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ORIGINAL ARTICLE

Aryl-oxadiazole Schiff bases: Synthesis, α -glucosidase *in vitro* inhibitory activity and their *in silico* studies



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KEYWORDS

Synthesis; Aryl-oxadiazole Schiff bases; α-glucosidase; Molecular docking; Structure-activity relationship (SAR) Abstract α -Glucosidase enzyme is a therapeutic target for diabetes mellitus and its inhibitors play a vital role in the treatment of this disease. A new series of aryl-oxadiazole Schiff bases (1–18) were synthesized and evaluated for α -glucosidase inhibitory potential. Fifteen compounds 1–8, 11–13, and 15–18 showed excellent inhibition with IC₅₀ values ranging from 0.30 ± 0.2 to 35.1 ± 0.80 µM as compared to the standard inhibitor acarbose (IC₅₀ = 38.45 ± 0.80 µM), nonetheless, the remaining compounds were found to have moderate activity. Among the series, compounds 7 (IC₅₀ = 0.30 ± 0.2 µM) with hydroxy groups at phenyl rings on either side of the oxadiazole ring was identified as the most potent inhibitor of α -glucosidase. The molecular docking studies were

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1878-5352 © 2020 Published by Elsevier B.V. on behalf of King Saud University. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/). conducted to understand the binding mode of active inhibitors with the active site of enzyme and results supported the experimental data.

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1. Introduction

Diabetes mellitus is a life threatening and chronic metabolic disorder caused by insufficient insulin secretion and characterized by hyperglycemia (Fatmawati et al., 2011). The enhanced level of post-prandial glucose is associated with type II diabetes mellitus and leads to the increased risk of developing atherosclerosis, stroke, and other coronary diseases (Rother, 2007). Thus reducing the post-prandial hyperglycemia by inhibiting the digestive enzymes such as α -glucosidase is an effective approach for the treatment of type II diabetes mellitus and other diabetic complications too (Casirola and Ferraris, 2006). α -Glucosidase is an enzyme located in the epithelium of small intestine and catalyzes the final step involved in the hydrolysis of disaccharides and polysaccharides into glucose. The activity of α -glucosidase is directly related to the concentrations of blood glucose, and inhibition of α glucosidase is crucial due to the potential effects of decreased postprandial blood glucose levels (Chiasson et al., 2003). α-Glucosidase inhibitors such as voglibose and acarbose are clinically used for controlling the rapid increase of blood glucose. However, they often leads to some side effects including diarrhea, abdominal pain, and other gastrointestinal disorders in chronic therapy (Kawamori et al., 2009). Therefore, the search for efficient and safe α -glucosidase inhibitors are necessary for the therapy of post-prandial hyperglycemia (see Table 1).

Among five-membered aromatic heterocycles, 1,3,4oxadiazoles have attracted considerable attention in recent decades due to their broad spectrum of pharmaceutical and biological activities (Suwinski, 2008). Many compounds containing this scaffold display antimicrobial (Zheng et al., 2018; Salar et al., 2015), antiviral (Du and Luo, 2010), antiinflammatory (Palaska et al., 2002), antihypertensive (Zhu et al., 2016), analgesic (Husain et al., 2009), anticonvulsant (Dogan et al., 2002), antidiabetic (O'Neal et al., 1962); antileismanial (Taha et al., 2017), and antitubercular activities (Pattan et al., 2009). They have also attracted attention in medicinal chemistry as potential therapeutic agents for the treatment of cancer (Holla et al., 2005) and HIV infections (El-Emam et al., 2004). In addition, 1,3,4-oxadiazole derivatives have been utilized as bioisosteric replacements for carboxylic acid (Omar et al., 1996), ester (Orlek et al., 1991), and amide (Leung et al., 2005) functional groups in biologically active compounds.

Our research group had synthesized and reported a number of heterocyclic compounds for their different pharmacological activities (Kazmi et al., 2018; Rahim et al., 2016; Rashid et al., 2016; Rahim et al., 2015; Noreen et al., 2017; Taha et al., 2016; Taha et al., 2017; Taha et al., 2016; Rahim et al., 2015; Rahim et al., 2016; Taha et al., 2017). Oxadiazoles and Schiff bases are among the most diverse heterocycles that showed a range of biological activities including α -glucosidase and both these core structures are already reported by our group as potential α -glucosidase inhibitors (Taha et al., 2017; Rahim et al., 2015; Rahim et al., 2015; Rahim et al., 2015). Therefore, in continuation of our previous research, we have designed and synthesized the molecules (1-18) bearing both functionalities in search of potential α -glucosidase inhibitors (Fig. 1).

2. Results and discussion

2.1. Chemistry

Compounds 1-18 were synthesized in three steps, first step involves the formation of Schiff base via reaction of aldehyde with semicarbazide in the presence of NaOAc, water and methanol were used as the reaction medium and it was heated at 25 °C for 10 min. The Schiff base thus formed undergoes cyclization in the presence of iodine and potassium carbonate using 1,4-dioxane as solvent, the reaction mixture was then refluxed at 80 °C for 4 h to afford aryl-oxadiazoles. The mixture which contain the desired organic compound was cooled and treated with 5% $Na_2S_2O_3$ followed by extraction using CH₂Cl₂/MeOH. The pure product which is obtained in the second step was further mixed and refluxed with different substituted benzaldehyde in methanol to give Schiff base of aryl-oxadiazole 1-18 which were crystallized from methanol (Scheme 1). The synthetic derivatives were characterized via different spectroscopic techniques such as ¹H-, ¹³C NMR, and HREIMS.

