2H), 4.85 (s, 2H, O-CH<sub>2</sub>).  $^{13}C$  NMR (126 MHz, DMSO- $d_6$ )  $\delta$  167.62, 157.75, 147.99, 145.83, 140.30, 138.80, 136.48, 135.52, 133.87, 132.96, 132.31, 130.44, 128.85, 128.24, 127.24, 125.91, 125.44, 124.72, 124.22, 115.50, 67.61. MS (70 eV,  $m/z$  [ $M^+$ ]) = 514. Anal Calcd for  $C_{29}H_{21}Cl_2N_3O_2$ , C, 67.71, H, 4.11, N, 8.17. Found C, 67.76, H, 4.12, N, 8.15.

**N-(2-bromophenyl)-2-(4-(4,5-diphenyl-1H-imidazol-2-yl)phenoxy)acetamide (7g)**

White solid; isolated yield: 85%, mp 236–238 °C. IR (KBr,  $\nu$ ): 3326, 2987, 1648  $cm^{-1}$ .  $^1H$  NMR (500 MHz, DMSO- $d_6$ )  $\delta$  12.59 (s, 1H), 8.10 (d,  $J = 7.8$  Hz, 2H), 7.89 (d,  $J = 7.5$  Hz, 1H), 7.71 (d,  $J = 7.6$  Hz, 1H), 7.60–7.50 (m, 4H), 7.49–7.27 (m, 7H), 7.25–7.03 (m, 4H), 4.87 (s, 2H, O-CH<sub>2</sub>).  $^{13}C$  NMR (126 MHz, DMSO- $d_6$ )  $\delta$  167.12, 157.99, 145.91, 140.26, 137.61, 135.86, 134.33, 133.14, 131.59, 130.38, 128.77, 128.43, 127.79, 127.47, 127.23, 125.87, 124.60, 123.43, 121.85, 120.32, 117.44, 115.52, 115.52, 67.56. MS (70 eV,  $m/z$  [ $M^+$ ]) = 523. Anal Calcd for  $C_{29}H_{22}BrN_3O_2$ , C, 66.42, H, 4.23, N, 8.01. Found C, 66.44, H, 4.21, N, 8.08.

**N-(3-bromophenyl)-2-(4-(4,5-diphenyl-1H-imidazol-2-yl)phenoxy)acetamide (7h)**

White solid; isolated yield: 86%, mp 214–216 °C. IR (KBr,  $\nu$ ): 3273, 3072, 2937, 1643  $cm^{-1}$ .  $^1H$  NMR (500 MHz, DMSO- $d_6$ )  $\delta$  12.53 (s, 1H), 8.02 (d,  $J = 7.8$  Hz, 2H), 7.62 – 7.48 (m, 6H), 7.47 – 7.17 (m, 9H), 7.04 (d,  $J = 7.8$  Hz, 2H), 4.75 (s, 2H, O-CH<sub>2</sub>).  $^{13}C$  NMR (126 MHz, DMSO- $d_6$ )  $\delta$  170.57, 158.39, 145.97, 138.95, 136.93, 135.92, 134.52, 133.23, 131.34, 128.81, 127.11, 124.05, 122.73, 121.52, 120.80, 119.71, 118.63, 117.69, 116.60, 115.11, 115.11, 113.36, 111.63, 65.03. MS (70 eV,  $m/z$  [ $M^+$ ]) = 523. Anal Calcd for  $C_{29}H_{22}BrN_3O_2$ , C, 66.42, H, 4.23, N, 8.01. Found C, 66.49, H, 4.22, N, 8.06.

**N-(4-bromophenyl)-2-(4-(4,5-diphenyl-1H-imidazol-2-yl)phenoxy)acetamide (7i)**

White solid; isolated yield: 86%, mp 224–226 °C. IR (KBr,  $\nu$ ): 3325, 2954, 1649  $cm^{-1}$ .  $^1H$  NMR (500 MHz, DMSO- $d_6$ )  $\delta$  13.01 – 11.95 (m, 1H), 8.03 (d,  $J = 8.5$  Hz, 2H), 7.60 – 7.23 (m, 15H), 7.05 (d,  $J = 8.5$  Hz, 2H), 4.76 (s, 2H, O-CH<sub>2</sub>).  $^{13}C$  NMR (126 MHz, DMSO- $d_6$ )  $\delta$  170.58, 158.41,

145.98, 136.09, 134.81, 133.08, 132.27, 131.13, 130.27, 128.86, 128.18, 127.51, 127.16, 125.77, 125.09, 124.00, 122.28, 121.28, 119.55, 115.12, 65.02. MS (70 eV,  $m/z$  [ $M^+$ ]) = 523. Anal Calcd for  $C_{29}H_{22}BrN_3O_2$ , C, 66.42, H, 4.23, N, 8.01. Found C, 66.40, H, 4.25, N, 8.01.

