MedChemComm

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/medchemcomm

Novel Quinoline Derivatives as Potent *In Vitro* α-Glucosidase Inhibitors: *In Silico* Studies and SAR Predictions

Muhammad Taha[a,b*], Nor Hadiani Ismail[a,b], Syahrul Imran[a,b], Abdul Wadood[c], Fazal Rahim[d], Muhammad Ali[e], and Ashfaq Ur Rehman[c]

[a]*Atta-ur-Rahman Institute for Natural Product Discovery, UniversitiTeknologi MARA, PuncakAlam42300,Malaysia*

[b]*Faculty of Applied Science Universiti Teknologi MARA, Shah Alam 40450,Selangor D. E., Malaysia*

[c]*Department of Biochemistry, Computational Medicinal Chemistry Laboratory, UCSS, Abdul Wali Khan University Mardan, Pakistan*

[d]*Depatment of Chemistry, Hazara University, Mansehra, Khyber Pakhtunkhwa, Pakistan*

[e]*Department of Chemistry, COMSATS Institute of Information Technology, University Road, Abbottabad-22060, KPK, Pakistan*

Abstract:

A new series of quinoline derivatives **6-30** was identified as potent α-glucosidase inhibitors. These analogs exhibited inhibitory potentials (IC_{50} values) in the ranges between 2.60 to 102.12 μM. Among the series, compounds **24** (2.60 ± 0.01 μM), **27** (2.60 ± 0.01 μM) and **20** (2.86 ± 0.01 μM) were found exceptionally potent (> 14 times ~ than the standard) inhibitors of α-glucosidase when compared to the standard acarbose (IC_{50} = 38.25 ± 0.12 μM). Molecular docking studies on two most active compounds **24** and **27** corroborated that compound **24** adopted linear position to optimally fit into the binding site of α-glucosidase. Observations for the best position of compound **24** showed a total of four interactions towards catalytically active site residues of α-glucosidase involving amino acid residues such as Phe-177 and Asp-214. Oxadiazole ring of compound **24** interacted with His-279. Compound **27** formed one hydrogen bonded interaction (*N*-methylacetamide) and three arene-arene interactions (quinoline and 1,3,4-oxadiazole moiety). Quinoline moiety of compound **27** formed two π-interactions with Phe-157. All compounds were tested for cytotoxicity but none of them found to be cytotoxic.

Keywords: Quinoline, oxadiazole, hydrazone, α-glucosidase, Molecular docking

* Correspondence and reprints
E-mail: taha_hej@yahoo.comand muhamm9000@puncakalam.uitm.edu.my, Tel: 0060193098141

1. Introduction

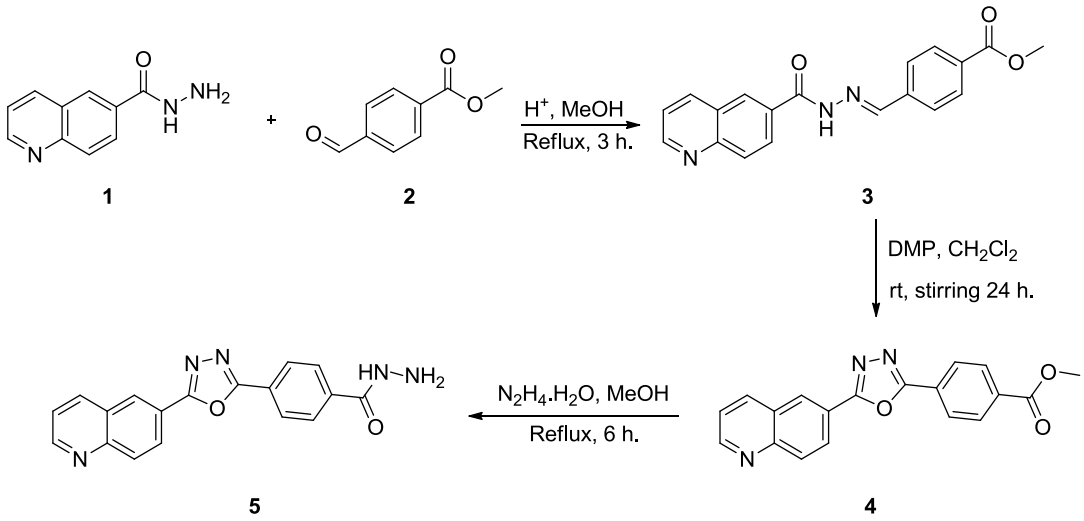
Diabetes is a disorder caused by shortage of insulin supply, insulin action, or both [1]. The disease is characterized by hyperglycemia (high blood sugar) and is predicted to reach 300 million people worldwide by 2025 [2]. Diabetes is often accompanied by ketosis and protein wasting [3] along with other complications such as retinopathy, neuropathy and peripheral vascular insufficiencies [4]. Insulin acts as principle hormone which controls the consumption of glucose by most of the body cells. Limited supply of insulin or reduction in sensitivity of its receptors plays an important role in the onset of diabetes [5]. Antidiabetic drugs had been reported to suppress diabetes by inhibiting production of glucose by the liver and increasing insulin secretion by pancreatic beta cells. Antidiabetic drugs were also found to increase glucose uptake by skeletal muscle and inhibit carbohydrate absorption in the small intestine [6]. α-Glucosidase inhibitors play pivotal role in controlling postprandial hyperglycemia (PPHG) with diabetic disorder since α-glucosidase is capable of increasing PPHG [7]. Further to this, the inhibition leads to decrease in starch disintegration and thus produces favorable outcome on glycemic index management of people with diabetes [8]. α-Glucosidase inhibitors such as acarbose and voglibose act as reversible and competitive inhibitors of α-glucosidase by slowing down the breakup of carbohydrates and delay glucose absorption [9].

Quinolines which have antifungal [10, 11], antimalarial [12], antibacterial [13], anthelmintic [14,15], anticancer [16,17], anticonvulsant [18], anti-inflammatory [19], and analgesic [20] properties also displayed control over diabetic disorders through induction of hypoglycemic activity as the function of glucidic metabolism [21-24]. It was proposed that quinolines are able to indirectly induce hypoglycemia *via* a mechanism similar to sulfonyl ureas. Quinolines block adenosine triphosphate (ATP)-potassium channels in the pancreatic beta cells which control calcium inflow [25]. Studies showed that quinoline derivatives such as lomefloxacin, enoxacin, pipemidic acid, sparfloxacin, and tosufloxacin are important in insulinotropic actions [23]. The effect of quinoline-induced hypoglycemia vary within the class with some quinolines such as gatifloxacin displaying greater effect on reducing glucose in blood and increasing insulin level [23]. As the result, diabetes had been specifically prescribed as *contra*- indication for usage of gatifloxacin [26]. The naturally occurring quinoline derivatives are reported for potent α-glucosidase inhibition potential recently [27, 28]. This finding motivated us to synthesize new quinoline derivatives. In this study, twenty five (25) quinoline derivatives bearing an oxadiazole moiety were synthesized and evaluated for their α-glucosidase inhibition potential. Besides identifying potent α-glucosidase inhibitors, this study has also been designed to establish the structure-activity relationship (SAR).

2. Results and Discussion

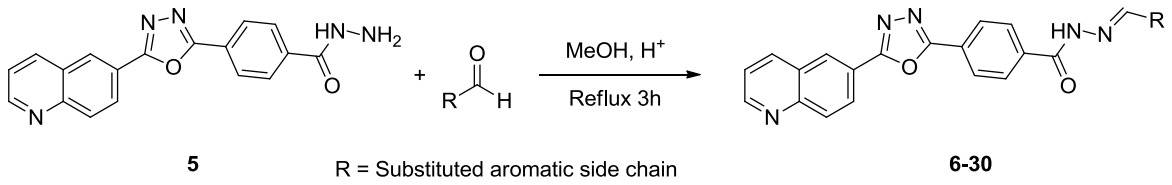
2.1 Chemistry

Twenty five (25) derivatives, **6-30**, of 4-(5-(quinolin-6-yl)-1,3,4-oxadiazol-2-yl)benzohydrazones were synthesized by reacting hydrazide **5** with different aromatic aldehydes. Hydrazide **5** was obtained in three steps (Scheme 1) starting from the condensation of quinolinylhydrazide **1** and aldehyde **2** to form hydrazone (**3**) which was then oxidatively cyclized to oxadiazole 4 by Dess-Martin reagent. Finally compound **4** was refluxed with hydrazine hydrate to afford 4-(5-(quinolin-6-yl)-1,3,4-oxadiazol-2-yl)benzohydrazide **5** in high yield **Scheme 1**.



