Chemical Papers
https://doi.org/10.1007/s11696-020-01246-7

ORIGINAL PAPER

Design, synthesis and biological evaluation of novel phthalimide-Schiff base-coumarin hybrids as potent α-glucosidase inhibitors

Maedeh Sherafati[1] · Maryam Mohammadi-Khanaposhtani[2] · Shahram Moradi[1] · Mohammad Sadegh Asgari[3] · Nadia Najafabadipour[4] · Mohammad Ali Faramarzi[4] · Mohammad Mahdavi[5] · Mahmood Biglar[5] · Bagher Larijani[5] · Haleh Hamedifar[6] · Mir Hamed Hajimiri[7]

Received: 1 February 2020 / Accepted: 7 June 2020

Abstract

We have designed and synthesized phthalimide-Schiff base-coumarin hybrids **8a**–**b**, **9a**–**d**, **10a**–**b**, and **11a**–**d** and evaluated them for α-glucosidase inhibitory potential against yeast form of this enzyme. For the synthesis of title compounds 4-hydroxybenzaldehyde, 4-hydroxy-3-methoxybenzaldehyde, 2-hydroxybenzaldehyde, 2-hydroxybenzaldehyde derivatives, coumarin-3-carbohydrazide, and coumarin-7-yloxy-acetohydrazide were used. In vitro α-glucosidase inhibition revealed that all the synthesized compounds exhibited outstanding α-glucosidase inhibition with IC_{50} values ranging between 85.2 ± 1.7 and 577.7 ± 7.5 μM when compared with the standard inhibitor acarbose having IC_{50} value 750.0 ± 12.0 μM. The most potent compounds were 4-hydroxybenzaldehyde derivative **8a** with coumarin-3-carbohydrazide moiety, 2-hydroxy-5-nitrobenzaldehyde derivative **11d** with coumarin-7-yloxy-acetohydrazide moiety, and 2-hydroxy-5-nitrobenzaldehyde derivative **9d** with coumarin-3-carbohydrazide moiety. Molecular docking studies were carried out to understand the interaction modes and binding energies of the most active compounds and standard drug acarbose. This studies predicted that compounds **8a**, **11d**, and **9d** (respectively with binding energies = − 10.77, − 8.65, and − 8.66 kcal/mol) bind to active site α-glucosidase more easily than acarbose (binding energy = − 4.04 kcal/mol).

Keywords α-Glucosidase · Docking study · Kinetic study · Phthalimide · Schiff base · Coumarin

Introduction

Diabetes mellitus (DM) is the most important disease related to carbohydrate metabolism. In type 1 of DM, defects in secretion of insulin as the main hormone in the regulation of carbohydrate metabolism are observed (Atkinson and

Maedeh Sherafati and Maryam Mohammadi-Khanaposhtani have contributed equally to this work.

✉ Mohammad Mahdavi
momahdavi@tums.ac.ir

✉ Mir Hamed Hajimiri
h.hajimiri@nanoalvand.com

[1] Department of Chemistry, Tehran North Branch, Islamic Azad University, Tehran, Iran

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

[3] School of Chemistry, College of Science, University of Tehran, Tehran, Iran

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

[5] Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

[6] CinnaGen Medical Biotechnology Research Center, Alborz University of Medical Sciences, Karaj, Iran

[7] Nano Alvand Company, Avicenna Tech Park, Tehran University of Medical Sciences, Tehran, Iran

Published online: 15 June 2020

Eisenbarth 2001). In the more common form of this disease, type 2, commonly, the body's resistance to insulin is seen which can be accompanied with inadequate insulin secretion (Saltiel 2001). Type 1 DM is managed by insulin and Type 2 DM is managed by different classes of drugs that are used alone or in combination with insulin, depending on the condition of the patient (Kahn et al. 2014). Most used drugs to treat Type 2 DM are oral and reduce blood glucose by a variety of mechanisms (Cheng and Fantus 2005). One of the important mechanisms for reducing blood glucose level is α-glucosidase inhibition; this enzyme converts carbohydrates to glucose. Several α-glucosidase inhibitors such as acarbose and miglitol are available in the pharmaceutical market for treatment of Type 2 DM (AG 1994). These drugs can lead to intestinal disturbances such as flatulence, bloating, and cramping and abdominal pain (Hollander 1992). Therefore, development of new potent α-glucosidase inhibitors with low side effects on intestine for treatment of the type 2 diabetes is an urgent need.

Phthalimide is a bicyclic compound with benzo-fused pyrrole-2,5-dione scaffold. This compound was used as an important segment in design numerous biologically active hybrid molecules with various properties such as antinoceptive, anti-inflammatory, antitumor, anti-convulsant, anti-microbial activities (Sharma et al. 2010). Furthermore, *N*-(3-phenoxypropyl)phthalimide derivatives **A** showed high inhibitory activity against α-glucosidase (Fig. 1) (Pascale et al. 2010).

One of the pharcophores widely used for design new α-glucosidase inhibitors is Schiff base (Imran et al. 2015; Taha et al. 2015; Zawawi et al. 2016). As can be seen in Fig. 1, 3-coumarincarbohydrazones **B** are Schiff base derivatives that can inhibit significantly α-glucosidase (Taha et al. 2018). On the other hand, 7-hydroxy coumarin derivative **C** also exhibited significant inhibitory activity against α-glucosidase (Fig. 1) (Singh et al. 2018). Furthermore, it is worthy to note that coumarin ring found in several potent α-glucosidase inhibitors (Mohammadi-Khanaposhtani et al. 2018; Xu et al. 2020).

In view of the importance of the phthalimide, Schiff base, and coumarin in the design of new and potent α-glucosidase inhibitors, in this work, phthalimide-Schiff base-coumarin hybrids **8a–b**, **9a–d**, **10a–b**, and **11a–d** were presented as novel α-glucosidase inhibitors (Fig. 1). These compounds with simple and efficient chemical reactions were synthesized and evaluated against yeast α-glucosidase. Kinetic and molecular modeling studies were also performed to evaluate the interactions of these compounds with α-glucosidase.

Experimental

Melting points of phthalimide-Schiff base-coumarin hybrids **8a–b**, **9a–d**, **10a–b**, and **11a–d** were measured on a Kofler hot stage apparatus. IR spectra and NMR (^{1}H and ^{13}C) were obtained by using a Bruker FT-500 and Nicolet Magna FTIR 550 spectrophotometer on KBr disks, respectively. Elemental analysis was recorded by an Elementar Analysensystem GmbH VarioEL CHN mode. Compounds **1**, **6**, and **7** were obtained according to previous described methods (Nagarapu et al. 2011; Secci et al. 2011; Wang et al. 2017).