2.2. *a-Glucosidase inhibitory activity*

We have synthesized aryl-oxadiazole bearing Schiff bases (1-**18**) and evaluated them for α -glucosidase inhibitory potential. All derivatives showed good to moderate inhibitory activities having IC₅₀ values ranging between 0.30 ± 0.2 -350.50 \pm 0.6 μ M as compared to the standard acarbose $(IC_{50} = 38.45 \pm 0.80 \,\mu\text{M})$. Fifteen compounds 1–8, 11–13, and 15-18 showed superior inhibition with IC50 values of $3.30 \pm 0.1, 1.20 \pm 0.1, 2.30 \pm 0.1, 1.10 \pm 0.10, 2.70 \pm 0.1,$ $0.6 \pm 0.05, \quad 0.30 \pm 0.2, \quad 3.60 \pm 0.1, \quad 35.1 \pm 0.80, \quad 32.06$ \pm 0.70, 22.40 \pm 0.6, 26.50 \pm 0.4, 19.10 \pm 0.4, 17.80 \pm 0.50 and $13.50 \pm 0.40 \,\mu\text{M}$, respectively, in comparison with the standard drug acarbose. However, three compounds 9, 10, and 14 displayed moderate inhibition with IC₅₀ values of 350.50 \pm 0.6, 45.80 \pm 1.1, and 48.50 \pm 0.6 $\mu M,$ respectively. To develop the better structure-activity relationship, we have divided the molecule in four parts; ring A, oxadiazole part, imine part, and ring B as shown in Fig. 2. The variations were carried out mainly on ring A and ring B, and different substitutions at variable positions of both rings showed interesting pattern in the activity.

2.2.1. Structure-activity relationship

Compound 7 (IC₅₀ = $0.30 \pm 0.2 \,\mu$ M) having hydroxyl groups at *para* position of ring A and ring B, respectively, was the

Compounds	Ring A	Ring B	$IC_{50} \pm SEM^{a} (\mu M)$		
1	O ₂ N	O ₂ N	$3.30~\pm~0.1$		
2	O ₂ N	CI	1.20 ± 0.1		
3		O ₂ N	2.30 ± 0.1		
4	H ₃ C CH ₃	O ₂ N	1.10 ± 0.10		
5		O ₂ N	$2.70~\pm~0.1$		
6	OH OH	но	0.6 ± 0.05		
7	OH	OH	0.30 ± 0.2		
8		O ₂ N	$3.60~\pm~0.1$		
9		O ₂ N	350.50 ± 0.6		
10		O ₂ N	$45.80~\pm~1.1$		
11		но	35.1 ± 0.80		
12		OH	$32.06~\pm~0.70$		
13		O ₂ N	$22.40~\pm~0.6$		
14		O ₂ N	$48.50~\pm~0.6$		
15			$26.50~\pm~0.4$		

Table 1(continued)

Compounds	Ring A	Ring B	$IC_{50} \pm SEM^{a} (\mu M)$
16		Cl	19.10 ± 0.4
17		но	$17.80~\pm~0.50$
18		OH	$13.50~\pm~0.40$
Acarbose			38.45 ± 0.80

SEM^a is the standard error of the mean, NA^b Not active, Acarbose^{std} standard inhibitor for α -glucosidase inhibitory activity.









Fig. 2 General structure of synthetic compounds (1–18).

most active compound of series. Its structurally similar compound 6 (IC₅₀ = $0.6 \pm 0.05 \mu$ M) with hydroxyl group at *meta* position of ring B displayed two folds less activity as compared to compound 7. However, both compounds exhibited potential inhibition in comparison with the standard acarbose. The activity of both these compounds may be due to the interaction of hydroxyl groups with the active site of enzyme. Compounds 4 and 5 with nitro groups on different positions of ring B showed a sharp decline in activity. Compound 4 (IC₅₀ = $1.10 \pm 0.10 \mu$ M) having nitro group at *ortho* position of ring B showed decreased activity, nevertheless, changing the position of nitro group from *ortho* to *meta* in compound 5 (IC₅₀ = $2.70 \pm 0.1 \mu$ M) resulted in further declined activity. It showed that the compounds with nitro group are less active as compared to hydroxyl substituted compounds (Fig. 3).

Compounds 1 and 8 bearing nitro groups on different positions of rings A and B, respectively, displayed variable inhibitory potential which showed that the change in positions of these groups provide a different binding site of ligandenzyme interaction. Compound 1 (IC₅₀ = $3.30 \pm 0.10 \mu$ M) having nitro group at *meta* positions of ring A and B, respectively, exhibited good inhibitory activity. Compound 8 (IC₅₀ = $3.60 \pm 0.1 \mu$ M) having nitro group at *para* position of ring A displayed comparable activity with compound 1. Nonetheless, compound 2 (IC₅₀ = $1.20 \pm 0.1 \mu$ M) having nitro at *meta* position of ring A and chloro group at *para* position of ring B showed better inhibitory potential as compared to compounds 1 and 8. Therefore, it can be concluded that the addition of chloro groups leads to the increased activity of compounds. Compound **3** (IC₅₀ = $2.30 \pm 0.1 \,\mu$ M) having dimethyl amino group at *para* position of ring A and nitro at *ortho* position of ring B also showed better inhibitory potential as compared to the standard acarbose. On comparison of compound **3** with **8**, it can be said that the replacement of nitro with dimethyl amino group resulted in better activity (Fig. 4).

Compounds 13-18 having benzyloxy substituent at para position of ring A exhibited good inhibitory activity as compared to the standard. Among them, compound 18 $(IC_{50} = 13.50 \pm 0.40 \,\mu\text{M})$ having hydroxyl group at para position of ring B was most active, however, its structurally similar analog 17 (IC₅₀ = $17.80 \pm 0.50 \,\mu\text{M}$) bearing hydroxyl at meta position showed decreased inhibition. The activity was further decreased when hydroxyl groups were replaced by two chloro groups in compound 16 (IC₅₀ = 19.10 \pm 0.4 μ M). Compound 13 (IC₅₀ = 22.40 \pm 0.6 μ M) having nitro at ortho position of ring B also showed better activity as compared to the standard acarbose (IC₅₀ = $38.45 \pm 0.80 \,\mu\text{M}$), however, changing the position of nitro group from ortho to meta resulted in two folds decreased activity in compound 14 $(IC_{50} = 48.50 \pm 0.6 \,\mu\text{M})$. Compound **15** $(IC_{50} = 26.50$ \pm 0.4 μ M) having benzyloxy group on both rings also showed good inhibitory activity (Fig. 5).