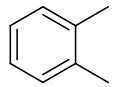
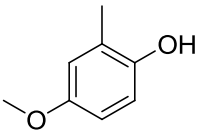
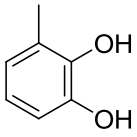
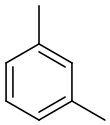
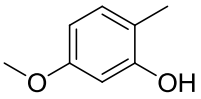
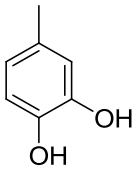
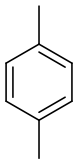
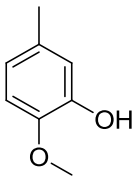
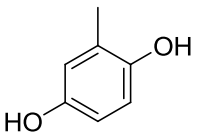
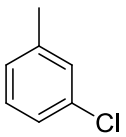
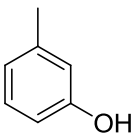
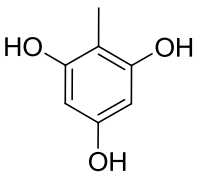
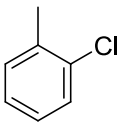
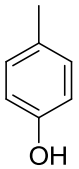
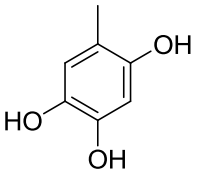
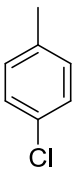
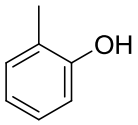
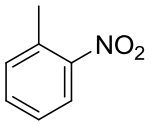
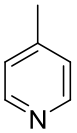
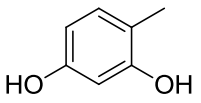
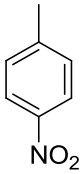
Scheme 1. Synthesis of 4-(5-(quinolin-6-yl)-1,3, 4-oxadiazol-2-yl) benzohydrazide 5

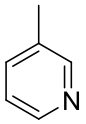
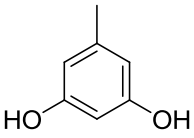
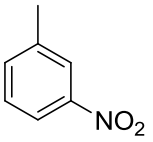
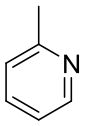
Compound **5** was treated with different aryl aldehydes to afford novel quinoline derivatives **6-30**. Structures of all the synthesized compounds **6-30** were confirmed using ^{1}H-NMR, ^{13}C-NMR, EIMS and elemental analysis **Scheme 2 (Table-1)**.



Scheme 2.Synthesis of 4-(5-(quinolin-6-yl)-1, 3, 4-oxadiazol-2-yl) benzohydrazones 6-30

Table 1: Synthesis of novel Quinoline derivatives 6-30

S. No	R	S.No	R	S.No	R
6		**15**		**23**	
7		**16**		**24**	
8		**17**		**25**	
9		**18**		**26**	
10		**19**		**27**	
11		**20**		**28**	
12		**21**		**29**	

13		**22**		**30**	
14		-	-	-	-

3. *In Vitro* α-Glucosidase Activity

Our continued efforts resulted in the identification of many lead molecules against various enzyme targets [29]. Herein, we are reporting novel hydrazone derivatives **6-30** carrying quinolone and oxadiazole backbones as extremely potent α-glucosidase inhibitors. Compounds **6-30** demonstrated varying degree of α-glucosidase inhibitory potential with IC_{50} values ranging between 2.60-102.12 μM (Table-2). Compounds **9**, **10, 11, 15**, **16**, **17, 19-28** and **30,** showed excellent activity when compared to the standard acarbose (IC_{50} = 38.25 ± 0.12 μM). Compounds **6**, **7**, **8**, **14**, **18** and **29** showed good to moderate activity, while compounds **12** and **13** showed less than 50 % inhibition therefore, they were not further evaluated for their IC_{50} values (Table-2).

Structure-activity relationship suggested that the activity of a specific molecule is superficially directed by the substitution present at aromatic residues of various aldehydes. The *meta*-chloro substituted analog **9** (IC_{50} = 30.15± 0.32 μM), *ortho*-chloro analog **10** (IC_{50} = 4.16 ± 0.01μM), *para*-chloro analog **11** (IC_{50} = 3.90 ± 0.01μM), 2-hydroxy-5-methoxy analog **15** (IC_{50} = 6.20 ± 0.02 μM), 2-hydroxy-4-methoxy analog 1**6** (IC_{50} = 9.20 ± 0.03μM), 3-hydroxy-4-methoxy analog **17** (IC_{50} = 21.20 ± 0.20 μM), *para*-hydroxy analog **19** (IC_{50} = 27.15 ± 0.28 μM), *ortho*-hydroxy analog **20** (IC_{50} = 2.86 ± 0.01 μM), 2,4-dihydroxy analog **21** (IC_{50} = 8.45 ± 0.05μM), 3,5-dihydroxy analog **22** (IC_{50} = 37.15 ± .30 μM), 2,3-dihydroxy analog **23** (IC_{50} = 6.8 ± 0.02 μM), 3,4-dihydroxy analog **24** (IC_{50} = 2.60 ± 0.01μM), 2,5-dihydroxy analog **25** (IC_{50} = 8.5 ± 0.60 μM), 2,4,6-trihydroxy analog **26** (IC_{50} = 8.12 ± 0.09 μM), 2,4,6-trihydroxy analog **27** (IC_{50} = 2.60 ± 0.01μM), *ortho*-nitro analog **28** (IC_{50} = 15.16 ± 0.40 μM) and *meta*-nitro analog **30** (IC_{50} = 36.5 ± 0.26μM) respectively showed tremendous α-glucosidase inhibitory potential among the series. Compound **24** (3,4-dihydroxy analog) and **27** (2,4,6-trihydroxy analog) are found to be the most potent inhibitors among the series with IC_{50} values 2.60 ± 0.01 and 2.60 ± 0.01μM, respectively. Most potent activity of these compounds might be attributed to two hydroxyl groups that apparently seemed to be involved in hydrogen bonding. Compound **20** was

found to be the second best inhibitor among the current series with IC_{50} value 2.86 ± 0.01 μM. This compound has hydroxy group at *ortho*- position of aromatic ring which might be responsible for the inhibition. Compounds **11** having a *para*-chloro group was found third most active compound with IC_{50} value of 3.90 ± 0.01μM. Some striking similarities in inhibitory potential of chloro- and hydroxyl substituted analogues has been observed. *Ortho*- chloro analoge **10** and *ortho*- hydroxyl analogue **20** displayed similar kind of inhibitory potentials with IC_{50} values of 4.16 ± 0.01 and 2.86 ± 0.01 μM, respectively. A similar behavior of inhibitory potentials for *meta*- analogues **9** and **18** was observed suggesting that electronic nature of group/atom is more important than the group/atom itself. However, the difference in the activity of *para*- analogues **11** and **19** could not be explained apparently.

The binding interactions of the most active compounds were confirmed through molecular docking studies.

Table-2: α-Glucosidase inhibitory potential of compounds **6-30**

Compounds	IC_{50} (μM ± SEM[a])	Compounds	IC_{50} (μM ± SEM[a])
6	80.14± 0.70	**19**	27.15 ± 0.28
7	100.46 ± 1.12	**20**	2.86 ± 0.01
8	102.12 ± 1.24	**21**	8.45 ± 0.05
9	30.15± 0.32	**22**	37.15 ± .30
10	4.16 ± 0.01	**23**	6.8 ± 0.02
11	3.90 ± 0.01	**24**	2.60 ± 0.01
12	NA[b]	**25**	8.5 ± 0.60
13	NA[b]	**26**	8.12 ± 0.09
14	40.46 ± 0.4	**27**	2.60 ± 0.01
15	6.20 ± 0.02	**28**	15.16 ± 0.40
16	9.20 ± 0.03	**29**	63.5 ± 0.34
17	21.20 ± 0.20	**30**	36.5 ± 0.26
18	39.16 ± 0.28	Standard: Acarbose[c]	38.25 ± 0.12 μM

SEM[a] is the standard error of the mean, NA[b] Not active, Acarbose[c] positive control for α-Glucosidase inhibitory potential

3.1 *In Silico* Studies

Crystal structure for α-glucosidase enzyme derived from *S. cerevisiae* is currently not available [30], however, it was found that isomaltase from *S. cerevisiae* (PDB: 3AJ7) showed the highest sequence identity (72 % and 38.5 %, respectively) [31]. The primary sequence of α-glucosidase was retrieved from UniProt protein resource data bank (http://www.uniprot.org/) under the access code P53341. Taking into consideration of the high sequence similarity, a homology model of α-glucosidase was therefore built from oligo-1,6-glucosidase using the same propriety as described [32].