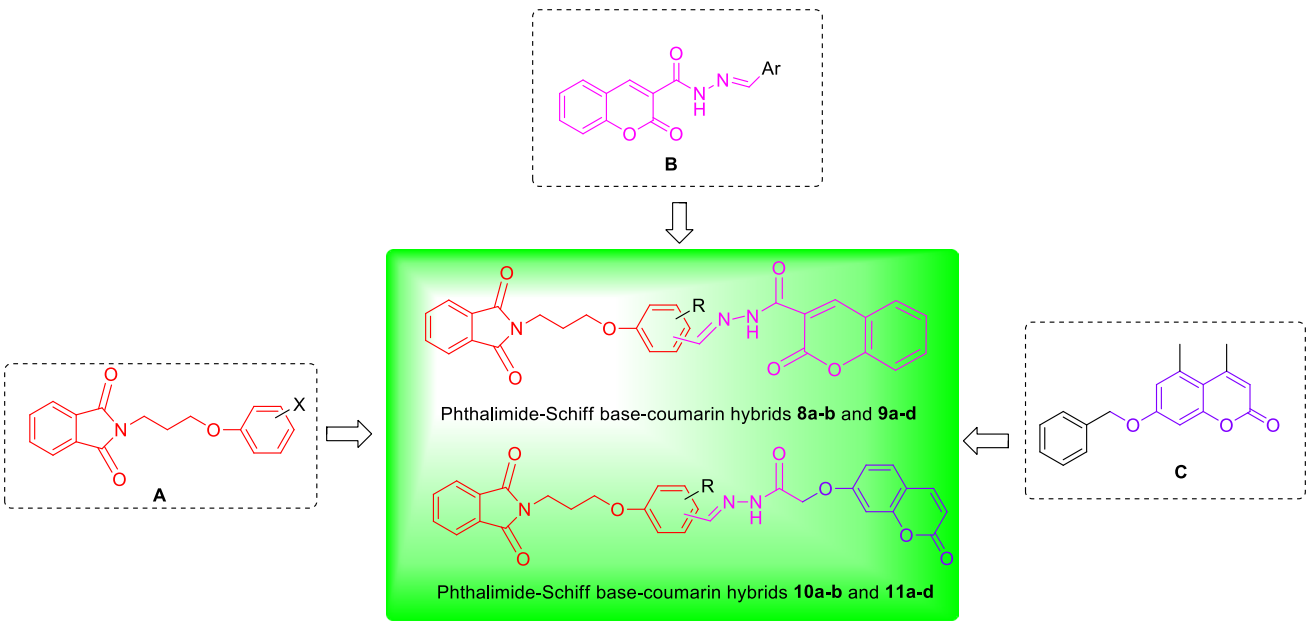


Fig. 1 Design of phthalimide-Schiff base-coumarin hybrids **8a–b**, **9a–d**, **10a–b**, and **11a–d** as potent α-glucosidase inhibitors

General procedure for the synthesis of 4-(3-(1,3-dioxoisoindolin-2-yl)propoxy)benzaldehyde (4) or 2-(3-(1,3-dioxoisoindolin-2-yl)propoxy) benzaldehyde derivatives (5a–e)

A mixture of 2-(3-bromopropyl)isoindoline-1,3-dione **1** (2 mmol, 0.53 g), 4-hydroxybenzaldehyde derivatives **2a**–**b** (2 mmol, 4-hydroxybenzaldehyde **2a**: 0.24 g; 4-hydroxy-3-methoxybenzaldehyde **2b**: 0.3 g) or 2-hydroxybenzaldehyde derivatives **3a**–**d** (2 mmol, 2-hydroxybenzaldehyde **3a**: 0.24 g; 2-hydroxy-3-methoxybenzaldehyde **3b**: 0.3 g; 2-hydroxy-5-bromobenzaldehyde **3c**: 0.4 g; 2-hydroxy-5-nitrobenzaldehyde **3d**: 0.33 g), and K_2CO_3 (2.4 mmol, 0.33 g) in DMF (50 mL) was stirred for 6–11 h at 80 °C. After completion of reaction (checked by TLC), water (100 mL) was added to reaction mixture and the obtained participates filtered off to give pure title compounds **4a**–**b** or **5a**–**d**.

General procedure for the synthesis of phthalimide-Schiff base-coumarin derivatives 8a–b, 9a–d, 10a–b, and 11a–d

A mixture of 4-(3-(1,3-dioxoisoindolin-2-yl)propoxy)benzaldehyde **4a**–**b** (1 mmol, 4-(3-(1,3-dioxoisoindolin-2-yl) propoxy)benzaldehyde **4a**: 0.31 g; 4-(3-(1,3-dioxoisoindolin-2-yl)propoxy)-3-methoxybenzaldehyde **4b**: 0.34 g) or 2-(3-(1,3-dioxoisoindolin-2-yl)propoxy)benzaldehyde derivatives **5a**–**d** (1 mmol, 2-(3-(1,3-dioxoisoindolin-2-yl) propoxy)benzaldehyde **5a**: 0.31 g; 2-(3-(1,3-dioxoisoindolin-2-yl)propoxy)-3-methoxybenzaldehyde **5b**: 0.34 g; 2-(3-(1,3-dioxoisoindolin-2-yl)propoxy)-5-bromobenzaldehyde **5c**: 0.39 g; 2-(3-(1,3-dioxoisoindolin-2-yl) propoxy)-5-nitrobenzaldehyde **5d**: 0.35 g) and 2-oxo-2H-chromene-3-carbohydrazide **6** (1 mmol, 0.2 g) or 2-((2-oxo-2H-chromen-7-yl)oxy)acetohydrazide **7** (1 mmol, 0.23 g) in the presence of PTSA (20 mol%) in ethanol (15 mL) was refluxed for 1–3. After completion of reaction (checked by TLC, eluent: petroleum ether/ethyl acetate = 1:1, retention factor (Rf) value = 0.3), reaction mixture was added to 25 mL of cold water, this new mixture was filtered off, and resulting residue was purified with recrystallization in ethanol for produce compounds **8a**–**b**, **9a**–**d**, **10a**–**b**, and **11a**–**d**.

(*E*)-*N*′-(4-(3-(1,3-dioxoisoindolin-2-yl)propoxy)benzylidene)-2-oxo-2H-chromene-3-carbohydrazide (8a)

White solid; yield 71%; m.p. 173–175 °C; IR (KBr, υ): 3284, 3075, 2924, 1667, 1641, 1084 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 9.05 (s, 1H, NH), 8.70 (s, 1H, coumarin), 8.49 (s, 1H, N=CH), 7.88 (d, J = 7.7 Hz, 1H, Ar), 7.83–7.76 (m, 6H, Ar), 7.71 (t, J = 9.0 Hz, 1H, Ar), 7.42–7.35 (m, 2H, Ar), 6.95 (d, J = 8.3 Hz, 2H, Ar), 4.12 (t, J = 5.8 Hz, 2H, O–CH_2), 3.76 (t, J = 6.6 Hz, 2H, N–CH_2), 2.09 (p, J = 6.1 Hz, 2H, CH_2); ^{13}C NMR (126 MHz, DMSO-d_6) δ 168.36, 163.82, 163.00, 156.37, 154.95, 149.03, 134.87, 134.71, 132.13, 130.68, 130.02, 127.47, 125.24, 123.37, 120.32, 118.21, 118.10, 116.55, 115.17, 66.53, 35.33, 27.90; Anal Calcd for $C_{28}H_{21}N_3O_6$, C, 67.87; H, 4.27; N, 8.48 found C, 67.81; H, 4.26; N, 8.49.