The compounds with anthranyl group attached to oxadiazoles were less active as compared to other synthetic compounds. Among them, compound **12** (IC₅₀ = 32.06 \pm 0.70 µM) bearing hydroxyl group at *para* position of ring B was most active. The activity was slightly decreased when the position of hydroxyl group was shifted from *para* to *meta* in compound **11** (IC₅₀ = 35.1 \pm 0.80 µM). The activity was further decreased in case of nitro substituted derivatives **9** and **10**. Compound **10** (IC₅₀ = 45.80 \pm 1.1 µM) having nitro group at *meta* position was less active as compared to standard. A sharp decline in the activity was observed when the nitro group was shifted to *ortho* position. This showed that the presence of bulky anthranyl group resulted in decreased activity of compounds and also the addition of nitro groups resulted in further decreased activity (Fig. 6).

On the basis of afore-mentioned observations it can be summarized that the compounds with hydroxyl groups on



Fig. 3 Structure-activity relationship of compounds 4, 5, 6, and 7.



Fig. 4 Structure-activity relationship of compounds 1, 2, 3, and 8.



Fig. 5 Structure-activity relationship of compounds 13, 14, 15, 16, 17, and 18.

both rings exhibited good inhibitory potential as compared to the compounds with nitro and bulky groups like anthranyl and benzyloxy. It was also observed that the positions of certain groups at particular positions also altered the inhibitory activity, the substitutions at *ortho* and *para* positions were mainly contributing in the activity. To understand the binding interaction of the most active analogs molecular docking study was performed.

2.2.2. Molecular docking studies

It was observed from the molecular docking study that the top ranked confirmation of all derivatives fit well inside the active site of the homology model of α -glucosidase (Arg212, Asp214, Glu276, Asp349 and Arg439) (Rahim et al., 2015). From the docking confirmation of the derivatives, it was revealed that the most active derivative 7 (IC₅₀ = 0.30 ± 0.2, docking

score = -8.7632) formed five hydrogen bonds and one π -H linkage with the Lys155, Val303, Phe311, and Arg439 residues of the binding pocket as shown in Fig. 7a. Lys155 and Arg439 formed π -H and polar interaction with the 1,3,4-oxadiazole moiety of the ligand. Val303 and Phe311 formed polar interactions with the hydroxyl (-OH) moieties of the derivative. The good inhibitory activity of the derivative might be due to the availability of the electron donating groups (-OH) and electronic cloud system of benzene moieties of the compound. The docking conformation of the second most active compound 6 (IC₅₀ = 0.6 ± 0.05) was observed having good interactions as well as good docking score (-8.6902). It was noticed that this compound has shown four hydrogen bonds with active site residues Phe311, Asp349 and Asn412 as shown in Fig. 7b. Phe311 and Asp349 were observed making hydrogen bonds with the -OH moieties of the compound while



Fig. 6 Structure-activity relationship of compounds 9, 10, 11, and 12.



Fig. 7 On active site of the α -glucosidase enzyme, the docking confirmations of the active analogs (a) three dimension binding mode of analog 7 (b) three dimension binding mode of analog 6 (c) three dimension binding mode of analog 4 (d) three dimension binding mode of analog 2.

Asn412 formed two H-bonds with the nitrogen atom (-N) of the oxadiazole moiety of the inhibitor. The presence of the electron donating groups (-OH) and π - π electron system of this compound might be the reason of its high potency. The activity of the derivative **7** is to some extent higher to deriva-

tive **6** that may be due to different position of -OH group on benzene ring.

The docking conformation of the third one most active compound **4** (IC₅₀ = 1.10 ± 0.10 , docking score = -8.3487) was observed that this compound formed three polar interac-

tions with the Lys155, Phe311 and Asp349 residues of the target enzyme Fig. 7c. Lys155 formed H-bond with the nitrogen atom of the oxadiazole moiety while Phe311 and Asp349 made H-bonds with nitro ($-NO_2$) and -OH moieties of the derivative, respectively. The potency of the derivative might be due to electron donating group (-OH) and electron withdrawing group ($-NO_2$).

The docking conformation of the compound **2** (IC₅₀ = 1.20 ± 0.1 , docking score = -8.1076) also showed good interactions with the active site residues of the target enzyme, however, slightly inferior inhibitory potential as com-

pared to compound **4** may be due to halogen groups, hydroxyl (–OH) group is electron donating while –Cl group is electron withdrawing. Compound **2** formed two H-acceptor and one π -H interactions with the Lys233, Asn412 and Asp349 residues of the enzyme as shown in Fig. 7d, Table 2.

3. Conclusion

Eighteen derivatives of aryl-oxadiazole bearing Schiff bases (1-18) were synthesized and evaluated for α -glucosidase

 Table 2
 Report of predicated interactions of docked confirmations and docking scores.