In silico studies revealed that all the active derivatives showed significant binding interactions with the important active site residues of the α-glucosidase enzyme. Analysis of the predicted binding conformations of our most active compounds **24** and **27** (IC_{50} = 2.60 ± 0.01 and 2.60 ± 0.01) showed that compound **24** can adopt a linear conformation for a better fit to the binding site of α-glucosidase. Compound **24** established four interactions with the active site residues of α-glucosidase. The active site residues Phe-177 and Phe-157 were found in arene-arene interactions with phenyl ring of the compound whereas the His-279 showed arene-cation interaction with oxadiazole ring of the compound. A single hydrogen bond was observed between the active site residue Asp-214 and hydroxyl moiety of the compound **Figure 1a**. About similar binding mode was observed for compound **27** as shown in **Figure 1b**. Like compound **24**, compound **27** also established two arene-arene, one arene-cation and one hydrogen bond with the active site residues of the enzyme. The strong bonding network observed for compound **24** and **27** in the active site of the enzyme might be one of the reasons for showing good biological activities of these compounds. Compound **20**, which is the second most active compound (IC_{50} = 2.86 ± 0.01) in the series showed interactions with four different active site residues Asn-241, Glu-276, Asp-214 and Arg-212 (**Figure 1c)**. The nitrogen atom of oxadiazole ring of the compound formed hydrogen bond with active site residue Asn-241 whereas the hydroxyl moiety of the compound established three hydrogen bonds with active site residues Arg-212, Asp-214 and Glu-276 respectively. The predicted docking conformation of compound **11** (IC_{50} = 3.90 ± 0.01) showed three hydrogen bonds with the active site residues Asn-241 and Thr-307 (**Figure 1d)**. About similar binding modes were observed for compounds **21, 15, 16, 26, 23, 10** and **25,** respectively.

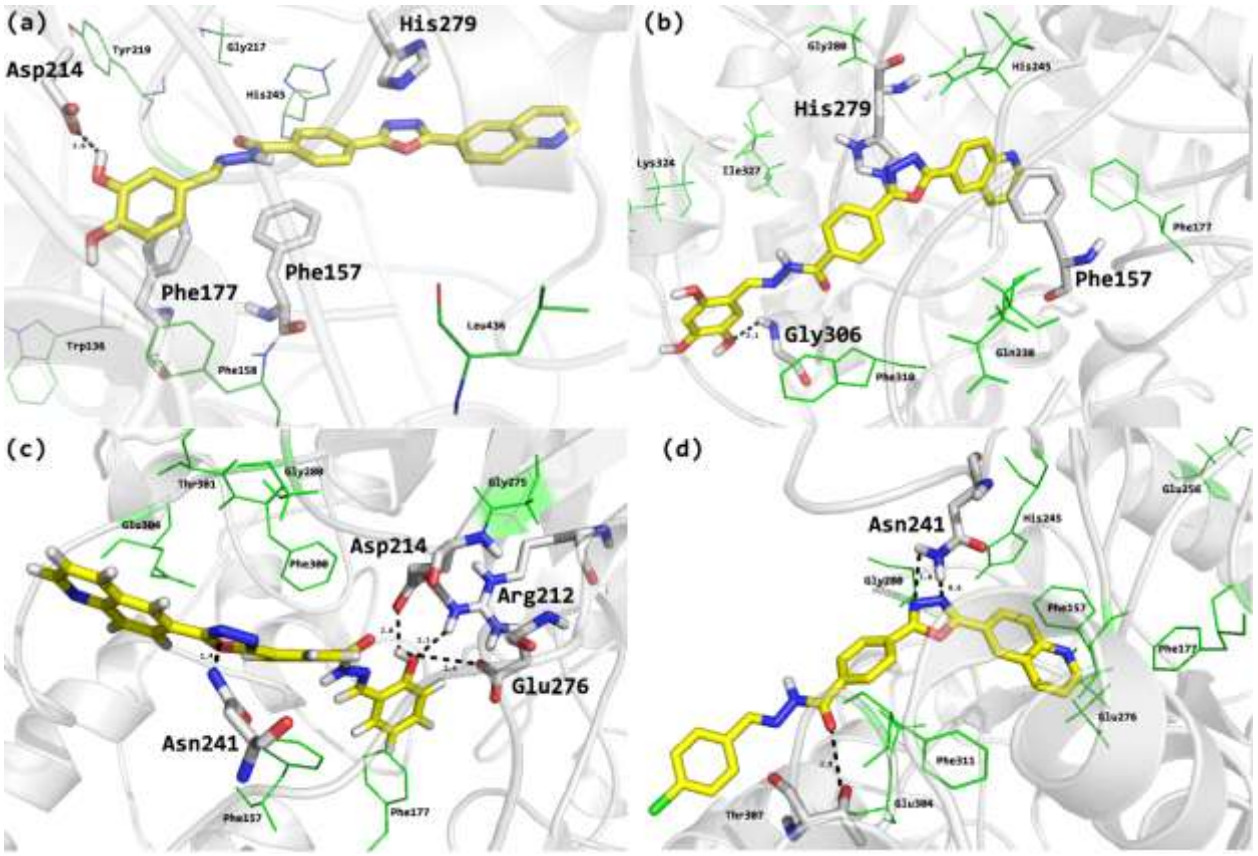


Figure 1: The binding interactions of compounds **24 (a), 27(b), 20(c) and 11(d)**.

In case of least active compounds **09, 17, 19, 28** and **30** poor interactions were observed against active site residues of the enzyme. For example in case of compound **09**, single hydrogen bond between carbonyl oxygen of the compound and active site residue Arg-312 was observed. Furthermore several hydrophobic interactions were also observed with active site residues Phe-310, Pro-309 and Phe-311 etc (**Figure 2a**). The poor interactions of these compounds with the active site resides might be one of the reasons for showing lower activities in the series. The inactive compounds **12** and **13** in the series were showed inactive behavior regarding interactions with the active site residues (**Figure 2b)**. The inactivity of these compounds may be due to the absence of polar moiety in the compounds.

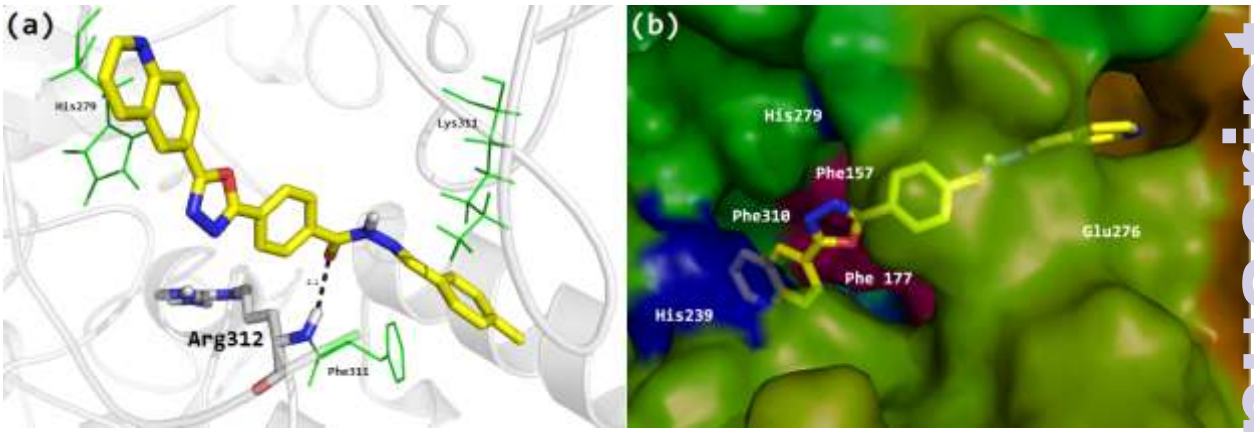


Figure 2. The binding conformation of least active compounds **09 (a)** and inactive compound **12 (b)** in the active of enzyme

4. Experimental

4.1. α-Glucosidase Inhibitory Assay

The α-glucosidase inhibition activity was performed with slight modifications as given by Fazal *et al* [34] Total volume of 100 μL reaction mixture contained, 70 μL 50 mM phosphate buffer pH 6.8, 10 μL (0.5 mM in methanol) test compound, followed by the addition of 10 μL (0.057 units, Sigma Inc.) enzyme solution in the buffer. The contents were mixed, pre-incubated for 10 min at 37 °C and pre-read at 400 nm. The reaction was initiated by the addition of 10 μL of 0.5 mM substrate (*p*-nitrophenyl glucopyranoside, Sigma Inc.). After 30 min of incubation at 37 °C, the absorbance of *p*-nitrophenol was measured at 400 nm using the Synergy HT 96-well plate reader, BioTek, USA. Acarbose was used as positive control. All experiments were carried out in triplicates (mean ± SEM, n = 3). Percent inhibition was calculated by the following equation:

Inhibition (%) = (Abs of Control-Abs of Test/Abs of Control)×100

Active compound solutions were suitably diluted and their inhibition studies were determined. Data obtained was used for the determination of IC_{50} values (concentration at which there is 50 % enzyme inhibition) using EZ-Fit Enzyme Kinetics Software (Perrella Scientific Inc. Amherst, USA).