(*E*)-*N*′-(4-(3-(1,3-dioxoisoindolin-2-yl)propoxy)-3-methoxybenzylidene)-2-oxo-2H-chromene-3-carbohydrazide (8b)

White solid; yield 69%; m.p. 180–182 °C; IR (KBr, υ): 3283, 3076, 2922, 1661, 1645, 1087 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 9.01 (s, 1H, NH), 8.72 (s, 1H, coumarin), 8.49 (s, 1H, N=CH), 7.91–7.88 (m, 2H, Ar), 7.74–7.70 (m, 2H, Ar), 7.48 (dd, J = 8.2, 1.7 Hz, 1H, Ar), 7.42–7.37 (m, 4H, Ar), 7.27 (s, 1H, Ar), 7.07 (d, J = 8.3 Hz, 1H, Ar), 4.13 (t, J = 5.7 Hz, 2H, O–CH_2), 3.77 (t, J = 6.4 Hz, 2H, N–CH_2), 3.53 (s, 3H, OCH_3), 2.11 (p, J = 6.0 Hz, 2H, CH_2); ^{13}C NMR (126 MHz, DMSO-d_6) δ 168.41, 163.01, 156.39, 154.96, 153.83, 149.54, 149.06, 134.90, 134.58, 132.28, 130.70, 129.98, 126.40, 125.26, 123.29, 120.75, 118.23, 118.11, 116.57, 112.23, 109.75, 67.38, 55.70, 35.85, 27.92; Anal Calcd for $C_{29}H_{23}N_3O_7$, C, 66.28; H, 4.41; N, 8.00 found C, 66.22; H, 4.36; N, 8.11.

(*E*)-*N*′-(2-(3-(1,3-dioxoisoindolin-2-yl)propoxy)benzylidene)-2-oxo-2H-chromene-3-carbohydrazide (9a)

White solid; yield 74%; m.p. 166–168 °C; IR (KBr, υ): 3281, 3075, 2922, 1666, 1641, 1089 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 9.01 (s, 1H, NH), 8.72 (s, 1H, coumarin), 8.41 (s, 1H, N=CH), 7.91–7.87 (m, 2H, Ar), 7.74–7.69 (m, 3H, Ar), 7.64–7.57 (m, 2H, Ar), 7.42–7.37 (m, 3H, Ar), 7.13 (d, J = 8.4 Hz, 1H, Ar), 7.02 (t, J = 7.5 Hz, 1H, Ar), 4.15 (d, J = 5.7 Hz, 2H, O–CH_2), 3.80 (t, J = 6.6 Hz, 2H, N–CH_2), 2.13 (p, J = 6.2 Hz, 2H, CH_2); ^{13}C NMR (126 MHz, DMSO-d_6) δ 168.37, 163.12, 163.01, 161.30, 156.38, 139.66, 136.76, 134.89, 134.73, 132.07, 130.69, 127.81, 125.25, 124.58, 123.36, 121.03, 118.22, 118.11, 116.56, 113.82, 112.19, 66.51, 35.23, 27.98; Anal Calcd for $C_{28}H_{21}N_3O_6$, C, 67.87; H, 4.27; N, 8.48 found C, 67.82; H, 4.29; N, 8.49.

(*E*)-*N*′-(2-(3-(1,3-dioxoisoindolin-2-yl)propoxy)-3-methoxybenzylidene)-2-oxo-2H-chromene-3-carbohydrazide (9b)

White solid; yield 68%; m.p. 154–156 °C; IR (KBr, υ): 3280, 3077, 2922, 1667, 1646, 1085 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 9.04 (s, 1H, NH), 8.74 (s, 1H, coumarin), 8.34 (s, 1H, N=CH), 7.91 (d, J = 7.5 Hz, 2H, Ar), 7.86–7.81 (m, 4H, Ar), 7.73 (t, J = 8.3 Hz, 2H, Ar), 7.34 (d, J = 8.1 Hz, 1H,

Ar), 7.26 (d, $J = 9.9$ Hz, 1H, Ar), 7.17 (t, $J = 8.3$ Hz, 1H, Ar), 4.31 (t, $J = 7.7$, 1.6 Hz, 2H, O–CH_2), 4.14 (t, $J = 6.1$ Hz, 2H, N–CH_2), 3.81 (s, 3H, OCH_3), 2.08 (p, $J = 6.5$ Hz, 2H, CH_2); ^{13}C NMR (126 MHz, DMSO-d_6) δ 168.39, 163.03, 156.41, 154.97, 153.19, 151.35, 134.91, 134.75, 132.15, 130.71, 129.75, 127.20, 125.28, 124.66, 123.41, 119.25, 118.72, 118.25, 118.14, 116.59, 72.29, 61.69, 35.20, 29.10; Anal Calcd for $C_{29}H_{23}N_3O_7$, C, 66.28; H, 4.41; N, 8.00 found C, 66.25; H, 4.46; N, 7.94.

(*E*)-*N*′-(5-bromo-2-(3-(1,3-dioxoisoindolin-2-yl) propoxy)benzylidene)-2-oxo-2H-chromene-3-carbohydrazide (9c)

White solid; yield 63%; m.p. 160–162 °C; IR (KBr, υ): 3285, 3072, 2928, 1668, 1642, 1088 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.07 (s, 1H, NH), 8.71 (s, 1H, coumarin), 8.41 (s, 1H, N=CH), 7.89 (dd, $J = 7.7$, 1.4 Hz, 1H, Ar), 7.84–7.79 (m, 4H, Ar), 7.74–7.69 (m, 1H, Ar), 7.48–7.43 (m, 2H, Ar), 7.42–7.36 (m, 2H, Ar), 7.27–7.26 (m, 1H, Ar), 4.08 (t, $J = 5.8$ Hz, 2H, O–CH_2), 3.77 (t, $J = 6.7$ Hz, 2H, N–CH_2), 2.08 (p, $J = 6.2$ Hz, 2H, CH_2); ^{13}C NMR (126 MHz, DMSO-d_6) δ 168.39, 163.01, 159.34, 156.38, 149.04, 137.98, 134.88, 134.71, 132.16, 130.69, 128.87, 126.68, 125.25, 123.38, 122.85, 121.55, 118.22, 118.11, 116.56, 113.96, 66.29, 35.41, 27.95; Anal Calcd for $C_{28}H_{20}BrN_3O_6$, C, 58.55; H, 3.51; N, 7.32 found C, 58.48; H, 3.57; N, 7.36.

(*E*)-*N*′-(2-(3-(1,3-dioxoisoindolin-2-yl)propoxy)-5-nitrobenzylidene)-2-oxo-2H-chromene-3-carbohydrazide (9d)

Yellow solid; yield 61%; m.p. 188–190 °C; IR (KBr, υ): 3281, 3077, 2929, 1662, 1648, 1089 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.01 (s, 1H, NH), 8.89 (s, 1H, coumarin), 8.72 (s, 1H, N=CH), 8.46–8.38 (m, 1H, Ar), 8.33 (s, 1H, Ar), 7.89 (d, $J = 7.7$ Hz, 2H, Ar), 7.72 (t, $J = 7.8$ Hz, 2H, Ar), 7.42–7.36 (m, 5H, Ar), 4.33 (t, $J = 5.6$ Hz, 2H, O–CH_2), 3.82 (t, $J = 6.4$ Hz, 2H, N–CH_2), 2.18 (p, $J = 5.9$ Hz, 2H, CH_2); ^{13}C NMR (126 MHz, DMSO-d_6) δ 168.41, 163.01, 154.95, 149.05, 145.03, 141.15, 134.90, 134.76, 132.07, 131.33, 130.70, 125.26, 124.25, 123.63, 123.39, 118.22, 118.11, 116.57, 115.05, 61.68, 35.00, 27.76; Anal Calcd for $C_{28}H_{20}N_4O_8$, C, 62.22; H, 3.73; N, 10.37 found C, 62.17; H, 3.66; N, 10.34.