### 2-(4-(4,5-diphenyl-1H-imidazol-2-yl)phenoxy)-N-(2-methyl-3-nitrophenyl)acetamide (7j)

White solid; isolated yield: 81%, mp 195–197 °C. IR (KBr,  $\nu$ ): 3288, 3098, 2963, 1655  $cm^{-1}$ .  $^1H$  NMR (500 MHz, DMSO- $d_6$ )  $\delta$  12.58 (s, 1H), 8.03 (d,  $J = 8.3$  Hz, 2H), 7.61–7.45 (m, 6H), 7.45–7.21 (m, 9H), 7.05 (d,  $J = 8.3$  Hz, 2H), 4.76 (s, 2H, O-CH<sub>2</sub>), 2.07 (s, 3H, CH<sub>3</sub>).  $^{13}C$  NMR (126 MHz, DMSO- $d_6$ )  $\delta$  170.58, 158.40, 145.98, 136.68, 134.99, 133.13, 131.55, 130.59, 129.76, 128.86, 128.16, 127.51, 127.14, 126.12, 125.08, 124.03, 122.45, 120.83, 118.76, 117.90, 115.12, 65.02, 19.03. MS (70 eV,  $m/z$  [ $M^+$ ]) = 504. Anal Calcd for  $C_{30}H_{24}N_4O_4$ , C, 71.42, H, 4.79, N, 11.10. Found C, 71.44, H, 4.76, N, 11.16.

### N-(3-chloro-2-methylphenyl)-2-(4-(4,5-diphenyl-1H-imidazol-2-yl)phenoxy)acetamide (7k)

White solid; isolated yield: 83%, mp 166–168 °C. IR (KBr,  $\nu$ ): 3283, 3086, 2963, 1650  $cm^{-1}$ .  $^1H$  NMR (500 MHz, DMSO- $d_6$ )  $\delta$  12.43 (s, 1H), 8.23 (d,  $J = 8.3$  Hz, 1H), 8.14 (d,  $J = 8.3$  Hz, 1H), 8.09 (d,  $J = 8.9$  Hz, 2H), 7.80 (t,  $J = 7.8$  Hz, 1H), 7.57–7.52 (m, 4H), 7.42–7.29 (m, 7H), 7.19 (d,  $J = 8.9$  Hz, 2H), 4.86 (s, 2H, O-CH<sub>2</sub>), 2.05 (s, 3H, CH<sub>3</sub>).  $^{13}C$  NMR (126 MHz, DMSO- $d_6$ )  $\delta$  195.29, 180.73, 167.92, 156.48, 144.75, 143.98, 142.84, 141.38, 140.41, 139.08, 138.34, 136.95, 136.02, 134.06, 132.71, 131.35, 130.07, 129.99, 127.18, 125.37, 123.63, 122.65, 120.98, 64.04, 18.85. MS (70 eV,  $m/z$  [ $M^+$ ]) = 493. Anal Calcd for  $C_{30}H_{24}ClN_3O_2$ , C, 72.94, H, 4.90, N, 8.51. Found C, 72.91, H, 4.88, N, 8.50.

### N-(2-chloro-3-fluorophenyl)-2-(4-(4,5-diphenyl-1H-imidazol-2-yl)phenoxy)acetamide (7l)

White solid; isolated yield: 87%, mp 177–19 °C. IR (KBr,  $\nu$ ): 3287, 3080, 2966, 1651  $cm^{-1}$ .  $^1H$  NMR (500 MHz, DMSO- $d_6$ )  $\delta$  12.56 (s, 1H), 8.07 (d,  $J = 8.5$  Hz, 2H), 7.80 (t,  $J = 7.5$  Hz, 1H), 7.55 (s, 5H), 7.47–7.39 (m, 3H), 7.38–7.30 (m, 3H), 7.27–7.20 (m, 2H), 7.14 (d,  $J = 8.5$  Hz, 2H), 4.89 (s, 2H, O-CH<sub>2</sub>).  $^{13}C$  NMR (126 MHz, DMSO- $d_6$ )  $\delta$  167.52, 164.28, 158.32, 149.55, 145.94, 137.31, 135.81, 130.39, 129.41, 129.32, 128.97, 128.81, 128.70, 128.23, 128.13, 127.81, 127.55, 127.41, 127.32, 127.17, 126.86, 126.01, 125.46, 124.36, 120.87, 120.50, 120.37, 115.36, 67.39. MS (70 eV,  $m/z$  [ $M^+$ ]) = 497. Anal Calcd for  $C_{29}H_{21}ClFN_3O_2$ , C, 69.95, H, 4.25, N, 8.44. Found C, 69.91, H, 4.24, N, 8.49.

## Pharmacology

### In vitro $\alpha$ -glucosidase inhibition assay

$\alpha$ -Glucosidase inhibition assay was evaluated on yeast  $\alpha$ -glucosidase (*Saccharomyces cerevisiae*, EC3.2.1.20, 20 U/mg) according to the previous reports [21–24]. First, the various concentrations of compounds **7a–l** (20  $\mu$ l),  $\alpha$ -glucosidase solution (20  $\mu$ l), and potassium phosphate buffer (135  $\mu$ l) were added to a 96-well plate and incubated at 37 °C for 10 min. Then *p*-nitrophenyl glucopyranoside (substrate, 25  $\mu$ l, 4 mM) was added to the latter plate and allowed to incubate at 37 °C for 20 min. Finally, the absorbance changes were measured at 405 nm by using spectrophotometer (Gen5, Power wave xs2, BioTek, America). Solvent (DMSO with final concentration of 10%) was used as negative control and acarbose was used as positive control. IC<sub>50</sub> values of title compounds **7a–l** were calculated from nonlinear regression curve using the Logit method.

### In vitro $\alpha$ -amylase inhibition assay

The inhibitory activity of the newly synthesized compounds **7a–l** against  $\alpha$ -amylase was obtained according to used method in our previous work [23].