4.2. (*E*)-methyl-4-((2-(quinoline-6-carbonyl)hydrazono)methyl)benzoate

(*E*)-Methyl-4-((2-(quinoline-6-carbonyl)hydrazono)methyl)benzoate (**3**) was synthesized by treating quinoline-6-carbohydrazide (**1**) (50 mmol) with methyl 4-formylbenzoate (**2**) (50 mmol) and catalytic amount of acetic in methanol. The reaction mixture was refluxed for 3 hours. The solvent was evaporated and crude product was recrystallized in methanol (Yield: 15.32 g, 92%). ^{1}H NMR (500 MHz, DMSO-d_6):δ12.27 (s, 1H, NH),9.03 (d, 1H, J = 4.0 Hz), 8.63 (s, 1H, CH=N-Ar) 8.57 (d, 1H, J =

7.0 Hz), 8.54 (s, 1H), 8.26 (d, 1H, *J* = 8.5 Hz), 8.17 (d, 2H, *J* = 9.0 Hz), 8.07 (d, 1H, *J* = 7.5 Hz), 7.93 (d, 2H, *J* = 8.0 Hz), 7.68 (dd, 1H, *J* = 4.5, 6.0 Hz), 3.89 (s, 3H, O-CH_3); ^{13}C NMR (125 MHz, DMSO-d_6):δ 165.8, 163.1, 152.1, 147.0, 146.7, 138.0, 137.6, 134.2, 132.3, 130.2, 129.9, 129.9, 129.5, 129.0, 129.0, 128.9, 127.6, 122.1, 51.4; Anal. Calcd for $C_{19}H_{15}N_3O_3$, C, 68.46; H, 4.54; N, 12.61; Found C, 68.47; H, 4.56; N, 12.59; EI MS *m/z* 333.11.

4.3. Methyl-4-(5-(quinolin-6-yl)-1,3,4-oxadiazol-2-yl)benzoate

The procedure for the oxidative cyclization was used as reported [35].Yield: 5.80 g, (85%); ^{1}H NMR (500 MHz, DMSO-d_6):δ 8.93 (d, 1H, *J* = 4.0 Hz), 8.47 (d, 1H, *J* = 7.0 Hz), 8.44 (s, 1H), 8.16 (d, 1H, *J* = 8.5 Hz), 8.17 (d, 2H, *J* = 9.0 Hz), 7.91 (d, 1H, *J* = 7.5 Hz), 7.82 (d, 2H, *J* = 8.0 Hz), 7.60 (dd, 1H, *J* = 4.5, 6.0 Hz), 3.80 (s, 3H, O-CH_3); ^{13}C NMR (125 MHz, DMSO-d_6):δ 165.8, 163.1, 152.1, 147.0, 146.7, 138.0, 137.6, 134.2, 132.3, 130.2, 129.9, 129.9, 129.5, 129.0, 129.0, 128.9, 127.6, 122.1, 51.4, ^{13}C NMR (125 MHz, DMSO-d_6):δ 165.8, 164.4, 164.4, 149.8, 148.3, 136.3, 134.2, 133.6, 130.2, 130.0, 129.3, 128.2, 127.3, 127.3, 127.0, 127.0, 127.1, 121.3, 51.4; Anal. Calcd for $C_{19}H_{13}N_3O_3$, C, 68.88; H, 3.95; N, 12.68; Found C, 68.87; H, 3.96; N, 12.69; EI MS *m/z* 331.

4.4. 4-(5-(Quinolin-6-yl)-1,3,4-oxadiazol-2-yl)benzohydrazide (5)

4-(5-(quinolin-6-yl)-1,3,4-oxadiazol-2-yl)benzohydrazide(**5**) was synthesized by adding (3.31 g, 10 mmol) in the mixture of (2mL hydrazine hydrate and 10mL MeOH) and refluxed for 6 hours. The excess hydrazine hydrate and solvent was evaporated and got pure product (**1**) (Yield: 2.88 g, 87%). M.p. above 250 $^{\circ}$C; ^{1}H NMR (500 MHz, DMSO-d_6):10.01 (s, 1H, NH), 9.06 (dd, 1H, *J* = 3.0, 2.0 Hz), 8.91 (d, 1H, 1H, *J* = 2.0 Hz) 8.64 (d, 1H, *J* = 7.5 Hz), 8.48(dd, 1H, *J* = 7.0, 2.0 Hz), 8.29 (d, 1H, *J* = 8.0 Hz), 8.26 (d, 2H, *J* = 9.0 Hz), 8.10 (d, 2H, *J* = 8.0 Hz), 7.71 (dd, 1H, *J* = 4.5, 6.0 Hz), 4.59 (s, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6):δ 1167.1, 164.4, 164.4, 149.8, 148.4, 136.3, 134.2, 133.6, 132.0, 130.1, 130.1, 129.4, 129.3, 128.3, 127.5, 127.5, 127.1, 121.4;Anal. Calcd for $C_{18}H_{13}N_5O_2$, C, 65.25; H, 3.95; N, 21.14; Found C, 65.26; H, 3.96; N, 21.15; EI MS *m/z* 331.

4.5. 4-(5-(quinolin-6-yl)-1,3,4-oxadiazol-2-yl)benzohydrazones 6-30

4-(5-(quinolin-6-yl)-1,3,4-oxadiazol-2-yl)benzohydrazide (**5**) was synthesized by adding (0.620g, 2 mmol) in the mixture of (2mL hydrazine hydrate and 10mL MeOH) and refluxed for 6 hours. The excess hydrazine hydrate and solvent was evaporated and got pure product (**1**) (Yield: 0.58 g, 94%)..

4.6. (*E*)-*N'*-(2-Methylbenzylidene)-4-(5-(quinolin-6-yl)-1,3,4-oxadiazol-2-yl)benzohydrazide (6)

Yield: 0.41 g (94%); Yellow solid, M.p. 267-269°C; ^{1}H NMR (500 MHz, DMSO-d_6): δ12.10 (s, 1H, NH), 9.06 (d, 1H, *J*= 4.0 Hz), 8.91 (s, 1H), 8.80 (s, 1H, CH=N-Ar), 8.65 (d, 1H, *J*= 8.5 Hz), 8.49 (d, 1H, *J*= 8.0 Hz), 8.37 (d, 2H, *J* = 8.5 Hz), 8.25 (d, 1H, *J* = 8.5 Hz), 8.21 (d, 2H, *J* = 8.5 Hz), 7.89 (d, 1H, *J* = 7.5 Hz), 7.67 (dd, 1H, *J* = 4.5, 6.0 Hz), 7.35 (d, 1H, *J* = 8.5 Hz), 7.31-7.29 (m, 2H) 2.67 (s, 3H);^{13}C NMR (125 MHz, DMSO-d_6):δ 168.5, 165.7, 164.3, 150.0, 145.8, 145.5, 136.7, 136.3, 133.1, 133.1, 132.0, 130.4, 130.2, 128.7, 128.7, 128.2, 127.4, 126.9, 126.9, 126.9, 126.2, 126.0, 125.7, 125.1, 122.1, 20.5; Anal. Calcd for $C_{26}H_{19}N_5O_2$, C = 72.04, H= 4.42, N= 16.16; Found C = 72.03, H= 4.44, N= 16.15; EI MS m/z (% rel. abund.): 433.2

4.7. (E)-N'-(3-methylbenzylidene)-4-(5-(quinolin-6-yl)-1,3,4-oxadiazol-2-yl)benzohydrazide (7)

Yield: 0.34 g (79%); White solid, M.p. 278-280 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ12.11 (s, 1H, NH), 9.07 (d, 1H, *J*= 4.0 Hz), 8.93 (s, 1H), 8.65 (d, 1H, *J*= 8.5 Hz), 8.50 (s, 1H, CH=N-Ar), 8.48 (d, 1H, *J*= 8.0 Hz), 8.37 (d, 2H, *J* = 8.5 Hz), 8.27 (d, 1H, *J* = 8.5 Hz), 8.21 (d, 2H, *J* = 8.5 Hz), 7.89 (dd, 1H, *J* = 7.0, 2.0 Hz), 7.61 (s, 1H), 7.57 (d, 1H, *J* = 6.0 Hz), 7.40 (t, 1H, *J* = 6.0 Hz), 7.30 (d, 1H, *J* = 6.0 Hz), 2.39 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6):δ 168.6, 165.9, 164.6, 150.0, 148.8, 145.1, 137.5, 136.8, 136.7, 133.2, 132.8, 130.4, 129.6, 128.7, 128.4, 128.4, 128.0, 127.4, 126.7, 126.7, 126.4, 126.1, 125.7, 125.1, 123.5, 122.1, 21.5;Anal. Calcd for $C_{26}H_{19}N_5O_2$, C = 72.04, H= 4.42, N= 16.16; Found C = 72.03, H= 4.44, N= 16.15; EI MS m/z (% rel. abund.): 433.3

4.8. (*E*)-*N'*-(4-methylbenzylidene)-4-(5-(quinolin-6-yl)-1,3,4-oxadiazol-2-yl)benzohydrazide (8)