(*E*)-*N*′-(4-(3-(1,3-dioxoisoindolin-2-yl)propoxy)benzylidene)-2-((2-oxo-2H-chromen-7-yl)oxy)acetohydrazide (10a)

White solid; yield 71%; m.p. 178–180 °C; IR (KBr, υ): 3277, 3071, 2925, 1669, 1641, 1085 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.04 (s, 1H, NH), 7.96 (d, $J = 9.5$ Hz, 1H), 7.85–7.78 (m, 6H), 7.60 (d, $J = 8.6$ Hz, 1H), 6.98–6.89 (m, 5H), 6.27 (d, $J = 9.5$ Hz, 1H), 4.73 (s, 2H, O=C–CH_2), 4.13 (t, $J = 5.9$ Hz, 2H, O–CH_2), 3.77 (t, $J = 6.7$ Hz, 2H, N–CH_2), 2.09 (p, $J = 5.9$ Hz, 2H, CH_2); ^{13}C NMR (126 MHz, DMSO-d_6) δ 170.31, 168.41, 165.79, 163.84, 161.64, 160.68, 157.89, 155.63, 144.67, 140.34, 134.74, 132.17, 130.04, 129.83, 123.40, 118.56, 115.20, 113.02, 112.97, 106.93, 101.87, 66.55, 65.98, 35.35, 27.89; Anal Calcd for $C_{29}H_{23}N_3O_7$, C, 66.28; H, 4.41; N, 8.00 found C, 66.22; H, 4.45; N, 8.02.

(*E*)-*N*′-(4-(3-(1,3-dioxoisoindolin-2-yl)propoxy)-3-methoxybenzylidene)-2-((2-oxo-2H-chromen-7-yl)oxy) acetohydrazide (10b)

White solid; yield 69%; m.p. 190–192 °C; IR (KBr, υ): 3284, 3073, 2927, 1661, 1645, 1088 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ δ 9.03 (s, 1H, NH), 7.84–7.78 (m, 3H), 7.62–7.59 (m, 4H), 7.50 (d, $J = 9.6$ Hz, 1H), 7.28 (s, 1H), 7.08 (d, $J = 8.3$ Hz, 1H), 6.94–6.93 (m, 2H), 6.27 (d, $J = 9.5$ Hz, 1H), 4.73 (s, 2H, O=C–CH_2), 4.14 (t, $J = 5.7$ Hz, 2H, O–CH_2), 3.77 (t, $J = 6.4$ Hz, 2H, N–CH_2), 3.53 (s, 3H, O–CH_3), 2.14–2.08 (m, 2H, CH_2); ^{13}C NMR (126 MHz, DMSO-d_6) δ 170.29, 168.45, 164.78, 161.63, 160.69, 155.63, 153.84, 149.55, 144.69, 134.61, 132.30, 129.99, 129.84, 126.44, 123.31, 118.04, 113.03, 112.99, 112.26, 109.77, 101.88, 67.40, 65.95, 55.71, 35.88, 30.77, 27.91; Anal Calcd for $C_{30}H_{25}N_3O_8$, C, 64.86; H, 4.54; N, 7.56 found C, 64.83; H, 4.51; N, 7.59.

(*E*)-*N*′-(2-(3-(1,3-dioxoisoindolin-2-yl)propoxy)benzylidene)-2-((2-oxo-2H-chromen-7-yl)oxy)acetohydrazide 11a

White solid; yield 66%; m.p. 159–161 °C; IR (KBr, υ): 3287, 3068, 2922, 1661, 1647, 1079 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.06 (s, 1H, NH), 7.95 (d, $J = 9.5$ Hz, 1H), 7.82–7.75 (m, 4H), 7.64–7.56 (m, 4H), 7.13 (d, $J = 8.4$ Hz, 1H), 7.02 (t, $J = 7.5$ Hz, 1H), 6.93 (d, $J = 10.1$ Hz, 2H), 6.27 (d, $J = 9.5$ Hz, 1H), 4.79 (s, 2H, O=C–CH_2), 4.15 (t, $J = 5.7$ Hz, 2H, O–CH_2), 3.80 (t, $J = 6.6$ Hz, 2H, N–CH_2), 2.13 (p, $J = 6.0$ Hz, 2H, CH_2); ^{13}C NMR (126 MHz, DMSO-d_6) δ 170.17, 168.38, 161.43, 161.29, 160.64, 155.62, 155.45, 144.61, 136.76, 134.71, 132.06, 129.87, 127.83, 124.58, 123.36, 121.03, 113.80, 113.14, 112.99, 101.89, 66.51, 65.55, 35.23, 27.98; Anal Calcd for $C_{29}H_{23}N_3O_7$, C, 66.28; H, 4.41; N, 8.00 found C, 66.22; H, 4.35; N, 8.08.

(*E*)-*N*′-(2-(3-(1,3-dioxoisoindolin-2-yl)propoxy)-3-methoxybenzylidene)-2-((2-oxo-2H-chromen-7-yl)oxy) acetohydrazide (11b)

White solid; yield 64%; m.p. 170–172 °C; IR (KBr, υ): 3283, 3071, 2928, 1669, 1643, 1086 cm^{-1}; ^{1}H NMR

(500 MHz, DMSO-d_6) δ 9.07 (s, 1H, NH), 7.99–7.98 (m, 2H), 7.97–7.95 (m, 1H), 7.88–7.85 (m, 2H), 7.83–7.80 (m, 2H), 7.62–7.60 (m, 2H), 7.35 (d, $J = 9.4$ Hz, 1H), 7.27 (d, $J = 9.2$ Hz, 1H), 7.18 (t, $J = 7.9$ Hz, 1H), 6.29 (d, $J = 9.5$ Hz, 1H), 4.81 (s, 2H, O=C–CH_2), 4.14 (t, $J = 6.1$ Hz, 2H, O–CH_2), 3.92–3.74 (m, 5H, OCH_3&N–CH_2), 2.10–2.06 (m, 2H, CH_2); ^{13}C NMR (126 MHz, DMSO-d_6) δ 170.09, 168.42, 164.86, 161.35, 160.65, 155.63, 153.17, 151.36, 144.66, 137.27, 134.75, 132.16, 129.92, 129.76, 124.68, 123.42, 119.26, 118.75, 113.22, 113.02, 101.92, 72.30, 65.38, 56.50, 35.21, 29.10; Anal Calcd for $C_{30}H_{25}N_3O_8$, C, 64.86; H, 4.54; N, 7.56 found C, 64.78; H, 4.56; N, 7.58.