Compounds	Docking score	Interactio	ns Report						
1	-6.6230	Ligand	Receptor	Interacti	on Distance	E (kcal/n	nol)		
		022	31	ND2	ASN	153	H-acceptor	3.01	-0.8
		O24	33	NZ	LYS	155	H-acceptor	3.34	-1.2
2	-8.1076	N2	2	ND2	ASN	412	H-acceptor	2.41	-2.8
		O23	32	NZ	LYS	233	H-acceptor	2.00	-4.1
		6-ring		CB	ASP	349	π-H	4.72	-0.7
3	-7.0524	022	31	NZ	LYS	155	H-acceptor	2.77	-0.9
		6-ring		CA	PHE	311	π -H	4.35	-0.4
		6-ring		6-ring	PHE	300	π-π	3.63	-0.0
4	-8.3487	O20	29	ODI	ASP	349	H-donor	3.74	-3.8
		N2	2	ND2	LYS	155	H-acceptor	2.70	-4.9
		6-ring		CA	PHE	311	π-H	1.92	-0.4
5	-6.6586	5-ring		CA	LYS	155	pi-H	4.05	-1.5
6	-8.6902	020	29	NH	PHE	311	H-donor	2.70	-2.1
		021	31	OD2	ASP	349	H-donor	2.63	-1.3
		N3	3	ND2	ASN	412	H-acceptor	2.71	-4.7
		N2	2	ND2	ASN	412	H-acceptor	2.00	-4.9
7	-8.7632	020	29	0	VAL	303	H-donor	2.12	-1.0
,	017002	021	31	Ő	PHE	311	H-donor	3.12	-2.6
		N2	2	NH1	ARG	439	H-acceptor	2.42	-3.4
		N3	3	NH1	ARG	439	H-acceptor	2.42	-0.8
		5-ring	U	CE	LYS	155	π-H	3 31	-2.0
8	-6.0100	021	30	N	GLN	238	H-acceptor	3.08	-2.0
0	0.0100	6-ring	50	CA	LYS	155	π-H	4 27	-1.0
		5-ring		CE	LYS	155	π-H	4 07	-1.4
9	-2 7615	5-ring		CE	LYS	155	π-H	3 47	_1.1
10	-4 1123	030	44	NZ	LYS	155	H-acceptor	3 33	-1.2
10	-4 2398	6-ring		CE	LYS	155	π-H	3 38	-0.5
11	4.2370	6-ring		N	ARG	312	π-H	3.69	-0.6
12	-4 8103	028	42	0	ASN	153	H-donor	2.86	_2.9
12	4.0105	N2	2	ČA	PHF	311	H-acceptor	3.51	-0.7
		N3	3	N	ARG	312	H-acceptor	3 10	-3.5
13	-5 3956	5-ring	5	CA	PHF	311	π-H	4 20	-1.1
15	-4.0081	N3	3	CA	PRO	309	H-acceptor	2 41	23.6
17	4.0001	029	45	CB	ASN	153	H-acceptor	2.41	36.7
		029	45	ND2	ASN	153	H-acceptor	2.50	-0.7
		6-ring	15	CD	ARG	439	π-H	4 33	-1.1
15	-50782	6-ring		N	ARG	312	π-H	3.81	-0.7
16	-5 4913	C16	22	0	ASP	349	H-donor	2 46	27
10	5.4715	6-ring	22	Č A	IVS	155	π-H	4.04	_0.3
17	-5 9653	6-ring		CD	ARG	439	π-H	4 33	-1.0
18	-5 9891	C14	18	0	ASP	349	H-donor	3 30	-0.6
10	-5.7671	6-ring	10		LVS	155	π-H	3.88	-0.0
		6-ring		CD2	PHE	300	π-H	3.41	_0.5
		6-ring		CD2	ARG	439	π-H	4 47	-0.8
Standard Acarbose	5 8034	O	20	ND2	ASN	412	H acceptor	7.77 2.04	-0.0
Standard Acaroose	-5.0954	0	67	NZ	LVS	155	H acceptor	2.94	-2.0
		N	58	OE1	GUU	276	ionic	2.94	-1.7
		0	67	0	ASD	2/0	H donor	2.71	-0.7
		0	84	NH1	ADC	/20	H accontor	2.70	-2.9
		0	04		AKU	439	n-acceptor	2.75	0.4

inhibitory potential. All synthetic derivatives showed good inhibitory activity. Compounds 6 and 7 were found to have hundred folds superior inhibitory activity as compared to the standard acarbose. SAR study revealed that the compounds with hydroxyl groups particularly at *ortho* and *para* positions were more active as compared to the compounds with nitro and Cl group. Molecular docking studies confirmed the binding sites and interactions of the synthetic ligands with the enzyme. So, it can be concluded that further structural modification of these active analogs may help to find a prospective anti-diabetic lead molecule.

4. Materials and methods

¹H- and ¹³C NMR spectra were recorded on Bruker 500 MHz spectrometers. Mass experiments were carried out on a Finnigan MAT-311A (Germany) mass spectrometer. Thin-layer chromatography (TLC) was monitored on pre-coated silica gel aluminum plates (Kieselgel 60, 254, E. Merck, Germany). Visualization of TLC chromatograms was performed at wavelengths of 254 and 365 nm. All reagents of analytical grades were purchased from Merck, Germany.

4.1. General method for the synthesis of oxadiazole derivatives (1–18)

To a stirred solution of aldehyde (1 mmol) in methanol (10 mL), semicarbazide (1 mmol) in distilled H₂O (10 mL) was added and refluxed in the presence of NaOAc (2 mmol) at 25 °C for 10 min. Progress of the reaction was monitored by TLC, upon completion, the solvent was evaporated under reduced pressure on a rotary evaporator. The residue obtained was further refluxed with iodine and potassium carbonate in 1,4-dioxane at 80 °C for 4 h. The reaction was continued until the starting material was completely consumed. On disappearance of starting material, the reaction mixture was cooled to room temperature and then it was reacted with 5% Na₂S₂O₃ followed by extraction with CH₂Cl₂/MeOH (9:1). The organic layer was then dried and washed with ether and ethyl acetate as eluent to remove impurities. The pure products thus obtained in the second step was further mixed and refluxed with different substituted benzaldehydes (1 mmol) in methanol (10 mL) to give desired products (1-18). The synthetic derivatives were crystallized from methanol and characterized through different spectroscopic techniques such as ¹H-, ¹³C NMR, and HREI-MS.