### Kinetic study

For kinetic study, the most potent compound **7h** was selected and 20  $\mu$ l of it in four different concentrations 0, 30, 60, and 90  $\mu$ M was incubated with 20  $\mu$ l of  $\alpha$ -glucosidase solution (1 U/ml) for 15 min at 30 °C. After that, the enzymatic reaction was started by adding 20  $\mu$ l of *p*-nitrophenyl glucopyranoside as substrate in concentrations 1–4 mM and the absorbance changes was determined for 20 min at 405 nm by using spectrophotometer (Gen5, Power wave xs2, BioTek, America).

### Molecular modeling study

Modeled  $\alpha$ -glucosidase was constructed according to the described method by Imran et al. [25, 26]. At first, a search was performed by using SWISS-MODEL to find an appropriate protein in the protein data bank (PDB) with a high sequence similarity with *S. cerevisiae*  $\alpha$ -glucosidase (used form of enzyme in enzymatic assay). As a result, isomaltase from *S. cerevisiae* (PDB code 3A4A) was selected with 72% identical and shares 85% similarity with the *S. cerevisiae*  $\alpha$ -glucosidase. Then this enzyme was subjected through sequence alignment and homology model using automated homology modeling pipeline SWISS-MODEL (managed by Swiss Institute of

Bioinformatics) and the quality of the obtained modeled enzyme (in pdb format) was verified using PROCHECK [27]. Pdb format of the modeled enzyme was converted to pdbqt coordinate by Auto dock Tools. Three-dimensional structures of the most potent compounds and standard inhibitor acarbose were built by MarvinSketch 5.8.3, 2012, ChemAxon (<http://www.chemaxon.com>) and were saved as pdb format and converted to pdbqt coordinate using Auto dock Tools. These pdbqts were used as an input file for the AUTOGRIID program. In the latter program, for each atom type in the ligand, maps were calculated with 0.375 Å spacing between grid points and center of grid box was placed at  $x = 12.5825$ ,  $y = 7.8955$ , and  $z = 12.519$  Å with dimensions  $40 \times 40 \times 40$  Å. Flexible ligand dockings were applied for the selected ligands. Each docked system was carried out by 50 runs of AUTODOCK search by the Lamarckian genetic algorithm. The best docking pose in term of binding energy for each ligand was selected for study of the interaction mode between  $\alpha$ -glucosidase and ligand.

### In vitro cytotoxicity assay

In vitro cytotoxic activity of the most potent compounds **7h**, **7a**, and **7d** was determined by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay according to literature [28]. For this propose, normal and cancer human cell lines were used.

### In silico druglikeness/ADME/toxicity study

In silico druglikeness/ADME/toxicity properties of standard drug acarbose and the most potent compounds **7h**, **7a**, and **7d** were predicted by using the preADMET online server (<http://preadmet.bmdrc.org/>) [29].

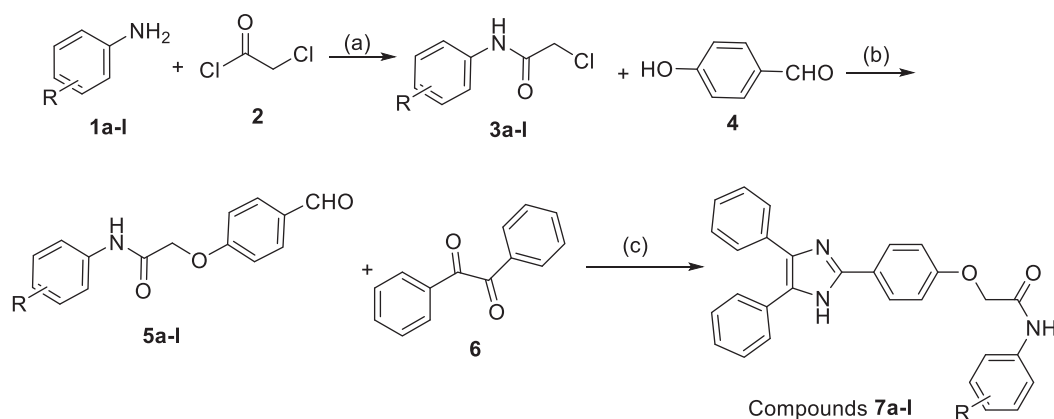
## Results and discussion

### Chemistry

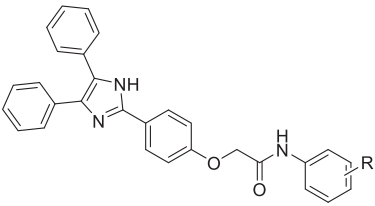
The synthetic routes for the synthesis of 4,5-diphenylimidazole-*N*-phenylacetamide derivatives **7a–l** has been depicted in Scheme 1. This synthesis process was started from the reaction between aniline derivatives **1a–l** and chloroacetyl chloride **2** in acetone at room temperature for 30 min to give 2-chloro-*N*-phenylacetamide derivatives **3a–l**. The latter compounds reacted with 4-hydroxybenzaldehyde **4** in the presence of KI and  $K_2CO_3$  in acetone at 80 °C for produce 2-(4-formylphenoxy)-*N*-phenylacetamides **5a–l**. In the final step, 2-(4-formylphenoxy)-*N*-phenylacetamides **5a–l** and benzil **6** in the presence of ammonium acetate in DMF at 100 °C converted to desired 4,5-diphenylimidazole-*N*-phenylacetamide derivatives **7a–l**.