Yield: 0.38 g (87%); White solid, M.p. 273-275°C; ^{1}H NMR (500 MHz, DMSO-d_6): δ12.01 (s, 1H, NH), 9.06 (d, 1H, *J*= 4.0 Hz), 8.92 (s, 1H), 8.65 (d, 1H, *J* = 8.0 Hz), 8.49 (d, 1H, *J* = 2.0 Hz), 8.47 (s, 1H, CH=N-Ar), 8.36 (d, 2H, *J* = 8.0 Hz), 8.27 (d, 1H, *J* = 9.0 Hz), 8.19 (d, 2H, *J* = 8.0 Hz), 7.71 (dd, 1H, *J* = 4.0, 4.0 Hz), 7.67 (d, 2H, *J* = 8.0 Hz), 7.31 (d, 2H, *J* = 8.0 Hz), 2.39 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6):δ 168.7, 165.3, 164.8, 150.1, 149.7, 145.5, 138.2, 136.3, 133.7, 132.1, 131.5, 130.5, 129.6, 129.6, 128.7, 128.7, 127.4, 127.4, 127.3, 125.9, 125.9, 126.4, 125.9, 125.1, 122.1, 21.13;Anal. Calcd for $C_{26}H_{19}N_5O_2$, C = 72.04, H= 4.42, N= 16.16; Found C = 72.03, H= 4.44, N= 16.15; EI MS m/z (% rel. abund.): 433.5

4.9. (*E*)-*N'*-(3-chlorobenzylidene)-4-(5-(quinolin-6-yl)-1,3,4-oxadiazol-2-yl)benzohydrazide (9)

Yield: 0.38 g (84%); White solid, M.p. 281-282°C;^{1}H NMR (500 MHz, DMSO-d_6): δ12.10 (s, 1H NH), 9.06 (d, 1H, *J*= 4.0 Hz), 8.91 (s, 1H), 8.80 (s, 1H, CH=N-Ar), 8.65 (d, 1H, *J*= 8.5 Hz), 8.49 (d, 1H, *J*= 8.0 Hz), 8.37 (d, 2H, *J* = 8.5 Hz), 8.25 (d, 1H, *J* = 8.5 Hz), 8.21 (d, 2H, *J* = 8.5 Hz), 7.89 (d, 1H, *J* = 7.5 Hz), 7.67 (dd, 1H, *J*= 4.5, 6.0 Hz), 7.35 (d, 1H, *J*= 8.5 Hz), 7.31-7.29 (m, 2H) 2.67 (s

3H); ^{13}C NMR (125 MHz, DMSO-d_6):δ 168.3, 165.7, 164.1, 150.8, 148.4, 145.1, 136.4, 135.4, 134.9, 133.1, 132.5, 130.8, 130.4, 128.5, 128.5, 127.9, 127.2, 126.4, 126.4, 126.0, 125.7, 125.3, 122.1; Anal.Calcd for $C_{25}H_{16}ClN_5O_2$, C = 66.16, H = 3.55, N = 15.43; Found C = 66.17, H = 3.53, N = 15.44, EI MS m/z (% rel. abund.): 453.2

4.10. (*E*)-*N'*-(2-chlorobenzylidene)-4-(5-(quinolin-6-yl)-1,3,4-oxadiazol-2-yl)benzohydrazide (10)

Yield: 0.35 g (78%); White solid, M.p. 279-281°C; ^{1}H NMR (500 MHz, DMSO-d_6): δ12.12 (s, 1H, NH), 9.06 (d, 1H, *J* = 4.0 Hz), 8.92 (s, 1H), 8.65 (d, 1H, *J* = 8.5 Hz), 8.50 (dd, 1H, *J* = 7.0, 2.0 Hz), 8.37 (d, 2H, *J* = 8.5 Hz), 8.30 (s, 1H, CH=N-Ar), 8.27 (d, 1H, *J* = 8.5 Hz), 8.23 (d, 2H, *J* = 8.5 Hz), 8.09 (d, 1H, *J* = 6.5 Hz), 7.71 (dd, 1H, *J* = 4.5, 4.0 Hz), 7.57 (d, 1H, *J*= 6.5 Hz), 7.48-7.46 (m, 2H) ^{13}C NMR (125 MHz, DMSO-d_6):δ 169.2, 165.7, 164.3, 150.9, 149.7, 145.3, 136.7, 133.4, 132.7, 132.9, 131.5, 130.7, 130.0, 128.3, 128.2, 128.2, 127.8, 127.5, 127.1, 126.6, 126.6, 126.0, 124.9, 124.2, 122.6;Anal. Calcd for $C_{25}H_{16}ClN_5O_2$, C = 66.16, H = 3.55, N = 15.43; Found C = 66.17, H = 3.53, N = 15.44; EI MS m/z (% rel. abund.): 453.5

4.11. (*E*)-*N'*-(4-chlorobenzylidene)-4-(5-(quinolin-6-yl)-1,3,4-oxadiazol-2-yl)benzohydrazide (11)

Yield: 0.34 g (74%); White solid, M.p. 282-284°C; ^{1}H NMR (500 MHz, DMSO-d_6): δ12.16 (s, 1H NH), 9.06 (dd, 1H, *J* = 3.0, 2.0 Hz), 8.91 (d, 1H, *J* = 2.0), 8.65 (d, 1H, *J* = 7.0 Hz), 8.50 (s, 1H, CH=N-Ar), 8.49 (dd, 1H, *J* = 7.0, 2.0 Hz), 8.37 (d, 2H, *J* = 8.5 Hz), 8.27 (d, 1H, *J* = 9.0 Hz), 8.20 (d, 2H, *J* = 8.5 Hz), 7.81 (d, 2H, *J* = 8.0 Hz), 7.72 (dd, 1H, *J* = 4.5, 4.0 Hz), 7.56 (d, 2H, *J* = 8.5 Hz); ^{13}C NMR (125 MHz, DMSO-d_6):δ 169.3, 167.3, 165.8, 151.9, 150.5, 144.8, 137.4, 135.3, 134.2, 133.1, 132.0, 130.2, 129.7, 129.7, 129.0, 129.0, 128.4, 128.4, 127.4, 126.5, 126.5, 126.3, 125.7, 125.1, 122.4; Anal. Calcd for $C_{25}H_{16}ClN_5O_2$, C = 66.16, H = 3.55, N = 15.43; Found C = 66.17, H = 3.53, N = 15.44; EI MS m/z (% rel. abund.): 453.1

4.12. (*E*)-*N'*-(pyridin-4-ylmethylene)-4-(5-(quinolin-6-yl)-1,3,4-oxadiazol-2-yl)benzohydrazide (12)

Yield: 0.34 g (82%); Yellow solid, M.p. 287-289 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ11.60 (s, 1H, NH), 9.06 (d, 1H, *J* = 4.0 Hz), 8.91(s, 1H), 8.68 (d, 2H, *J* = 4.0 Hz), 8.64 (d, 1H, *J* = 8.0 Hz), 8.49 (d, 1H, *J* = 2.0 Hz), 4.49 (s, 1H, CH=N-Ar), 8.37 (d, 2H, *J* = 8.5 Hz), 8.27 (d, 1H, *J* = 8.5 Hz), 8.21 (d, 2H, *J* = 7.5 Hz), 7.72-7.69 (m, 3H), ^{13}C NMR (125 MHz, DMSO-d_6):δ 168.8, 165.6, 164.5, 150.0 150.0, 149.1, 145.3, 140.4, 136.2, 133.6, 132.2, 130.2, 128.9, 128.9, 127.6, 126.9, 126.9, 126.0, 125.7, 125.2, 122.4, 122.4, 121.2; Anal. Calcd for $C_{24}H_{16}N_6O_2$, C = 68.56, H = 3.84, N = 19.99; Found C = 68.58, H = 3.83, N = 20.01 EI MS m/z (% rel. abund.): 420.2

4.13. (E)-*N'*-(pyridin-3-ylmethylene)-4-(5-(quinolin-6-yl)-1,3,4-oxadiazol-2-yl)benzohydrazide (13)

Yield: 0.37 g (89%); White solid, M.p. 278-280°C; ^{1}H NMR (500 MHz, DMSO-d_6): δ12.25 (s, 1H, NH), 9.06 (dd, 1H, *J* = 3.0, 2.0 Hz), 8.91 (d, 2H, *J* = 2.0), 8.64 (d, 2H, *J* = 7.0 Hz), 8.56 (s, 1H, CH=N-Ar), 8.49 (dd, 1H, *J* = 7.0, 2.0 Hz), 8.37 (d, 2H, *J* = 8.5 Hz), 8.27 (d, 1H, *J* = 8.5 Hz), 8.21 (d, 3H, *J* = 8.5 Hz), 7.71 (dd, 1H, *J* = 4.5, 4.0 Hz), 7.53 (dd, 1H, *J* = 5.0, 5.5 Hz); ^{13}C NMR (125 MHz, DMSO-d_6):δ 168.3, 165.3, 164.1, 154.9, 150.2, 148.2, 146.3, 145.7, 137.5, 136.6, 133.2, 131.7, 130.2, 128.6, 128.6, 127.6, 126.7, 126.7, 126.30, 125.6, 125.3, 123.2, 122.5, 119.2; Anal. Calcd for $C_{24}H_{16}N_6O_2$, C = 68.56, H = 3.84, N = 19.99; Found C = 68.57, H = 3.85, N = 19.98 EI MS m/z (% rel. abund.): 420.1