4.2. (E)-1-(3-Nitrophenyl)-N-(5-(3-nitrophenyl)-1,3,4-oxadiazol-2-yl)methanimine (1)

Yield: 82%, ¹H NMR (500 MHz, DMSO d_6) δ 8.97 (s, 1H, —CH=N), 8.58 (d, J = 1.4 Hz, 1H, H-2), 8.48 (d, J = 1.6 Hz, 1H, H-2'), 8.42(dd, J = 8.1, 1.2 Hz, 1H, H-6), 8.30 (d, J = 8.5 Hz, 1H, H-4), 8.23(dd, J = 8.3, 1.1 Hz, 1H, H-6'), 8.07 (d, J = 8.4 Hz, 1H, H-4'), 7.82 (dd, J = 8.4, 8.1 Hz, 1H, H-5), 7.61 (dd, J = 8.2, 8.4 Hz, 1H, H-5'), ¹³C NMR (125 MHz, DMSO d_6): δ 164.0, 164.0, 160.2, 148.3, 148.1, 137.0, 135.1, 133.4, 130.0, 129.6, 127.1, 126.0, 125.7, 123.7, 122.6, HREI-MS m/z : Calcd for C₁₅H₉N₅O₅, 339.0604, Found: 339.0600. 4.3. (E)-1-(4-Chlorophenyl)-N-(5-(2-nitrophenyl)-1,3,4oxadiazol-2-yl)methanimine (2)

Yield: 78%, ¹H NMR (500 MHz, DMSO d_6) δ 9.02 (s, 1H, --CH=N), 8.01 (d, J = 8.3 Hz, 1H, H-6), 7.98 (dd, J = 8.4, 1.4 Hz, 1H, H-3), 7.94 (dd, J = 8.0, 1.4 Hz, 2H, H-2'/6'), 7.87 (m, 1H, H-5), 7.70 (m, 1H, H-4), 7.57 (dd, J = 8.2, 1.5 Hz, 2H, H-3'/5'), ¹³C NMR (125 MHz, DMSO d_6): δ 164.0, 164.0, 160.2, 146.7, 136.5, 135.1, 134.4, 131.4, 130.3, 130.3, 129.5, 128.7, 128.7, 128.2, 124.2, HREI-MS m/z : Calcd for C₁₅H₉ClN₄O₃, 328.0363, Found: 328.0360.

4.4. (E)-N,N-Dimethyl-4-(5-((2-nitrobenzylidene)amino)-1,3,4oxadiazol-2-yl)aniline (3)

Yield: 73%, ¹H NMR (500 MHz, DMSO d_6) δ 9.04 (s, 1H, --CH=N), 8.04 (d, J = 8.5 Hz, 1H, H-6'), 7.96 (dd, J = 8.1, 1.3 Hz, 1H, H-3'), 7.70 (m, 1H, H-5'), 7.62 (m, 1H, H-4'), 7.57 (dd, J = 8.0, 1.4 Hz, 2H, H-2/6), 6.90 (dd, J = 8.2, 1.6 Hz, 2H, H-3/5), 3.00 (s, 6H, --CH₃), ¹³C NMR (125 MHz, DMSO d_6): δ 164.0, 164.0, 160.2, 155.1, 147.6, 134.7, 131.8, 130.0, 128.3, 128.3, 128.3, 124.1, 115.4, 112.5, 112.5, 41.1, 41.1, HREI-MS m/z : Calcd for C₁₇H₁₅N₅O₃, 337.1175, Found: 337.1170.

4.5. (E)-4-(5-((2-Nitrobenzylidene)amino)-1,3,4-oxadiazol-2yl)phenol (4)

Yield: 80%, ¹H NMR (500 MHz, DMSO d_6) δ 9.69 (s, 1H, OH), 9.06 (s, 1H, -CH=N), 8.08 (d, J = 8.6 Hz, 1H, H-6'), 8.00 (dd, J = 8.3, 1.7 Hz, 1H, H-3'), 7.74 (m, 1H, H-5'), 7.64 (m, 1H, H-4'), 7.87 (dd, J = 8.2, 1.1 Hz, 2H, H-2/6), 6.89 (dd, J = 8.4, 1.3 Hz, 2H, H-3/5), ¹³C NMR (125 MHz, DMSO d_6): δ 164.0, 164.0, 160.2, 158.3, 147.5, 134.7, 131.7, 130.0, 128.3, 124.1, 118.6, 116.2, 116.2, 116.1, 116.1, HREI-MS m/z: Calcd for C₁₅H₁₀N₄O₄, 310.0702, Found: 310.0700.

4.6. (*E*)-4-(5-((3-Nitrobenzylidene)amino)-1,3,4-oxadiazol-2yl)phenol (5)

Yield: 84%, ¹H NMR (500 MHz, DMSO d_6) δ 9.72 (s, 1H, OH), 9.10 (s, 1H, -CH=N), 8.53 (d, J = 1.6 Hz, 1H, H-2'), 8.28 (dd, J = 8.5, 1.4 Hz, 1H, H-6'), 8.12 (d, J = 8.6 Hz, 1H, H-4'), 7.88 (dd, J = 8.4, 1.4 Hz, 2H, H-2/6), 7.66 (dd, J = 8.3, 8.1 Hz, 1H, H-5'), 6.94 (dd, J = 8.2, 1.4 Hz, 2H, H-3/5), ¹³C NMR (125 MHz, DMSO d_6): δ 164.0, 164.0, 160.2, 158.3, 148.1, 137.0, 135.1, 129.5, 126.0, 125.7, 118.6, 116.2, 116.2, 116.1, 1HREI-MS m/z: Calcd for C₁₅H₁₀N₄O₄, 310.0702, Found: 310.0700.