(*E*)-*N*′-(5-bromo-2-(3-(1,3-dioxoisoindolin-2-yl)propoxy)benzylidene)-2-((2-oxo-2H-chromen-7-yl)oxy) acetohydrazide (11c)

White solid; yield 63%; m.p. 166–168 °C; IR (KBr, υ): 3279, 3074, 2929, 1661, 1645, 1081 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.06 (s, 1H, NH), 7.96 (d, $J = 9.5$ Hz, 2H), 7.61 (m, 3H), 7.46 (d, $J = 6.3$ Hz, 2H), 7.14–7.09 (m, 1H), 6.95–6.91 (m, 4H), 6.28 (d, $J = 9.5$ Hz, 1H), 4.76 (s, 2H, O=C–CH_2), 4.09 (t, $J = 5.9$ Hz, 2H, O–CH_2), 3.78 (t, $J = 6.7$ Hz, 2H, N–CH_2), 2.08 (d, $J = 6.1$ Hz, 2H, CH_2); ^{13}C NMR (126 MHz, DMSO-d_6) δ 170.24, 168.43, 161.53, 160.67, 159.35, 155.63, 144.66, 137.99, 134.73, 132.18, 130.72, 129.86, 123.40, 122.87, 121.58, 117.61, 113.98, 113.10, 113.02, 106.54, 101.89, 66.31, 65.74, 35.42, 27.93; Anal Calcd for $C_{29}H_{22}BrN_3O_7$, C, 57.63; H, 3.67; N, 6.95 found C, 57.69; H, 3.66; N, 6.91.

(*E*)-*N*′-(2-(3-(1,3-dioxoisoindolin-2-yl)propoxy)-5-nitrobenzylidene)-2-((2-oxo-2H-chromen-7-yl)oxy) acetohydrazide (11d)

Yellow solid; yield 63%; m.p. 195–197 °C; IR (KBr, υ): 3281, 3073, 2927, 1661, 1642, 1087 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ δ 9.02 (s, 1H, NH), 8.45 (dd, $J = 9.2$, 3.0 Hz, 1H), 8.35 (d, $J = 3.0$ Hz, 1H), 7.97 (m, 4H), 7.82–7.79 (m, 4H), 7.60 (s, 1H), 7.38 (d, $J = 9.3$ Hz, 1H), 6.27 (d, $J = 9.5$ Hz, 1H), 4.80 (s, 2H, O=C–CH_2), 4.33 (t, $J = 5.7$ Hz, 2H, O–CH_2), 3.82 (t, $J = 6.5$ Hz, 2H, N–CH_2), 2.18 (p, $J = 6.1$ Hz, 2H, CH_2); ^{13}C NMR (126 MHz, DMSO-d_6) δ 170.11, 168.44, 165.29, 161.38, 160.64, 155.62, 144.65, 141.18, 134.77, 132.09, 131.36, 129.90, 124.28, 123.68, 123.41, 115.06, 113.19, 113.14, 113.01, 107.03, 101.90, 67.94, 65.43, 35.01, 27.75; Anal Calcd for $C_{29}H_{22}N_4O_9$, C, 61.05; H, 3.89; N, 9.82 found C, 61.00; H, 3.88; N, 9.86.

Biological evaluations

In vitro α-glucosidase inhibition of phthalimide-Schiff base-coumarin hybrids **8a–b**, **9a–d**, **10a–b**, and **11a–d**, kinetic analysis of the most potent compound **8a**, and docking study of the standard drug and the most potent compounds **8a**, **11d**, and **9d** in the active site of α-glucosidase were performed exactly according to our previous work (Adib et al. 2018).

Results and discussion

Chemistry

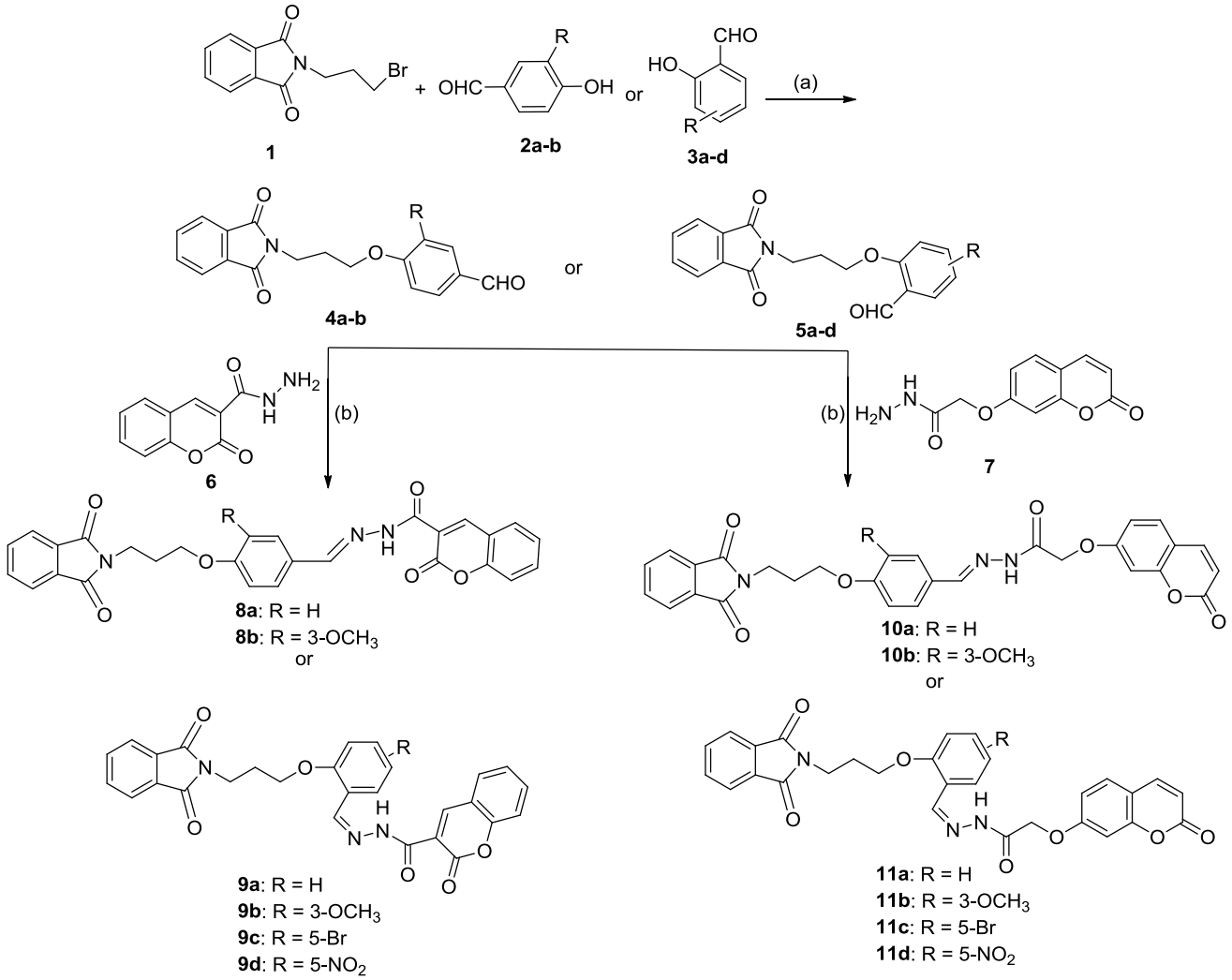
Chemical reactions for preparation of phthalimide-Schiff base-coumarin hybrids **8a–b**, **9a–d**, **10a–b**, and **11a–d** are depicted in Scheme 1. These reaction were started with reaction between 2-(3-bromopropyl)isoindoline-1,3-dione **1** and 4-hydroxybenzaldehyde derivatives **2a–b** or 2-hydroxybenzaldehyde derivatives **3a–d** in presence of K_2CO_3 in DMF to give aldehyde derivatives **4a–b** or **5a–d**. The next step, depending on the type of used coumarin, target compounds were obtained. For preparation of 3-coumarincarbohydrazone-phthalimides **8a–b** or **9a–d**, we used of reaction between aldehyde derivatives **4a–b** or **5a–d** and 2-oxo-2H-chromene-3-carbohydrazide **6** in the presence of PTSA in ethanol and for synthesis of coumarin-7-yloxy-carbohydrazone-phthalimides **10a–b** or **11a–d**, aldehyde derivatives **4a–b** or **5a–d** reacted with 2-((2-oxo-2H-chromen-7-yl)oxy) acetohydrazide **7** in the latter condition.