4.14. (*E*)-*N'*-(pyridin-2-ylmethylene)-4-(5-(quinolin-6-yl)-1,3,4-oxadiazol-2-yl)benzohydrazide (14)

Yield: 0.35 g (83%); White solid, M.p. 287-289°C; ^{1}H NMR (500 MHz, DMSO-d_6): δ12.27 (s, 1H, NH), 9.06 (dd, 1H, *J* = 3.0, 2.0 Hz), 8.91 (d, 1H, *J* = 2.0), 8.65 (d, 1H, *J* = 7.5 Hz), 8.54 (s, 1H, CH=N-Ar), 8.49 (dd, 1H, *J* = 7.0, 2.0 Hz), 8.38 (d, 2H, *J* = 8.0 Hz), 8.27 (d, 1H, *J* = 9.0 Hz), 8.22 (d, 2H, *J* = 8.0 Hz), 8.04 (d, 1H, *J* = 8.0 Hz), 7.94 (t, 1H, *J* = 7.0 Hz), 7.71 (dd, 1H, *J* = 4.5, 4.0 Hz), 7.94 (t, 1H, *J* = 6.5 Hz); ^{13}C NMR (125 MHz, DMSO-d_6):δ 169.7, 164.7, 163.5, 154.2, 150.8, 148.3, 146.6, 145.5, 137.6, 136.4, 133.1, 132.0, 130.7, 128.4, 128.4, 127.6, 126.8, 126.8, 126.2, 125.7, 125.1, 123.7, 122.5, 119.2 (s).; Anal. Calcd for $C_{24}H_{16}N_6O_2$, C = 68.56, H = 3.84, N = 19.99; Found C = 68.58, H = 3.83, N = 20.01 EI MS m/z (% rel. abund.): 420.3

4.15. (*E*)-*N'*-(2-hydroxy-5-methoxybenzylidene)-4-(5-(quinolin-6-yl)-1,3,4-oxadiazol-2-yl)benzohydrazide (15)

Yield: 0.42 g (91%); Light yellow solid, M.p. 286-288°C;^{1}H NMR (500 MHz, DMSO-d_6): δ10.64 (s, 2H, NH, OH), 9.06 (d, 1H, *J*= 4.0 Hz), 8.92 (s, 1H), 8.70 (s, 1H, CH=N-Ar), 8.65 (d, 1H, *J*= 8.0 Hz), 8.50 (dd, 1H, *J* = 7.0, 2.0 Hz), 8.37 (d, 2H, *J* = 8.5 Hz), 8.27 (d, 1H, *J* = 9.0 Hz), 8.21 (d, 2H, *J* = 8.5 Hz), 7.71 (dd, 1H, *J* = 4.5, 4.0 Hz), 7.19 (d, 1H, *J* = 3.0 Hz), 6.96 (dd, 1H, *J* = 6.0, 3.0 Hz), 6.90 (d, 1H, *J* = 9.0 Hz), 3.76 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6):δ 168.4, 165.8, 164.1, 154.6, 152.4, 150.9, 149.62, 145.53, 136.47, 133.41, 132.09, 130.02, 128.7, 128.7, 127.44, 126.90, 126.9, 126.10 125.97, 125.13, 122.31, 121.70, 116.58, 116.33, 112.80, 56.03; Anal. Calcd for $C_{26}H_{19}N_5O_4$, C = 67.09, H = 4.11, N, 15.05; Found C = 67.09, H = 4.11, N = 15.05; EI MS m/z (% rel. abund.): 465.4

4.16. (*E*)-*N'*-(2-hydroxy-4-methoxybenzylidene)-4-(5-(quinolin-6-yl)-1,3,4-oxadiazol-2-yl)benzohydrazide (16)

Yield: 0.35 g (76%); White solid, M.p. 272-274°C; ^{1}H NMR (500 MHz, DMSO-d_6): δ11.64 (s, 2H, NH, OH), 9.06 (dd, 1H, *J* = 3.0, 2.0 Hz), 8.91 (d, 1H, *J* = 3.0), 8.64 (d, 1H, *J* = 8.0 Hz), 8.60 (s, 1H, CH=N-Ar), 8.49 (dd, 1H, *J* = 6.5, 2.0 Hz), 8.36 (d, 2H, *J* = 8.5 Hz), 8.27 (d, 1H, *J* = 8.5 Hz), 8.20 (d, 2H, *J* = 8.5 Hz), 7.71 (dd, 1H, *J* = 4.5, 4.0 Hz), 7.48 (d, 1H, *J* = 8.5 Hz), 6.55 (dd, 1H, *J* = 6.0, 2.0 Hz), 6.90 (d, 1H, *J* = 2.0 Hz), 3.79 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6):δ 168.3, 165.4, 164.3, 162.1, 161.3, 151.5, 150.1, 145.6, 136.5, 133.5, 132.2, 130.9, 130.2, 128.5, 128.5, 127.6, 126.8, 126.8, 126.3, 125.8, 125.3, 122.5, 113.6, 107.4, 102.2, 56.2;Anal. Calcd for $C_{26}H_{19}N_5O_4$, C = 67.09, H = 4.11, N 15.05; Found C = 67.09, H = 4.11, N = 15.05; EI MS m/z (% rel. abund.): 465.3

4.17. (*E*)-*N'*-(3-hydroxy-4-methoxybenzylidene)-4-(5-(quinolin-6-yl)-1,3,4-oxadiazol-2-yl)benzohydrazide (17)

Yield: 0.39 g (84%); Light yellow solid, M.p. 275-277°C; ^{1}H NMR (500 MHz, DMSO-d_6): δ11.92 (s, 1H, NH), 9.29 (s, 1H, OH), 9.06 (dd, 1H, *J*= 3.0, 2.0 Hz), 8.91 (d, 1H, *J*= 2.0), 8.65 (d, 1H, *J*= 8.5 Hz), 8.49 (dd, 1H, *J*= 7.0, 2.0 Hz), 8.35 (s, 1H, CH=N-Ar), 8.34 (d, 2H, *J*= 8.0 Hz), 8.27 (d, 1H, *J*= 9.0 Hz), 8.20 (d, 2H, *J*= 8.0 Hz), 7.71 (dd, 1H, *J*= 4.5, 4.0 Hz), 7.30 (s, 1H), 7.11 (d, 1H, *J*= 9.0 Hz), 7.01 (d, 1H, *J*= 9.0 Hz), ^{13}C NMR (125 MHz, DMSO-d_6): δ 168.4, 165.1, 164.3, 150.2, 149.1, 148.8, 146.5, 145.5, 136.7, 133.1, 132.0, 130.0, 129.7, 128.3, 128.3, 127.4, 126.7, 126.7, 126.1, 125.6, 125.1, 122.1, 120.3, 115.74, 115.2, 56.4;Anal. Calcd for $C_{26}H_{19}N_5O_4$, C = 67.09, H = 4.11, N, 15.05; Found C = 67.09, H = 4.11, N = 15.05; EI MS m/z (% rel. abund.): 465.3

4.18. (*E*)-*N'*-(3-hydroxybenzylidene)-4-(5-(quinolin-6-yl)-1,3,4-oxadiazol-2-yl)benzohydrazide (18)

Yield: 0.39 g (90%); Yellow solid, M.p. above 296-298°C; ^{1}H NMR (500 MHz, DMSO-d_6): δ12.02 (s 1H, NH), 9.68 (s, 1H, OH), 9.06 (dd, 1H, *J* = 3.0, 2.0 Hz), 8.91 (d, 1H, *J* = 2.0), 8.65 (d, 1H, *J* = 8.0 Hz), 8.49 (dd, 1H, *J* = 7.0, 2.0 Hz), 8.42 (s, 1H, CH=N-Ar), 8.36 (d, 2H, *J* = 8.5 Hz), 8.27 (d, 1H, *J* = 9.0 Hz), 8.20 (d, 2H, *J* = 8.5 Hz), 7.71 (dd, 1H, *J* = 4.5, 4.0 Hz), 7.30 (t, 1H, *J* = 8.0 Hz), 7.24 (s, 1H), 7.15 (d, 1H, *J* = 8.0 Hz), 6.87 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (125 MHz, DMSO-d_6):$\delta\delta$ 168.5, 164.1, 163.8, 156.7, 150.9, 148.6, 145.5, 138.1, 137.7, 135.4, 132.0, 130.9, 130.0, 128.8, 128.8, 127.2, 126.7, 126.7, 126.2, 125.7, 125.1, 122.1, 120.3, 119.6, 114.3 (s).; Anal. Calcd for $C_{25}H_{17}N_5O_3$, C = 68.96, H = 3.94; N = 16.08; Found C = 68.96, H = 3.94; N = 16.08; EI MS m/z (% rel. abund.): 435.4

4.19. (*E*)-*N'*-(4-hydroxybenzylidene)-4-(5-(quinolin-6-yl)-1,3,4-oxadiazol-2-yl)benzohydrazide (19)