4.7. (*E*)-3-(((5-(4-Hydroxyphenyl)-1,3,4-oxadiazol-2-yl)imino) methyl)phenol (**6**)

Yield: 86%, ¹H NMR (500 MHz, DMSO d_6) δ 9.74 (s, 1H, OH), 9.47 (s, 1H, OH), 9.12 (s, 1H, —CH=N), 7.87 (dd, J = 8.1, 1.2 Hz, 2H, H-2/6), 7.35 (dd, J = 8.3, 1.6 Hz, 1H, H-6'), 7.27 (d, J = 1.5 Hz, 1H, H-2'), 7.16 (dd, J = 8.0, 8.3 Hz, 1H, H-5'), 6.97 (d, J = 8.2 Hz, 1H, H-4'), 6.95 (dd, J = 8.5, 1.7 Hz, 2H, H-3/5), ¹³C NMR (125 MHz, DMSO d_6): δ 164.0, 164.0, 160.2, 158.4, 158.3, 138.5, 130.0, 121.7, 118.5,

118.0, 116.2, 116.2, 116.1, 116.1, 114.7, HREI-MS *m*/*z* : Calcd for C₁₅H₁₁N₃O₃, 281.0800, Found: 281.0798.

4.8. (E)-4-(5-((4-Hydroxybenzylidene)amino)-1,3,4-oxadiazol-2-yl)phenol (7)

Yield: 77%, ¹H NMR (500 MHz, DMSO d_6) δ 9.77 (s, 2H, OH), 9.15 (s, 1H, —CH=N), 7.89 (dd, J = 8.4, 1.5 Hz, 2H, H-2/6), 7.70 (dd, J = 8.2, 1.3 Hz, 2H, H-2'/6'), 6.96 (dd, J = 8.1, 1.6 Hz, 2H, H-3/5), 6.88 (dd, J = 8.2, 1.3 Hz, 2H, H-3'/5'), ¹³C NMR (125 MHz, DMSO d_6): δ 164.0, 164.0, 160.7, 160.2, 158.3, 130.5, 130.5, 129.1, 118.5, 116.2, 116.2, 116.1, 116.1, 116.1, HREI-MS m/z : Calcd for C₁₅H₁₁N₃O₃, 281.0800, Found: 281.0798.

4.9. (E)-1-(2-Nitrophenyl)-N-(5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl)methanimine (**8**)

Yield: 79%, ¹H NMR (500 MHz, DMSO d_6) δ 9.04 (s, 1H, --CH=N), 8.45 (dd, J = 8.7, 1.6 Hz, 2H, H-3/5), 8.27 (dd, J = 8.4, 1.7 Hz, 2H, H-2/6), 8.10 (d, J = 8.5 Hz, 1H, H-6'), 7.95 (d, J = 8.4 Hz, 1H, H-3'), 7.67 (m, 1H, H-5'), 7.55 (m, 1H, H-4'), ¹³C NMR (125 MHz, DMSO d_6): δ 164.0, 164.0, 160.2, 147.7, 147.6, 134.7, 132.0, 131.7, 130.7, 130.7, 130.0, 128.6, 128.6, 128.2, 124.2, HREI-MS m/z : Calcd for C₁₅H₉N₅O₅, 339.0604, Found: 339.0600.

4.10. (E)-N-(5-(Anthracen-9-yl)-1,3,4-oxadiazol-2-yl)-1-(2nitrophenyl)methanimine (**9**)

Yield: 83%, ¹H NMR (500 MHz, DMSO d_6) δ 9.11 (s, 1H, --CH=N), 8.51 (s, 1H, H-6), 8.17 (d, J = 8.6 Hz, 2H, H-2/10), 8.03 (d, J = 8.7 Hz, 1H, H-6'), 7.99 (d, J = 8.2 Hz, 2H, H-5/7), 7.92 (d, J = 8.6 Hz, 1H, H-3'), 7.64 (m, 1H, H-5'), 7.52 (m, 1H, H-4'), 7.46 (m, 2H, H-4/8), 7.41 (m, 2H, H-3/9), ¹³C NMR (125 MHz, DMSO d_6): δ 164.0, 164.0, 160.2, 147.6, 134.7, 134.0, 132.0, 132.0, 131.7, 130.2, 130.2, 130.0, 129.7, 128.3, 128.0, 128.0, 125.5, 125.5, 125.5, 125.5, 124.2, 124.2, 124.2, HREI-MS m/z : Calcd for C₂₃H₁₄N₄O₃, 394.1066, Found: 394.1061.

4.11. (E)-N-(5-(Anthracen-9-yl)-1,3,4-oxadiazol-2-yl)-1-(3-nitrophenyl)methanimine (10)

Yield: 81%, ¹H NMR (500 MHz, DMSO d_6) δ 8.94 (s, 1H, --CH=N), 8.61 (s, 1H, H-6), 8.53 (d, J = 1.6 Hz, 1H, H-2'), 8.31 (d, J = 8.5 Hz, 1H, H-6'), 8.24 (dd, J = 8.5, 1.4 Hz, 2H, H-2/10), 8.13 (d, J = 8.0 Hz, 1H, H-4'), 8.05(d, J = 8.4 Hz, 2H, H-5/7), 7.60 (dd, J = 8.7, 1.6 Hz, 1H, H-5'),7.52 (m, 2H, H-4/8), 7.40 (m, 2H, H-3/9), ¹³C NMR (125 MHz, DMSO d_6): δ 164.0, 164.0, 160.2, 148.2, 137.0, 135.1, 134.0, 132.0, 132.0, 130.2, 130.2, 129.7, 129.5, 128.0, 128.0, 126.0, 125.7, 125.4, 125.4, 125.4, 125.4, 124.2, 124.2, HREI-MS m/z : Calcd for C₂₃H₁₄N₄O₃, 394.1066, Found: 394.1061.