### $\alpha$ -Glucosidase and $\alpha$ -amylase inhibitory activities

In vitro anti- $\alpha$ -glucosidase activity of the synthesized 4,5-diphenylimidazole-*N*-phenylacetamide derivatives **7a–l** was evaluated and the obtained results were compared with acarbose as a standard  $\alpha$ -glucosidase inhibitor ( $IC_{50} = 750.0 \pm 9.6 \mu M$ ). As can be seen in Table 1, the  $IC_{50}$  values of the studied compounds demonstrated that all the synthesized compounds **7a–l** were more potent than acarbose ( $IC_{50s} \leq 598.5 \pm 8.0 \mu M$ ). In the synthesis of these compounds, aniline and various aniline derivatives with electron-donating groups such as methyl, ethyl, and methoxy and electron-withdrawing groups such as chloro, bromo, nitro, and fluoro were used in order to optimize  $\alpha$ -glucosidase inhibition. The most potent compounds were 3-bromo and un-substituted compounds **7h** and **7a** with  $IC_{50}$  values =  $90.0 \pm 2.5$  and  $103.6 \pm 4.0 \mu M$ , respectively.



**Scheme 1** Synthetic routes to the target compounds **7a–l**: (a) Acetone, r.t. 30 min; (b) KI,  $K_2CO_3$ , Acetone, 80 °C, 4 h; (c)  $NH_4OAc$ , DMF, 100 °C, 8 h

**Table 1** In vitro  $\alpha$ -glucosidase and  $\alpha$ -amylase inhibitory activities of the synthesized compounds **7a–l**


Compound	R	IC <sub>50</sub> (μM) <sup>a</sup>	
		$\alpha$ -glucosidase	$\alpha$ -amylase
<b>7a</b>	H	103.6 ± 4.0	>500
<b>7b</b>	4-CH <sub>3</sub>	411.5 ± 7.3	>500
<b>7c</b>	4-Ethyl	402.0 ± 7.0	>500
<b>7d</b>	4-OCH <sub>3</sub>	154.1 ± 4.7	>500
<b>7e</b>	4-Cl	314.5 ± 6.5	>500
<b>7f</b>	2,6-Dichloro	161.5 ± 6.6	>500
<b>7g</b>	2-Br	179.8 ± 4.4	>500
<b>7h</b>	3-Br	90.0 ± 2.5	>500
<b>7i</b>	4-Br	598.5 ± 8.0	>500
<b>7j</b>	2-CH <sub>3</sub> -3-NO <sub>2</sub>	396.0 ± 6.0	>500
<b>7k</b>	2-CH <sub>3</sub> -3-Cl	303.1 ± 6.0	>500
<b>7l</b>	2-Cl-3-F	215.3 ± 5.0	>500
Acarbose	—	750.0 ± 9.6	108 ± 0.71

Furthermore, 4-methoxy derivative **7d**, 2,6-dichloro derivative **7f** and 2-bromo derivative **7g** exhibited good anti- $\alpha$ -glucosidase activity (IC<sub>50</sub> values  $\leq 179.8 \pm 4.4$  μM).

The  $\alpha$ -glucosidase inhibitory activity of 4,5-diphenylimidazole-*N*-phenylacetamide derivatives **7a–l** demonstrated that 3-bromo derivative **7h** showed the most potent activity, while 4-bromo derivative **7i** was less active compound among the synthesized compounds. Moreover, movement of bromo substituent of 3-position to 2-position, as in compound **7g**, led to a moderate decrease in the inhibitory activity.

The second potent compound among the synthesized compounds was un-substituted compound **7a**. Introduction of 4-methyl, 4-ethyl, or 4-chloro on *N*-phenylacetamide ring dramatically deteriorated anti- $\alpha$ -glucosidase as observed in compounds **7b**, **7c**, and **7e** while introduction of 4-methoxy substituent on the latter ring, as in compound **7d**, slightly decreased inhibitory activity in comparison to un-substituted compound **7a**.

Among the two-substituted compounds **7f** and **7j–l**, 2,6-dichloro derivative **7f** exhibited the best inhibitory activity.

$\alpha$ -Amylase inhibition assay of the synthesized compounds **7a–l** was also carried out and obtained data revealed that all the title compounds (IC<sub>50</sub> values  $>500$  μM) in comparison to acarbose (IC<sub>50</sub> =  $108 \pm 0.71$  μM) were inactive.

## Kinetic study against $\alpha$ -glucosidase

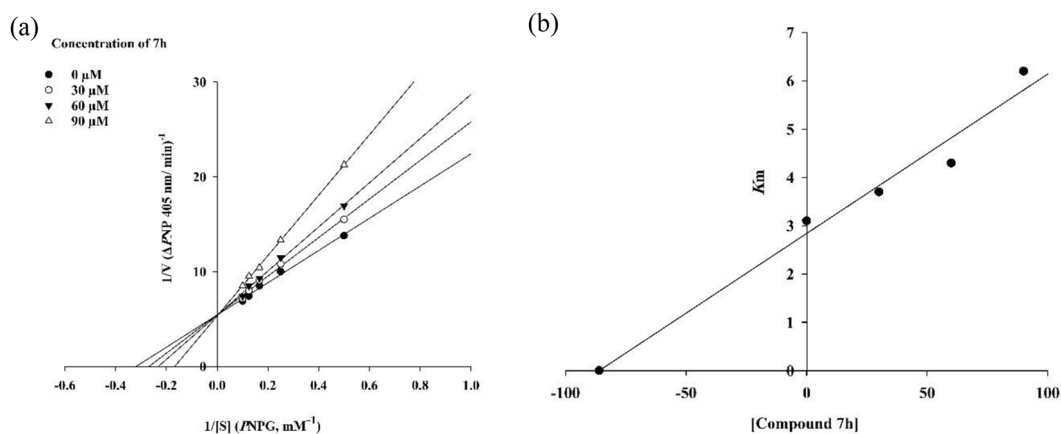
Kinetic study of the most potent compound **7h** was carried out in order to evaluate mechanism of  $\alpha$ -glucosidase inhibition of the new compounds. As was shown in Fig. 3a, with increase of concentration of the compound **7h**,  $V_{\max}$  remained unchanged while  $K_m$  increased. Therefore, compound **7h** was a competitive inhibitor against  $\alpha$ -glucosidase. The value of  $K_i$  for compound **7h** was  $86.3 \pm 0.11$  μM (Fig. 3b).