In vitro α-glucosidase inhibition activity

The α-glucosidase inhibitory activity of the synthesized phthalimide-Schiff base-coumarin hybrids was evaluated against yeast α-glucosidase and the obtained results were compared with acarbose as a standard inhibitor ($IC_{50} = 750.0 \pm 12.0$ μM). The IC_{50} values of the synthesized compounds **8a–b, 9a–d, 10a–b, and 11a–d** demonstrated that all these compounds were more potent than acarbose (IC_{50}s $\leq 577.7 \pm 7.5$ μM) (Table 1). The most potent compound was compound **8a** with inhibitory activity around ninefold more than acarbose.

In order to evaluate the structure–activity relationships and to optimize of anti-α-glucosidase activity, 4-hydroxybenzaldehydes **2a–b**, 2-hydroxybenzaldehyde derivatives **3a–d**, coumarin-3-carbohydrazide **6**, and coumarin-7-yloxy-acetohydrazide **7** were used in the synthesis of the title compounds.

As can be seen in Table 1, 4-hydroxybenzaldehyde derivative **8a** with coumarin-3-carbohydrazide moiety showed the highest inhibitory activity among the synthesized



Scheme 1 Reaction scheme for synthesis of phthalimide-hydrazone-coumarin hybrids **8a–b**, **9a–d**, **10a–b**, and **11a–d**. Reagents and condition: **a** K_2CO_3, DMF, 80 °C, 6–11 h; **b** PTSA, ethanol, reflux, 1–3 h

compounds. 4-Hydroxy-3-methoxybenzaldehyde derivative **8b** containing coumarin-3-carbohydrazide and 4-hydroxybenzaldehyde derivatives **10a–b** containing coumarin-7-yloxy-acetohydrazide were significantly weaker than 4-hydroxybenzaldehyde derivative **8a** against α-glucosidase.

Among the 2-hydroxybenzaldehyde derivatives **9a–d** containing coumarin-3-carbohydrazide moiety, 2-hydroxy-5-nitrobenzaldehyde derivative **9d** with electron-withdrawing substituent nitro was the most potent compound. Replacement of nitro group with other electron-withdrawing substituent bromo, as in compound **9c**, led to a slight decrease in the inhibitory activity. Moreover, 2-hydroxybenzaldehyde and 2-hydroxy-3-methoxybenzaldehyde derivatives **9a–b** cannot inhibit α-glucosidase well bromo and nitro derivatives **9c–d**. In summary, in this series the trend of the inhibitory activity based on the substituent on phenoxy group produced from benzaldehyde derivatives was 5-nitro > 5-bromo > H > 3-methoxy. Interestingly, the trend of the inhibitory activity in the 2-hydroxybenzaldehyde derivatives **11a–d** containing coumarin-7-yloxy-acetohydrazide is similar to their corresponding analogs with coumarin-3-carbohydrazide moiety.

The comparison of IC_{50} values of 2-hydroxybenzaldehy derivatives containing coumarin-7-yloxy-acetohydrazide with their corresponding coumarin-3-carbohydrazide analogs against α-glucosidase revealed that coumarin-7-yloxy-acetohydrazide derivatives were more active than their coumarin-3-carbohydrazide analogs.

As can be seen in Table 1, parent compounds **4a–b** and **5a–d** did not show inhibitory activity against α-glucosidase. Moreover, we have not been able to determine the inhibitory activity of parent compounds **6** and **7** due to non-solubility in standard solvent used in biological evaluation.

Table 1 In vitro α-glucosidase inhibitory activities of compounds **8a–b**, **9a–d**, **10a–b**, and **11a–d** and parent compounds **4a–b**, **5a–d**, **6**, and **7**

Compound	IC_{50} (μM)[a]	Compound	IC_{50} (μM)[a]
8a	85.2 ± 1.7	**11c**	112.0 ± 2.5
8b	423.3 ± 5.0	**11d**	94.2 ± 2.0
9a	248.3 ± 3.5	**4a**	> 750
9b	360.6 ± 4.4	**4b**	> 750
9c	124.0 ± 2.6	**5a**	> 750
9d	104.5 ± 2.2	**5b**	> 750
10a	447.2 ± 5.5	**5c**	> 750
10b	577.7 ± 7.5	**5d**	> 750
11a	219.1 ± 3.0	**6**	ND[b]
11b	347.3 ± 4.0	**7**	ND[b]
Acarbose	750.0 ± 12.0	Acarbose	750.0 ± 12.0

[a]Values are mean ± SD. All experiments were performed in triplet

[b]Not determined

Structures and inhibitory activities of the most potent compounds **A** and **B** and compound **C** that were used as lead compounds for designing of phthalimide-Schiff base-coumarin hybrids are shown in Fig. 2 (Pascale et al. 2010; Taha et al. 2018; Singh et al. 2018). As can be seen in Fig. 2, the most potent compound among the *N*-(3-phenoxypropyl) phthalimide derivatives **A** was compound **A4** with an inhibitory activity around 4.5-fold more than standard inhibitor acarbose. The comparison of IC_{50} values of *N*-(3-phenoxypropyl)phthalimide derivative **A4** with the most potent new compounds **8a**, **11d**, and **9d** revealed that the latter our new hybrid compounds in comparison to simple *N*-(3-phenoxypropyl)phthalimide derivatives were more active against α-glucosidase. In contrast, lead compounds **B** with coumarin-3-carbohydrazone scaffold can be acted better than phthalimide-coumarin-3-carbohydrazone derivatives **8a** and **9d** against α-glucosidase (Fig. 2). On the other hand, observed IC_{50} value of coumarin derivative **C** (3.6-fold more potent than acarbose) demonstrated that replacement of benzyl group in 7-position with phthalimide-Schiff base led to a significant increase in anti-α-glucosidase activity as observed in compound **11d** (7.9-fold more potent than acarbose) (Fig. 2).

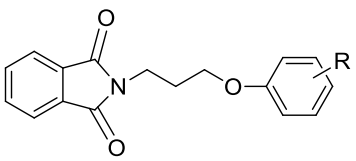
Kinetic study

The kinetic study of the most potent compound **8a** was carried out in order to determination of the type of inhibition and K_i value of this compound against α-glucosidase. As can be depicted in Fig. 3a, with increasing the concentration of compound **8a** (inhibitor), the value of V_{max} remained constant and the value of K_m increased. Therefore compound **8a** is a competitive inhibitor for α-glucosidase. Moreover, the secondary plot between K_m and various concentrations of compound **8a** gave an estimate of K_i (Inhibition constant) value of 80 μM for compound **8a** (Fig. 3b).