4.12. (E)-3-(((5-(Anthracen-9-yl)-1,3,4-oxadiazol-2-yl)imino) methyl)phenol (11)

Yield: 74%, ¹H NMR (500 MHz, DMSO d_6) δ 9.50 (s, 1H, OH), 8.91 (s, 1H, -CH=N), 8.63 (s, 1H, H-6), 8.26 (dd, J = 8.3, 1.6 Hz, 2H, H-2/10), 8.07 (d, J = 8.6 Hz, 2H, H-

5/7), 7.57 (m, 2H, H-4/8), 7.38 (m, 2H, H-3/9), 7.28 (dd, J = 8.3, 1.3 Hz, 1H, H-6'), 7.21 (dd, J = 1.2 Hz, 1H, H-2'), 7.10 (dd, J = 8.5, 8.3 Hz, 1H, H-5'), 6.90 (d, J = 8.0 Hz, 1H, H-4'), ¹³C NMR (125 MHz, DMSO d_6): δ 164.0, 164.0, 160.2, 158.5, 138.6, 134.0, 132.0, 132.0, 130.3, 130.3, 130.0, 129.7, 128.0, 128.0, 125.4, 125.4, 125.4, 125.4, 124.2, 124.2, 121.7, 118.0, 114.7, HREI-MS m/z: Calcd for C₂₃H₁₅N₃O₂, 365.1164, Found: 365.1160.

4.13. (E)-4-(((5-(Anthracen-9-yl)-1,3,4-oxadiazol-2-yl)imino) methyl)phenol (12)

Yield: 76%, ¹H NMR (500 MHz, DMSO d_6) δ 9.77 (s, 1H, OH), 8.90 (s, 1H, -CH=N), 8.69 (s, 1H, H-6), 8.30 (dd, J = 8.6, 1.2 Hz, 2H, H-2/10), 8.11 (d, J = 8.3 Hz, 2H, H-5/7), 7.61 (dd, J = 8.5, 1.7 Hz, 2H, H-2'/6'), 7.62 (m, 2H, H-4/8), 7.35 (m, 2H, H-3/9), 6.82 (dd, J = 8.0, 1.2 Hz, 2H, H-3'/5'), ¹³C NMR (125 MHz, DMSO d_6): δ 164.0, 164.0, 160.6, 160.2, 134.0, 132.0, 132.0, 130.4, 130.4, 130.2, 130.2, 129.6, 129.2, 128.0, 128.0, 125.4, 125.4, 125.4, 125.4, 124.2, 124.2, 116.1, 116.1, HREI-MS m/z: Calcd for C₂₃H₁₅N₃O₂, 365.1164, Found: 365.1160.

4.14. (E)-N-(5-(4-(Benzyloxy)phenyl)-1,3,4-oxadiazol-2-yl)-1-(2-nitrophenyl)methanimine (13)

Yield: 85%, ¹H NMR (500 MHz, DMSO d_6) δ 9.09 (s, 1H, --CH=N), 8.09 (d, J = 8.4 Hz, 1H, H-6'), 8.04 (dd, J = 8.7, 1.6 Hz, 2H, H-2/6), 7.87 (d, J = 8.3 Hz, 1H, H-3'), 7.60 (m, 1H, H-5'), 7.51 (m, 1H, H-4'), 7.45 (dd, J = 8.2, 1.4 Hz, 2H, H-2″/6″), 7.37 (dd, J = 8.5, 1.7 Hz, 2H, H-3″/5″), 7.29 (m, 1H, H-4″), 7.00 (dd, J = 8.7, 1.2 Hz, 2H, H-3/5), 5.13 (s, 2H, --CH₂), ¹³C NMR (125 MHz, DMSO d_6): δ 164.0, 164.0, 160.2, 159.2, 147.7, 136.5, 134.7, 131.7, 130.0, 128.8, 128.8, 128.3, 127.4, 127.0, 127.0, 124.2, 118.3, 115.7, 115.7, 114.6, 114.6, 70.6, HREI-MS m/z: Calcd for C₂₂H₁₆N₄O₄, 400.1172, Found: 400.1168.

4.15. (E)-N-(5-(4-(Benzyloxy)phenyl)-1,3,4-oxadiazol-2-yl)-1-(3-nitrophenyl)methanimine (14)

Yield: 87%, ¹H NMR (500 MHz, DMSO d_6) δ 8.84 (s, 1H, --CH=N), 8.65 (d, J = 1.8 Hz, 1H, H-2'), 8.35 (dd, J = 8.5, 1.6 Hz, 1H, H-6'), 8.15 (d, J = 8.1 Hz, 1H, H-4'), 8.07 (dd, J = 8.0, 1.5 Hz, 2H, H-2/6), 7.71 (dd, J = 8.3, 8.4 Hz, 1H, H-5'), 7.50 (dd, J = 8.2, 1.4 Hz, 2H, H-2"/6"), 7.33 (dd, J = 8.5, 1.1 Hz, 2H, H-3"/5"), 7.22 (m, 1H, H-4"), 6.98 (dd, J = 8.4, 1.4 Hz, 2H, H-3/5), 5.11 (s, 2H, --CH₂), ¹³C NMR (125 MHz, DMSO d_6): δ 164.0, 164.0, 160.2, 159.2, 148.2, 137.0, 136.5, 135.1, 129.5, 128.7, 128.7, 127.5, 127.0, 127.0, 126.0, 125.7, 118.3, 115.7, 115.7, 114.6, 114.6, 70.6, HREI-MS m/z: Calcd for C₂₂H₁₆N₄O₄, 400.1172, Found: 400.1168.

4.16. (E)-1-(4-(Benzyloxy)phenyl)-N-(5-(4-(benzyloxy)phenyl)-1,3,4-oxadiazol-2-yl)methanimine (15)

Yield: 81%, ¹H NMR (500 MHz, DMSO d_6) δ 8.86 (s, 1H, -CH=N), 8.00 (dd, J = 8.3, 1.6 Hz, 2H, H-2/6), 7.97 (dd, J = 8.5, 1.6 Hz, 2H, H-2"/6"), 7.43 (dd, J = 8.2, 1.4 Hz, 4H, H-2"/6"/2"/6"), 7.32 (dd, J = 8.6, 1.4 Hz, 4H, H-3"/5"/3"/5 "'), 7.27 (m, 2H, H-4"/4"), 7.10 (dd, J = 8.7, 1.5 Hz, 2H,

H-3"/5"), 6.96 (dd, J = 8.2, 1.2 Hz, 2H, H-3/5), 5.18 (s, 4H, -CH₂), ¹³C NMR (125 MHz, DMSO d_6): δ 164.0, 164.0, 161.1, 160.2, 159.2, 136.5, 136.5, 130.0, 130.0, 128.7, 128.7, 128.7, 128.7, 128.5, 127.4, 127.4, 127.0, 127.0, 127.0, 127.0, 118.3, 115.7, 115.7, 114.6, 114.6, 114.2, 114.2, 70.6, 70.6, HREI-MS m/z: Calcd for C₂₉H₂₃N₃O₃, 461.1739, Found: 461.1736.