## $\alpha$ -Glucosidase molecular modeling study

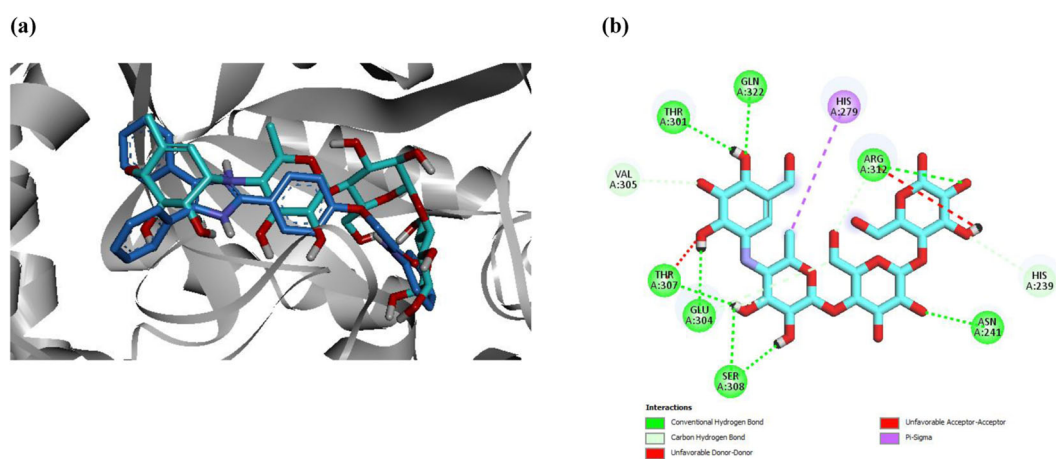
In order to clarify interaction modes of the newly synthesized compounds in the active site of  $\alpha$ -glucosidase, molecular modeling was conducted on the modeled form of this enzyme using Auto Dock Tools (version 1.5.6) [21]. For docking purposes, acarbose as standard inhibitor and most potent compounds **7h** and **7a** were selected and docked in the  $\alpha$ -glucosidase active site. The superimposed structure of acarbose and the most potent compound **7h** in the active site of target enzyme is shown in Fig. 4a. Analysis of the best pose of acarbose revealed that this inhibitor with binding energy of  $-4.04$  kcal/mol, interacted with the  $\alpha$ -glucosidase active site residues Gln322, Thr301, Glu304, Ser308, Arg312, Thr307, and Asn241 via hydrogen bonds (Fig. 4b). Furthermore, acarbose formed a hydrophobic interaction with His279, several non-classical hydrogen bonds with Arg312, Glu304, Val305, and His239, and two unfavorable interactions with Arg312 and Thr307.

The most potent compound **7h** established a hydrogen bond with Thr307 via NH unit of imidazole ring and a  $\pi$ -anion interaction with Glu304 via phenoxy group (Fig. 5a). Imidazole ring and phenoxy group also interacted with residue Pro309 through hydrophobic interactions. This amino acid also established a non-classical hydrogen bond with compound **7h**. Phenyl rings attached to imidazole ring interacted with Ala326 and Val316 via hydrophobic interactions. Furthermore, *N*-3-bromophenylacetamid moiety of compound **7h** established the following interactions: two hydrophobic interactions with residues Phe158 and Arg312 through 3-bromo substituent and phenyl ring, respectively, and a non-classical hydrogen bond with residue Phe311 through carbonyl unit.

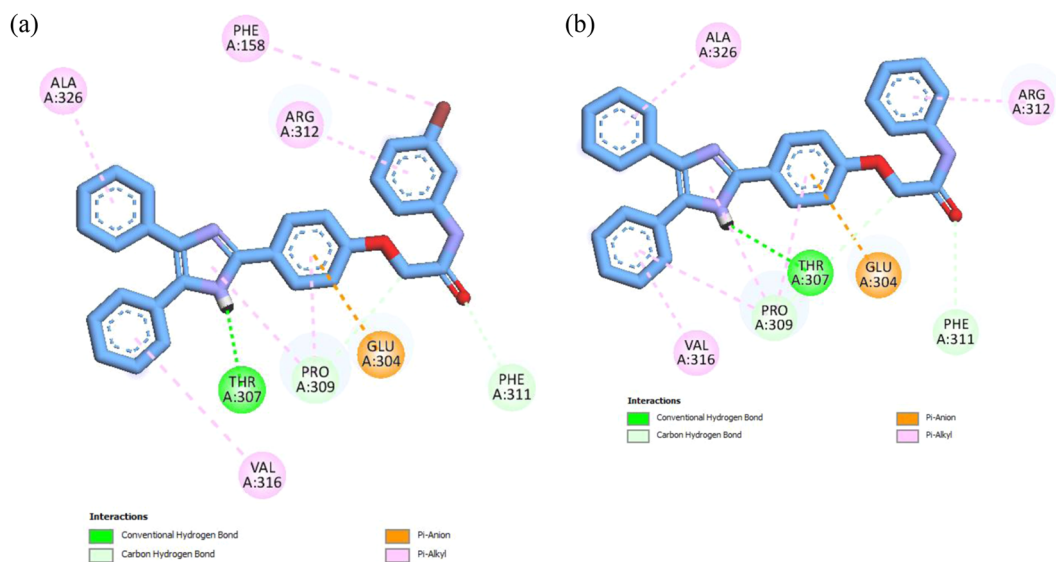
The comparison of interaction modes of the most potent compound **7h** containing *N*-3-bromophenylacetamid moiety with the second potent compound **7a** with *N*-phenylacetamid moiety demonstrated that compound **7h** established an additional hydrophobic interaction with active site residue Phe158 via 3-bromo substituent (Fig. 5). It should also be noted that compound **7a** created an additional hydrophobic interaction with Pro309 via 5-phenyl ring in comparison to compound **7h** (Fig. 5b). Other established interactions are the same in the both compounds **7h** and **7a**. Details of interaction modes of compounds **7h** and **7a** are listed in Table 2.