Docking study

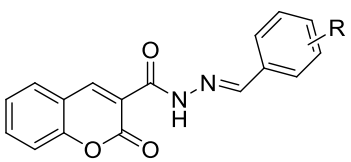
In order to clarify interactions of the synthesized compounds in the active site of α-glucosidase, docking study of the standard inhibitor acarbose and the most potent compounds **8**, **11d**, and **9d** was performed on the modeled α-glucosidase by AutodockTools (version 1.5.6) (Adib et al. 2018). As can be seen in Fig. 4, the standard drug interacted with the residues Asn241, Glu304, Thr307, Pro309, Ser308, Arg312, His279, Thr301, and Gln322.

The most potent compound **8a** established a hydrogen bond and two hydrophobic interactions with active site residue Arg312 through phthalimide moiety (Fig. 4). Phenoxy group of this compound formed a π-anion and a hydrophobic interaction with Glu304 and Pro309, respectively. In



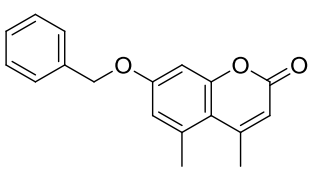
Compounds **A**

A1: R = H, IC_{50} = 240 ± 40 μM
A2: R = 4-Cl, IC_{50} = 59.0 ± 0.5 μM
A3: R = 2,3-Dichloro, IC_{50} =15.0 ± 0.8 μM
A4: R = 3,4-Dichloro, IC_{50} =7.55 ± 0.25 μM
A5: R = 2-CH3-4-Chloro, IC_{50} =8.9 ± 0.4 μM
A5: R = 2,6-dimethyl-4-Chloro, IC_{50} = 9.5 ± 0.3 μM
Acarbose: 34 ± 4 μM



Compounds **B**

B1: R = 2-Hydroxy, IC_{50} = 1.10 ± 0.01 μM
B2: R = 2,3-Dihydroxy, IC_{50} = 3.15 ± 0.1 μM
B3: R = 4-Methoxy, IC_{50} = 4.26 ± 0.1 μM
Acarbose: IC_{50} = 39.45 ± 0.10 μM



Compound **C**

IC_{50} = 11.084±0.117 μg/mL
Acarbose: 40.578±5.999 μg/mL

Fig. 2 Structures and inhibitory activities of the most potent derivatives of lead compounds **A** and **B** and lead compound **C**

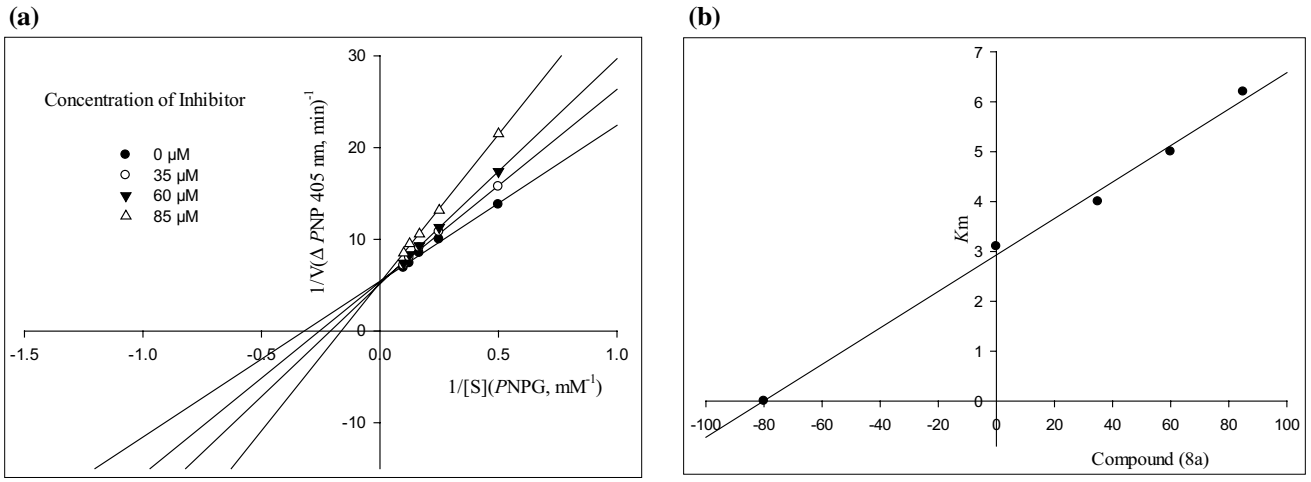


Fig. 3 **a** Lineweaver–Burk plots for the inhibition of α-glucosidase by compound **8a** and **b** the secondary plot between K_m and various concentrations of compound **8a**

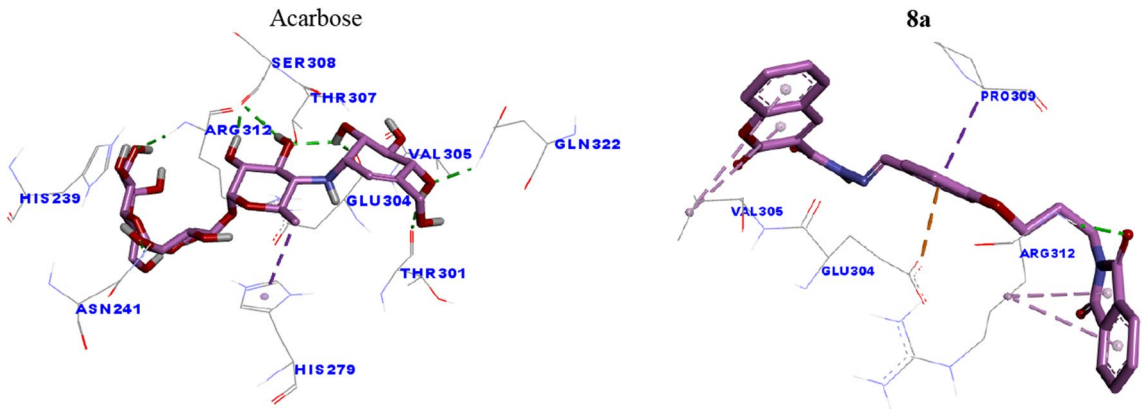


Fig. 4 Acarbose and compound **8a** in the active site of α-glucosidase

addition, two hydrophobic interactions were also observed between coumarin moiety of compound **8a** and active site residue Val305.

In the case of the second active compound **11d**, 5-nitro substituent and oxygen atom of phenoxy moiety formed hydrogen bonds with Asn241 and His279, respectively (Fig. 5). Furthermore, phenyl group of phenoxy moiety established two π-π interactions with His239 and His279. Several hydrophobic interactions were also observed between phthalimide and coumarin moiety of the compound **11d** and the active site residues Arg312, Tyr313, Val305, and Pro309.

The third most potent compound **9d** formed hydrogen bonds with Arg312 and Pro309 through carbonyl unit of coumarin moiety and carbonyl and NH units of carbohydrazide moiety (Fig. 5). This compound also created hydrophobic interactions with Val305, Pro309, and Arg312 through phthalimide, phenoxy, and coumarin moieties, respectively.