Yield: 0.37 g (85%); Light yellow solid, M.p. 286-288°C; ^{1}H NMR (500 MHz, DMSO-d_6): δ11.89 (s, 2H, NH, OH), 9.06 (dd, 1H, *J*= 3.0, 2.0 Hz), 8.91 (d, 1H, *J*= 2.0), 8.65 (d, 1H, *J*= 8.5 Hz), 8.49 (dd, 1H, *J*= 7.0, 2.0 Hz), 8.39 (s, 1H, CH=N-Ar), 8.35 (d, 2H, *J*= 8.5 Hz), 8.27 (d, 1H, *J*= 8.5 Hz), 8.18 (d, 2H, *J*= 8.5 Hz), 7.71 (dd, 1H, *J*= 4.5, 4.0 Hz), 7.61 (d, 2H, *J*= 8.5 Hz), 6.88 (d, 2H, *J*= 8.5 Hz), ^{13}C NMR (125 MHz, DMSO-d_6):δ 168.2, 165.7, 164.1, 158.3, 150.9, 149.3, 145.3, 136.6, 133.2, 132.7, 130.2, 129.7, 129.7, 128.5, 128.5, 127.7, 126.9, 126.7, 126.7, 126.2, 125.6, 125.1, 122.3, 115.2, 115.2;Anal. Calcd for $C_{25}H_{17}N_5O_3$, C = 68.96, H = 3.94; N = 16.08; Found C = 68.96, H = 3.94; N = 16.08; EI MS m/z (% rel. abund.): 435.3

4.20. (*E*)-*N'*-(2-hydroxybenzylidene)-4-(5-(quinolin-6-yl)-1,3,4-oxadiazol-2-yl)benzohydrazide (20)

Yield: 0.37 g (84%); White solid, M.p. 295-297°C; ^{1}H NMR (500 MHz, DMSO-d_6): δ12.30 (s, 1H, NH), 11.25 (s, 1H, OH), 9.06 (dd, 1H, *J* = 3.0, 2.0 Hz), 8.92 (d, 1H, *J* = 2.0), 8.70 (s, 1H, CH=N-Ar), 8.65 (d, 1H, *J* = 7.5 Hz), 8.50 (dd, 1H, *J* = 7.0, 2.0 Hz), 8.38 (d, 2H, *J* = 8.5 Hz), 8.27 (d, 1H, *J* = 8.5 Hz), 8.22 (d, 2H, *J* = 8.5 Hz), 7.71 (dd, 1H, *J* = 4.5, 4.0 Hz), 7.60 (d, 1H, *J* = 7.5 Hz), 7.34 (t, 1H, *J* = 7.0 Hz), 6.96-6.93 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6):δ168.3, 165.1, 164.7, 158.5, 151.2, 150.7, 145.4, 136.8, 133.1,132.9, 130.0, 129.5, 128.5, 128.3, 128.3, 127.1, 126.8, 126.8, 126.2, 125.8, 125.2, 122.1, 121.2, 120.5, 117.2 (s).; Anal. Calcd for $C_{25}H_{17}N_5O_3$, C = 68.96, H = 3.94; N = 16.08; Found C = 68.96, H = 3.94; N = 16.08; EI MS m/z (% rel. abund.): 435.5

4.21. (*E*)-*N'*-(2,4-Dihydroxybenzylidene)-4-(5-(quinolin-6-yl)-1,3,4-oxadiazol-2-yl)benzohydrazide (21)

Yield: 0.42 g (94%); Yellow solid, M.p 284-286°C; ^{1}H NMR (500 MHz, DMSO-d_6): δ12.10 (s, 1H NH), 11.40 (s, 1H, OH), 10.01 (s, 1H, OH), 9.03 (d, 1H, *J* = 4.0 Hz), 8.85 (s, 1H), 8.60 (d, 1H, *J* = 8.0 Hz), 8.59 (s, 1H, CH=N-Ar) 8.44 (dd, 1H, *J* = 7.5, 2.0 Hz), 8.32 (d, 2H, *J* = 8.0 Hz),8.23 (d, 1H, *J* = 8.5 Hz), 8.18 (d, 2H, *J* = 8.0 Hz), 7.67 (dd, 1H, *J* = 4.5, 6.0 Hz), 7.35 (d, 1H, *J*= 8.5 Hz), 6.39 (dd, 1H, *J*= 6.5, 2.0 Hz), 6.34 (d, 1H, *J*= 2.0 Hz);^{13}C NMR (125 MHz, DMSO-d_6):δ 168.4, 165.3, 164.6, 160.7, 160.1, 151.3, 150.5, 145.0, 136.7, 133.1, 132.6, 130.7, 130.0, 128.7, 128.7, 127.3, 126.7, 1267, 126.2. 125.1, 125.5, 122.4, 113.1, 109.2, 103.8; Anal. Calcd for $C_{25}H_{17}N_5O_4$, C = 66.51, H = 3.80, N = 15.51, Found C = 66.52, H = 3.78, N = 15.50; EI MS m/z (% rel. abund.): 451.5

4.22. (*E*)-*N'*-(3,5-dihydroxybenzylidene)-4-(5-(quinolin-6-yl)-1,3,4-oxadiazol-2-yl)benzohydrazide (22)

Yield: 0.42 g (92%); White solid, M.p. 291-293 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ11.95 (s, 1H, NH), 9.50 (s, 2H, OH), 9.06 (d, 1H, J = 4.0 Hz), 8.91 (d, 1H, J = 2.0), 8.64 (d, 1H, J = 8.0 Hz), 8.49 (dd, 1H, J = 7.0, 2.0 Hz), 8.36 (d, 2H, J = 8.0 Hz), 8.30(s, 1H, CH=N-Ar), 8.27 (d, 1H, J = 8.5 Hz), 8.19 (d, 2H, J = 8.5 Hz), 7.71 (dd, 1H, J = 4.5, 4.0 Hz), 6.65 (d, 1H, J = 2.0 Hz), 6.28 (s, 1H, Hz), ^{13}C NMR (125 MHz, DMSO-d_6):δ 168.7, 165.1, 164.7, 158.5, 158.5, 150.9, 147.2, 145.5, 138.7, 136.4, 133.4, 132.1, 130.8, 128.6, 128.6, 127.4, 126.7, 126.7, 126.4, 125.6, 125.3, 122.1, 107.2, 107.2, 104.2 (s).Anal.Calcd for $C_{25}H_{17}N_5O_4$, C = 66.51, H = 3.80, N = 15.51, Found C = 66.52, H = 3.78, N = 15.50; EI MS m/z (% rel. abund.): 451.6

4.23. (*E*)-*N'*-(2,3-dihydroxybenzylidene)-4-(5-(quinolin-6-yl)-1,3,4-oxadiazol-2-yl)benzohydrazide (23)

Yield: 0.41 g (91%); Light yellow solid, M.p. 302-303°C; ^{1}H NMR (500 MHz, DMSO-d_6): δ12.35 (s, 1H, NH), 11.03 (s, 1H, OH), 9.29 (s, 1H, OH), 9.06 (dd, 1H, J = 3.0, 2.0 Hz), 8.91 (d, 1H, J = 2.0), 8.67 (s, 1H, CH=N-Ar), 8.65 (d, 1H, J = 8.0 Hz), 8.50 (dd, 1H, J = 7.0, 2.0 Hz), 8.38 (d, 2H, J = 7.5 Hz), 8.27 (d, 1H, J = 9.0 Hz), 8.22 (d, 2H, J = 8.5 Hz), 7.71 (dd, 1H, J = 4.5, 4.0 Hz), 7.02 (d, 1H, J = 7.5 Hz), 6.89(d, 1H, J = 7.0 Hz), 6.79 (t, 1H, J = 7.5 Hz), ^{13}C NMR (125 MHz, DMSO-d_6):δ 167.6, 165.3, 164.3, 150.7, 149.2, 146.6, 145.1, 144.7, 136.2, 133.4, 132.9, 130.1, 128.4, 128.4, 127.4, 126.8, 126.8, 126.5, 125.7, 125.1, 122.1, 122.5, 121.3, 119.4, 119.85;Anal. Calcd for $C_{25}H_{17}N_5O_4$, C = 66.51, H = 3.80, N = 15.51, Found C = 66.52, H = 3.78, N = 15.50; EI MS m/z (% rel. abund.): 451.7

4.24. (*E*)-*N'*-(3,4-dihydroxybenzylidene)-4-(5-(quinolin-6-yl)-1,3,4-oxadiazol-2-yl)benzohydrazide (24)