**Fig. 3** **a** The inhibition type and **b**  $K_i$  value determination of the most potent compound **7h**



**Fig. 4** **(a)** Superimposition structure of acarbose (cyan) and the most potent compound **7h** (blue); **(b)** interaction mode of acarbose in the active site of  $\alpha$ -glucosidase



**Fig. 5** **(a)** The interaction modes of the most potent compounds **7h** and **(b)** **7a** in the active site of  $\alpha$ -glucosidase



**Table 2** Interaction mode details of the compounds **7h** and **7a**

Compound	Interaction	Interacting unit of the ligand	Amino acid	Distance (Å)
<b>7h</b>	Hydrophobic	A phenyl ring of 4,5-diphenylimidazole moiety	Ala326	4.55
	Hydrophobic	A phenyl ring of 4,5-diphenylimidazole moiety	Val316	5.38
	H-bond	NH unit of imidazole ring	Thr307	2.09
	Hydrophobic	Imidazole ring	Pro309	4.42
	Hydrophobic	Phenoxy group	Pro309	4.86
	$\pi$ -anion	Phenoxy group	Glu304	3.41
	Non-classical hydrogen bond	-CH <sub>2</sub> -C=O	Phe311	3.07
	Non-classical hydrogen bond	-CH <sub>2</sub> -C=O	Pro309	3.34
	Hydrophobic	<i>N</i> -3-Bromophenyl moiety	Arg312	4.04
	Hydrophobic	<i>N</i> -3-Bromophenyl moiety	Arg312	5.28
<b>7a</b>	Hydrophobic	A phenyl ring of 4,5-diphenylimidazole moiety	Ala326	5.17
	Hydrophobic	A phenyl ring of 4,5-diphenylimidazole moiety	Val316	5.01
	Hydrophobic	A phenyl ring of 4,5-diphenylimidazole moiety	Pro309	5.31
	H-bond	NH unit of imidazole ring	Thr307	2.01
	Hydrophobic	Imidazole ring	Pro309	4.23
	Hydrophobic	Phenoxy group	Pro309	5.14
	$\pi$ -anion	Phenoxy group	Glu304	3.41
	Non-classical hydrogen bond	-CH <sub>2</sub> -C=O	Phe311	2.99
	Non-classical hydrogen bond	-CH <sub>2</sub> -C=O	Pro309	3.37
	Hydrophobic	<i>N</i> -phenyl moiety	Arg312	4.7

The calculation of binding energies of acarbose (−4.04 kcal/mol) and compounds **7h** (−11.32 kcal/mol) and **7a** (−10.65 kcal/mol) demonstrated that our newly synthesized compounds bind to  $\alpha$ -glucosidase more easily than acarbose. These findings are in agreement with the obtained data of in vitro enzyme inhibition assay (Table 1, compounds **7h** and **7a** vs. acarbose).

### In vitro cytotoxicity assay

In vitro cytotoxicity of compounds **7h**, **7a**, and **7d** was evaluated against normal cells HDF and cancer cells MCF-7 by MTT assay [28]. As can be seen in Table 3, the selected compounds were non-cytotoxic at 200  $\mu$ M against studied cells in comparison to standard cytotoxic agent etoposide.

### In silico druglikeness, ADME, and toxicity studies

Druglikeness/ADME/T properties of acarbose as standard drug and new compounds **7h**, **7a**, and **7d** as the most potent inhibitors were predicted by the online software

**Table 3** Cytotoxic activity of compounds **7j**, **7k**, and **7a**

Compound	Cytotoxicity (IC <sub>50</sub> $\mu$ M) <sup>a</sup>	
	MCF-7	HDF
<b>7j</b>	>200	>200
<b>7k</b>	>200	>200
<b>7a</b>	>200	>200
Etoposide	22.08 $\pm$ 0.39	92.7 $\pm$ 1.2

<sup>a</sup>Values are the mean  $\pm$  SD

PreADMET [29]. The obtained results are listed in Table 4. As can be seen in this table, compounds **7a** and **7d** are drug-like in terms of Rule of Five and MDDR-like rule while compound **7h** and acarbose only follow MDDR-like rule. Our new compounds **7h**, **7a**, and **7d** have Caco2 cell permeability and human oral absorption higher of acarbose. The predicted values of blood–brain barrier permeability for any of the studied compounds are not in the acceptable range. Predicting the toxicity of the all selected compounds showed that all the studied compounds were mutagenic