Further studies on binding energies of the compound **8a** and acarbose showed that compound **8a** has a lower free binding energy (− 10.77 kcal/mol) in comparison to acarbose (− 4.04 kcal/mol) and therefore binds to α-glucosidase more easily than acarbose. On the other hand, values of binding energies of the second and third most potent compounds **11d** (− 8.65 kcal/mol) and **9d** (− 8.66 kcal/mol) are approximately same together and more than the most potent compound **8a**. The mentioned results are in accordance with in vitro evaluation results (Table 1).

Conclusion

The synthesized phthalimide-Schiff base-coumarin hybrids **8a–b**, **9a–d**, **10a–b**, and **11a–d** exhibited in vitro α-glucosidase inhibition activity better than the reference inhibitor acarbose. Among the synthesized compounds,

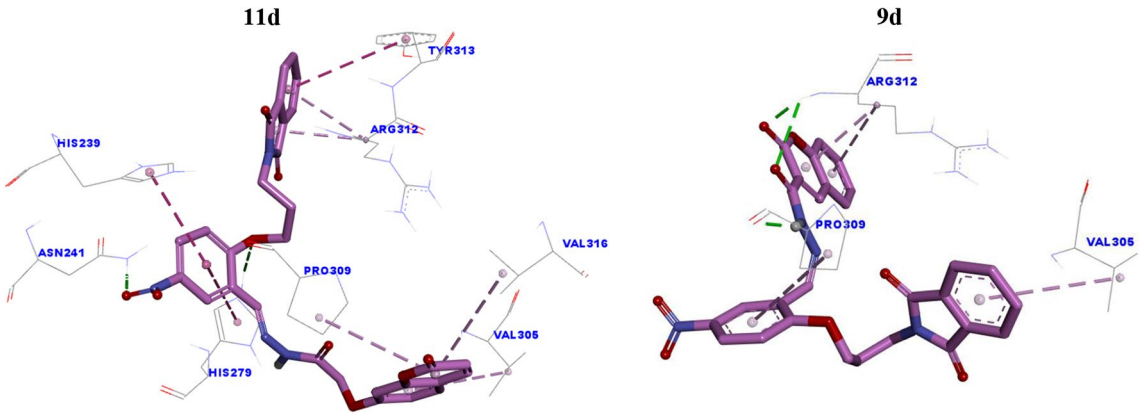


Fig. 5 Compounds **11d** and **9d** in the active site of α-glucosidase

compounds **8a**, **11d**, and **9d** showed the highest inhibitory activity. The comparison of IC_{50} values of the synthesized compounds **8a–b**, **9a–d**, **10a–b**, and **11a–d** with their parent molecules **4a–b** and **5a–d** with *N*-(3-phenoxypropyl) phthalimide scaffold against α-glucosidase revealed that all the new compounds were more active than their parent compounds. Kinetic study of compound **8a** demonstrated that this compound is a competitive inhibitor for α-glucosidase. Docking study of the synthesized most potent compounds confirmed that they with low binding energy in comparison with standard inhibitor acarbose attached to α-glucosidase active site. These results are in agreement with the results obtained from biological evaluation.

References

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

AG HBB (1994) Pharmacology of α-glucosidase inhibition. Eur J Clin Investig 24:3–10

Atkinson MA, Eisenbarth GS (2001) Type 1 diabetes: new perspectives on disease pathogenesis and treatment. Lancet 358:221–229. https://doi.org/10.1016/S0140-6736(01)05415-0

Cheng AY, Fantus IG (2005) Oral antihyperglycemic therapy for type 2 diabetes mellitus. CMAJ 172:213–226. https://doi.org/10.1503/cmaj.1031414

Hollander P (1992) Safety profile of acarbose, an α-glucosidase inhibitor. Drugs 44:47–53. https://doi.org/10.2165/00003495-199200443-00007

Imran S, Taha M, Ismail NH, Kashif SM, Rahim F, Jamil W, Hariono M, Yusuf M, Wahab H (2015) Synthesis of novel flavone hydrazones: in-vitro evaluation of α-glucosidase inhibition, QSAR analysis and docking studies. Eur J Med Chem 105:156–170. https://doi.org/10.1016/j.ejmech.2015.10.017

Kahn SE, Cooper ME, Del Prato S (2014) Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present, and future. Lancet 383:1068–1083. https://doi.org/10.1016/S0140-6736(13)62154-6

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 Compd 5:1–12

Nagarapu L, Mateti J, Gaikwad HK, Bantu R, Rani MS, Subhashini NP (2011) Synthesis and anti-inflammatory activity of some novel 3-phenyl-N-[3-(4-phenylpiperazin-1yl) propyl]-1H-pyrazole-5-carboxamide derivatives. Bioorg Med Chem Lett 21:4138–4140. https://doi.org/10.1016/j.bmcl.2011.05.105

Pascale R, Carocci A, Catalano A, Lentini G, Spagnoletta A, Cavalluzzi MM, De Santis F, De Palma A, Scalera V, Franchini C (2010) New N-(phenoxydecyl) phthalimide derivatives displaying potent inhibition activity towards α-glucosidase. Bioorg Med Chem 18:5903–5914. https://doi.org/10.1016/j.bmc.2010.06.088

Saltiel AR (2001) New perspectives into the molecular pathogenesis and treatment of type 2 diabetes. Cell 104:517–529. https://doi.org/10.1016/S0092-8674(01)00239-2

Secci D, Carradori S, Bolasco A, Chimenti P, Yáñez M, Ortuso F, Alcaro S (2011) Synthesis and selective human monoamine oxidase inhibition of 3-carbonyl, 3-acyl, and 3-carboxyhydrazido coumarin derivatives. Eur J Med Chem 46:4846–4852. https://doi.org/10.1016/j.ejmech.2011.07.017

Sharma U, Kumar P, Kumar N, Singh B (2010) Recent advances in the chemistry of phthalimide analogues and their therapeutic potential. Mini Rev Med Chem 10:678–704. https://doi.org/10.2174/138955710791572442

Singh P, Ngcoya N, Mopuri R, Kerru N, Manhas N, Ebenezer O, Islam MS (2018) α-Glucosidase inhibition, antioxidant and docking studies of hydroxycoumarins and their mono and bis O-alkylated/acetylated analogs. Lett Drug Des Discov 15:127–135. https://doi.org/10.2174/1570180814666170602081941

Taha M, Ismail NH, Imran S, Rokei MQ, Saad SM, Khan KM (2015) Synthesis of new oxadiazole derivatives as α-glucosidase inhibitors. Bioorg Med Chem 23:4155–4162. https://doi.org/10.1016/j.bmc.2015.06.060

Taha M, Shah SA, Afifi M, Imran S, Sultan S, Rahim F, Khan KM (2018) Synthesis, α-glucosidase inhibition and molecular docking study of coumarin based derivatives. Bioorg Chem 77:586–592. https://doi.org/10.1016/j.bioorg.2018.01.033

Wang G, Wang J, He D, Li X, Li J, Peng Z (2017) Synthesis, in vitro evaluation and molecular docking studies of novel coumarin-isatin derivatives as α-glucosidase inhibitors. Chem Biol Drug Des 89:456–463. https://doi.org/10.1111/cbdd.12867

Xu XT, Deng XY, Chen J, Liang QM, Zhang K, Li DL, Wu PP, Zheng X, Zhou RP, Jiang ZY, Ma AJ (2020) Synthesis and biological evaluation of coumarin derivatives as α-glucosidase inhibitors. Eur J Med Chem 189:112013. https://doi.org/10.1016/j.ejmech.2019.112013

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