4.17. (E)-N-(5-(4-(Benzyloxy)phenyl)-1,3,4-oxadiazol-2-yl)-1-(2,4-dichlorophenyl)methanimine (16)

Yield: 72%, ¹H NMR (500 MHz, DMSO d_6) δ 8.96 (s, 1H, —CH=N), 8.06 (dd, J = 8.6, 1.3 Hz, 2H, H-2/6), 8.01 (d, J = 8.8 Hz, 1H, H-6'), 7.68 (s, 1H, H-3'), 7.45 (d, J = 8.5 Hz, 1H, H-5'), 7.41 (dd, J = 8.3, 1.7 Hz, 2H, H-2"/6"), 7.36 (dd, J = 8.2, 1.3 Hz, 2H, H-3"/5"), 7.25 (m, 1H, H-4"), 7.07 (dd, J = 8.4, 1.4 Hz, 2H, H-3/5), 5.20 (s, 2H, —CH₂), ¹³C NMR (125 MHz, DMSO d_6): δ 164.0, 164.0, 160.2, 159.2, 136.5, 131.4, 131.1, 129.2, 129.1, 128.7, 128.7, 128.1, 127.4, 127.0, 127.0, 127.0, 118.3, 115.7, 115.7, 114.6, 114.6, 70.6, HREI-MS m/z : Calcd for C₂₂H₁₅C₁₂N₃O₂, 423.0541, Found: 423.0538.

4.18. (E)-3-(((5-(4-(Benzyloxy)phenyl)-1,3,4-oxadiazol-2-yl) imino)methyl)phenol (17)

Yield: 78%, ¹H NMR (500 MHz, DMSO d_6) δ 9.51 (s, 1H, OH), 8.92 (s, 1H, —CH=N), 8.10 (dd, J = 8.4, 1.5 Hz, 2H, H-2/6), 7.66 (dd, J = 8.5, 1.6 Hz, 2H, H-2″/6″), 7.31 (dd, J = 8.4, 1.4 Hz, 2H, H-3″/5″), 7.23 (m, 1H, H-4″), 7.19 (dd, J = 8.1, 1.2 Hz, 1H, H-6′), 7.15 (d, J = 1.1 Hz, 1H, H-2′), 7.10 (dd, J = 8.6, 8.4 Hz, 1H, H-5′), 7.09 (dd, J = 8.1, 1.5 Hz, 2H, H-3/5), 6.95 (d, J = 8.3 Hz, 1H, H-4′), 5.22 (s, 2H, —CH₂), ¹³C NMR (125 MHz, DMSO d_6): δ 164.0, 164.0, 160.2, 159.2, 158.4, 138.5, 136.5, 130.0, 128.7, 128.7, 127.4, 127.0, 127.0, 121.7, 118.3, 118.0, 115.7, 115.7, 114.7, 114.6, 114.6, 70.6, HREI-MS m/z : Calcd for C₂₂H₁₇N₃O₃, 371.1270, Found: 371.1265.

4.19. (E)-4-(((5-(4-(Benzyloxy)phenyl)-1,3,4-oxadiazol-2-yl) imino)methyl)phenol (18)

Yield: 81%, ¹H NMR (500 MHz, DMSO d_6) δ 9.80 (s, 1H, OH), 8.90 (s, 1H, -CH=N), 8.00 (dd, J = 8.6, 1.3 Hz, 2H, H-2/6), 7.54 (dd, J = 8.2, 1.5 Hz, 2H, H-2'/6'), 7.38 (dd, J = 8.2, 1.5 Hz, 2H, H-2''/6'), 7.33 (dd, J = 8.7, 1.6 Hz, 2H, H-3''/5''), 7.21 (m, 1H, H-4''), 7.11 (dd, J = 8.3, 1.2 Hz, 2H, H-3/5), 6.80 (dd, J = 8.0, 1.1 Hz, 2H, H-3'/5'), 5.19 (s, 2H, -CH₂), ¹³C NMR (125 MHz, DMSO d_6): δ 164.0, 164.0, 160.6, 160.2, 159.2, 136.5, 130.4, 130.4, 129.2, 128.7, 128.7, 127.4, 127.0, 127.0, 118.3, 116.2, 116.2, 115.7, 115.7, 114.6, 114.6, 70.6, HREI-MS m/z : Calcd for C₂₂H₁₇N₃O₃, 371.1270, Found: 371.1265.

5. Biological assays

5.1. a-Glucosidase inhibitory assay

In 96 well plate, $135 \,\mu\text{L}$ of 50 mM phosphate saline buffer pH (6.8) and 20 μL of the test sample with 70% DMSO were

added. The plate was incubated for 15 min after the addition of 20 μ L of enzyme to each well. SpectraMax Microplate reader was used to pre-read the plate after incubation. Subsequently 25 μ L of the substrate (*pNPG*) was added and samples were read using SpectraMax Microplate reader at 400 nm for 30 min. The normal reading was taken and the percent inhibition was calculated (Taha et al., 2017).

5.2. Molecular docking assay

The interactions of inhibitor molecule with protein target are easily explored through molecular docking study (Rahim et al., 2015). MOE-Dock program was used to carry out molecular docking, to guess the binding interactions of these molecules in the active sites of α -glucosidase enzyme. We used homology model as defined by Rahim et al. (2015).

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