**Table 4** Druglikeness/ADME/T profile of the most potent compounds **7h**, **7a**, and **7d**

Druglikeness/ ADME/T <sup>a</sup>	Compound			
	7h	7a	7d	Acarbose
Rule of Five	Violated	Suitable	Suitable	Violated
MDDR-like rule	Drug-like	Drug-like	Drug-like	Drug-like
Caco2	50.9767	42.8665	53.6636	9.44448
HIA	94.473763	93.925345	94.049149	0.000000
BBB	9.57151	6.69769	4.50937	0.0271005
Ames test	Mutagen	Mutagen	Mutagen	Mutagen
hERG inhibition	High risk	High risk	High risk	Ambiguous
Carcino Mouse	Negative	Negative	Negative	Positive
Carcin Rat	Positive	Positive	Positive	Negative

<sup>a</sup>The recommended ranges for Caco2: <25 poor, >500 great, HIA: >80% is high and <25% is poor, BBB = -3.0 to 1.2, and Skin\_Permeability = -8.0 to -1.0

(Ames test). Moreover, in silico toxicity assay also predicted that new compounds **7h**, **7a**, and **7d** are high risk in terms of cardiotoxicity while cardiotoxicity of acarbose is ambiguous. Finally, all the test compounds have carcinogenic effect on rat while acarbose has carcinogenic effect on mouse.

## Conclusion

In conclusion, we have designed and synthesized a series of new 4,5-diphenylimidazole-*N*-phenylacetamide derivatives **7a–i** and studied  $\alpha$ -glucosidase and  $\alpha$ -amylase inhibitory activities of these compounds. All the synthesized compounds were more potent than standard inhibitor, and among them, compounds **7h**, **7a**, **7d**, **7f**, and **7g** exhibited excellent anti- $\alpha$ -glucosidase activity with  $IC_{50} \leq 179.8 \pm 4.4 \mu\text{M}$ . On the other hand, these compounds were inactive against  $\alpha$ -amylase in comparison to acarbose. Compound **7h** ( $IC_{50} = 90.0 \pm 2.5 \mu\text{M}$ ) with *N*-3-bromophenylacetamid moiety was found to be the most active compound against  $\alpha$ -glucosidase and was a competitive inhibitor. Furthermore, molecular modeling study was performed to investigate the interaction modes and binding energies of the most active analogs in the  $\alpha$ -glucosidase active site. In vitro cytotoxicity assay of the most potent compound revealed that these compounds are non-cytotoxic in comparison to standard cytotoxic agent etoposide. Furthermore, in silico druglikeness/ADME/toxicity properties of the most active compounds were predicted by a reliable online software.

**Funding** This work was financially supported by Babol University of Medical Sciences (the grant number: 724132438). The ethics code for this study is IR.MUBABOL.HRI.REC.1398.181.

## Compliance with ethical standards

**Conflict of interest** The authors declare no competing interests.

**Publisher's note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

## References

- Zimmet P, Alberti KG, Kaufman F, Tajima N, Silink M, Arslanian S, et al. The metabolic syndrome in children and adolescents—an IDF consensus report. *Pediatr Diabetes*. 2007;8:299–306.
- Ozougwu JC, Obimba KC, Belonwu CD, Unakalamba CB. The pathogenesis and pathophysiology of type 1 and type 2 diabetes mellitus. *J Physiol Pharm*. 2013;4:46–57.
- Fronzo DE. The triumvirate: SS-cell, muscle, liver—a collusion responsible for NIDDM. *Diabetes*. 1988;37:667–87.
- Chamberlain JJ, Kalyani RR, Leal S, Rhinehart AS, Shubrook JH, Skolnik N, et al. Treatment of type 1 diabetes: synopsis of the 2017 American Diabetes Association Standards of Medical Care in Diabetes. *Ann Intern Med*. 2017;167:493–8.
- Cervera A, Wajcberg E, Sriwijitkamol A, Fernandez M, Zuo P, Triplitt C, et al. Mechanism of action of exenatide to reduce postprandial hyperglycemia in type 2 diabetes. *Am J Physiol Endocrinol Metab*. 2008;294:E846–52.
- Derosa G, Maffioli P.  $\alpha$ -Glucosidase inhibitors and their use in clinical practice. *Arch Med Sci AMS*. 2012;8:899.
- Leroux-Stewart J, Rabasa-Lhoret R, Chiasson JL.  $\alpha$ -Glucosidase inhibitors. *Ther Diabetes Mellit Relat Disord*. 2014;2:416.
- Dong Y, Zhang B, Sun W, Xing Y. Intervention of prediabetes by flavonoids from *Oroxylum indicum*. In: Watson RR, Preedy VR, editors. *Bioactive food as dietary interventions for diabetes*. London: Academic Press, p. 559–575 2019.
- Asif M. A mini review: biological significances of nitrogen heteroatom containing heterocyclic compounds. *Int J Bioorg Chem*. 2017;2:146–52.
- Hossain M, Nanda AK. A review on heterocyclic: synthesis and their application in medicinal chemistry of imidazole moiety. *Science*. 2018;6:83–94.
- Shalini K, Sharma PK, Kumar N. Imidazole and its biological activities: a review. *Der Chem Sin*. 2010;1:36–47.
- Bhatnagar A, Sharma PK, Kumar N. A review on “Imidazoles”: their chemistry and pharmacological potentials. *Int J PharmTech Res*. 2011;3:268–82.
- Gupta V, Kant V. A review on biological activity of imidazole and thiazole moieties and their derivatives. *Sci Int*. 2013;1:253–60.
- Rani N, Sharma A, Kumar Gupta G, Singh R. Imidazoles as potential antifungal agents: a review. *Mini Rev Med Chem*. 2013;13:1626–55.
- Yar M, Bajda M, Shahzad S, Ullah N, Gilani MA, Ashraf M, et al. Organocatalyzed solvent free an efficient novel synthesis of 2, 4, 5-trisubstituted imidazoles for  $\alpha$ -glucosidase inhibition to treat diabetes. *Bioorg Chem*. 2015;58:65–71.
- Asgari MS, Mohammadi-Khanaposhtani M, Sharafi Z, Faramarzi MA, Rastegar H, Esfahani EN, et al. Design and synthesis of 4,5-diphenyl-imidazol-1,2,3-triazole hybrids as new anti-diabetic agents: in vitro  $\alpha$ -glucosidase inhibition, kinetic and docking studies. *Mol Divers*. 2020. <https://doi.org/10.1007/s11030-020-10072-8>
- Saeedi M, Mohammadi-Khanaposhtani M, Asgari MS, Eghbalnejad N, Imanparast S, Faramarzi MA, et al. Design, synthesis, in vitro, and in silico studies of novel diarylimidazole-1,2,3-triazole hybrids as potent  $\alpha$ -glucosidase inhibitors. *Bioorg Med Chem*. 2019;27:115148.

18. Mohammadi-Khanaposhtani M, Rezaei S, Khalifeh R, Imanparast S, Faramarzi MA, Bahadorikhalili S, et al. Design, synthesis, docking study,  $\alpha$ -glucosidase inhibition, and cytotoxic activities of acridine linked to thioacetamides as novel agents in treatment of type 2 diabetes. *Bioorg Chem.* 2018;80:288–95.
19. Ye GJ, Lan T, Huang ZX, Cheng XN, Cai CY, Ding SM, et al. Design and synthesis of novel xanthone-triazole derivatives as potential antidiabetic agents:  $\alpha$ -Glucosidase inhibition and glucose uptake promotion. *Eur J Med Chem.* 2019;177:362–73.
20. Asemanipoor N, Mohammadi-Khanaposhtani M, Moradi S, Vahidi M, Asadi M, Faramarzi MA, et al. Synthesis and biological evaluation of new benzimidazole-1, 2, 3-triazole hybrids as potential  $\alpha$ -glucosidase inhibitors. *Bioorg Chem.* 2020;95:103482.
21. Adib M, Peytam F, Rahmanian-Jazi M, Mahernia S, Bijanzadeh HR, Jahani M, et al. New 6-amino-pyrido[2, 3-d] pyrimidine-2, 4-diones as novel agents to treat type 2 diabetes: a simple and efficient synthesis,  $\alpha$ -glucosidase inhibition, molecular modeling and kinetic study. *Eur J Med Chem.* 2018;155:353–63.
22. Sepehri N, Asemanipoor N, Mousavianfard SA, Hoseini S, Faramarzi MA, Adib M, et al. New acridine-9-carboxamide linked to 1, 2, 3-triazole-*N*-phenylacetamide derivatives as potent  $\alpha$ -glucosidase inhibitors: design, synthesis, in vitro, and in silico biological evaluations. *Med Chem Res.* 2020;29:1836–45.
23. Asgari MS, Mohammadi-Khanaposhtani M, Kiani M, Ranjbar PR, Zabihi E, Pourbagher R, et al. Biscoumarin-1, 2, 3-triazole hybrids as novel anti-diabetic agents: design, synthesis, in vitro  $\alpha$ -glucosidase inhibition, kinetic, and docking studies. *Bioorg Chem.* 2019;92:103206.
24. Sherafati M, Mohammadi-Khanaposhtani M, Moradi S, Asgari MS, Najafabadipour N, Faramarzi MA, et al. Design, synthesis and biological evaluation of novel phthalimide-Schiff base-coumarin hybrids as potent  $\alpha$ -glucosidase inhibitors. *Chem Pap.* 2020;74:4379–88.
25. Imran S, Taha M, Ismail NH, Kashif SM, Rahim F, Jamil W, et al. Synthesis of novel flavone hydrazones: in-vitro evaluation of  $\alpha$ -glucosidase inhibition, QSAR analysis and docking studies. *Eur J Med Chem.* 2015;105:156–70.
26. Imran S, Taha M, Ismail NH, Kashif SM, Rahim F, Jamil W, et al. Synthesis, in vitro and docking studies of new flavone ethers as  $\alpha$ -glucosidase inhibitors. *Chem Biol Drug Des.* 2016;87:361–73.
27. Kiefer F, Arnold K, Künzli M, Bordoli L, Schwede T. The SWISS-MODEL Repository and associated resources. *Nucleic Acids Res.* 2009;37:D387–92.
28. Abolhasani MH, Safavi M, Goodarzi MT, Kassae SM, Azin M. Identification and anti-cancer activity in 2D and 3D cell culture evaluation of an Iranian isolated marine microalgae *Picochlorum* sp. RCC486. *DARU J Pharm Sci.* 2018;26:105–16.
29. Bioinformatics and Molecular Design Research Center. Pre-ADMET program. Bioinformatics and Molecular Design Research Center, Seoul, South Korea. 2014. <http://preadmet.bmdrc.org>