Yield: 0.43 g (95%); Light yellow solid, M.p. 283-285°C; ^{1}H NMR (500 MHz, DMSO-d_6): δ11.95 (s 1H, NH), 9.79 (s, 1H, OH), 9.60 (s, 1H, OH), 9.06 (d, 1H, J = 4.0 Hz), 8.91 (s, 1H), 8.65 (d, 1H, J = 8.0 Hz), 8.49 (d, 1H, J = 8.5 Hz), 8.35 (s, 1H, CH=N-Ar), 8.33 (d, 2H, J = 9.0 Hz), 8.27 (d, 1H, J = 9.0 Hz), 8.18 (d, 2H, J = 8.5 Hz), 7.71 (dd, 1H, J = 4.5, 4.0 Hz), 7.28 (s, 1H), 6.98 (d, 1H, J= 8.0 Hz), 6.82 (d, 1H, J= 8.0 Hz), ^{13}C NMR (125 MHz, DMSO-d_6):δ 168.1, 165.3, 164.3, 150.0, 148.9, 148.3, 145.3, 136.7, 133.4, 132.9, 130.2, 128.6, 128.6, 127.3, 127.4, 126.7, 126.7, 126.3, 125.6, 125.1, 122.4, 121.1, 116.7, 116.7Anal. Calcd for $C_{25}H_{17}N_5O_4$, C = 66.51, H = 3.80, N = 15.51, Found C = 66.52, H = 3.78, N = 15.50; EI MS m/z (% rel. abund.): 451.6

4.25. (*E*)-*N'*-(2,5-dihydroxybenzylidene)-4-(5-(quinolin-6-yl)-1,3,4-oxadiazol-2-yl)benzohydrazide (25)

Yield: 0.42 g (92%); Light orange solid, M.p. 285-287°C; ^{1}H NMR (500 MHz, DMSO-d_6): δ12.20 (s, 1H, NH), 10.33 (s, 1H, OH), 9.06 (dd, 1H, J = 3.0, 2.0 Hz), 9.02 (s, 1H, OH), 8.91 (d, 1H, J = 2.0), 8.64 (s, 1H, CH=N-Ar), 8.63 (d, 1H, J = 7.0 Hz), 8.49 (dd, 1H, J = 7.0, 2.0 Hz), 8.36 (d, 2H, J = 8.5 Hz), 8.26 (d, 1H, J = 8.5 Hz), 8.21 (d, 2H, J = 8.5 Hz), 7.71 (dd, 1H, J = 4.5, 4.0 Hz), 7.03 (d, 1H, J = 2.0 Hz), 6.79-6.74 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6):δ 168.3, 165.7, 164.3, 152.1, 151.3, 150.0, 149.2, 145.6, 136.7, 133.4, 132.9, 130.2, 128.7, 128.7, 127.3, 126.7, 126.7, 126.1, 125.4, 125.1, 122.6, 122.1, 121.2, 118.3, 116.1Anal. Calcd for $C_{25}H_{17}N_5O_4$, C = 66.51, H = 3.80, N = 15.51, Found C = 66.52, H = 3.78, N = 15.50; EI MS m/z (% rel. abund.): 451.3

4.26. (*E*)-4-(5-(quinolin-6-yl)-1,3,4-oxadiazol-2-yl)-*N'*-(2,4,6-trihydroxybenzylidene)benzohydrazide (26)

Yield: 0.34 g (73%); White solid, M.p 305-307°C; ^{1}H NMR (500 MHz, DMSO-d_6): δ12.11 (s, 1H, NH), 11.12 (s, 2H, OH), 9.90 (s, 1H, OH), 9.06 (dd, 1H, J = 2.0, 3.0 Hz), 8.91 (d, 1H, J = 2.0), 8.86 (s, 1H, CH=N-Ar), 8.64 (d, 1H, J = 7.5 Hz), 8.49 (dd, 1H, J = 7.0, 2.0 Hz), 8.36 (d, 2H, J = 8.5 Hz), 8.27 (d, 1H, J = 8.5 Hz), 8.20 (d, 2H, J = 8.5 Hz), 7.71 (dd, 1H, J = 4.5, 4.0 Hz), 5.87 (s, 2H, Hz), ^{13}C NMR (125 MHz, DMSO-d_6):δ 168.5, 165.3, 164.3, 163.6, 161.4, 161.4, 150.7, 145.5, 144.6, 136.1, 133.1, 132.6, 130.2, 128.6, 128.6, 127.4, 126.4, 126.4, 126.2, 125.4, 124.8, 122.6, 106.0, 95.6, 95.6, Anal. Calcd for $C_{25}H_{17}N_5O_5$, C = 64.24, H = 3.67, N = 14.98; Found C = 64.26, H = 3.68, N = 14.97; EI MS m/z (% rel. abund.): 467.

4.27. (*E*)-4-(5-(quinolin-6-yl)-1,3,4-oxadiazol-2-yl)-*N'*-(2,4,5-trihydroxybenzylidene)benzohydrazide (27)

Yield: 0.40 g (85%); Yellow solid, M.p. above 305-307°C; ^{1}H NMR (500 MHz, DMSO-d_6): δ12.01 (s, 1H, NH), 10.55 (s, 1H, OH), 9.56 (s, 2H, OH), 9.06 (dd, 1H, J = 3.0, 2.0 Hz), 9.06 (s, 1H), 8.63 (d, 1H, J = 8.5 Hz), 8.52 (s, 1H, CH=N-Ar), 8.49 (dd, 1H, J = 7.0, 2.0 Hz), 8.35 (d, 2H, J = 8.5 Hz), 8.26 (d, 1H, J = 8.5 Hz), 8.19 (d, 2H, J = 8.5 Hz), 7.71 (dd, 1H, J = 4.5, 4.0 Hz), 6.94 (s, 1H), 6.36 (s, 1H), 7.03 (d, 1H, J = 2.0 Hz), 6.79-6.74 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6):δ 169.5, 164.7, 164.3, 153.8, 150.8, 150.9, 149.2, 145.3, 140.2, 136.7, 133.4, 132.4, 130.2, 128.7 , 128.7, 127. 4, 126.8, 126.8, 126.0, 125.5, 125.1, 122.4, 117.2, 112.1, 102.8 (s); Anal.Calcd for $C_{25}H_{17}N_5O_5$, C = 64.24, H = 3.67, N = 14.98; Found C = 64.26, H = 3.68, N = 14.97; EI MS m/z (% rel. abund.): 467.5

4.28. (*E*)-*N'*-(2-nitrobenzylidene)-4-(5-(quinolin-6-yl)-1,3,4-oxadiazol-2-yl)benzohydrazide (28)

Yield: 0.32 g (68%); White solid, M.p. 294-296°C; ^{1}H NMR (500 MHz, DMSO-d_6): δ12.43 (s, 1H, NH), 9.06 (d, 1H, J = 4.0 Hz), 8.93 (d, 1H, J = 2.0), 8.91 (s, 1H, CH=N-Ar), 8.66 (d, 1H, J = 8.5 Hz), 8.50 (dd, 1H, J = 7.0, 2.0 Hz), 8.38 (d, 2H, J = 8.5 Hz), 8.26 (d, 1H, J = 8.5 Hz), 8.21 (d, 2H, J = 8.5 Hz), 8.18 (d, 1H, J = 8.0 Hz), 8.13 (d, 1H, J = 7.0 Hz), 7.88 (t, 1H, J = 7.0 Hz), 7.74-7.69 (m, 2H);^{13}C NMR (125 MHz, DMSO-d_6):δ164.4, 164.4, 163.1, 149.8, 148.3, 147.7, 143.1, 136.3, 134.8, 134.2, 133.6, 132.7, 131.8, 130.1, 130.1, 130.1, 129.4, 129.3, 128.3, 128.3, 127.5, 127.5, 127.1, 124.1, 121.4; Anal. Calcd for $C_{25}H_{16}N_6O_4$, C = 64.65, H = 3.47, N = 18.10, Found C = 64.66, H = 3.78, N = 18.09; EI MS m/z (% rel. abund.): 464.

4.29. (*E*)-*N'*-(4-nitrobenzylidene)-4-(5-(quinolin-6-yl)-1,3,4-oxadiazol-2-yl)benzohydrazide (29)

Yield: 0.37 g (79%); Light yellow solid, M.p. 287-289°C;^{1}H NMR (500 MHz, DMSO-d_6): δ12.39 (s, 1H, NH), 9.07 (dd, 1H, J = 3.0, 2.0 Hz), 8.93 (d, 1H, J = 2.0 Hz), 8.66 (d, 1H, J = 8.0 Hz), 8.61 (s, 1H, CH=N-Ar), 8.50 (dd, 1H, J = 7.0, 2.0 Hz), 8.39 (d, 2H, J = 8.0 Hz),8.35 (d, 2H, J = 8.5 Hz), 8.26 (d, 1H, J = 8.0 Hz), 8.21 (d, 2H, J = 8.0 Hz), 8.08 (d, 2H, J = 8.0 Hz), 7.88 (t, 1H, J = 7.0 Hz); ^{13}C 164.4, 164.4, 163.2, 150.1, 149.8, 148.3, 146.7, 139.7, 136.2, 134.2, 133.6, 132.7, 130.1, 130.1, 129.4, 129.3, 128.3, 127.5, 127.1, 127.1, 124.1, 124.1, 124.0, 124.0, 121.4; Anal. Calcd for $C_{25}H_{16}N_6O_4$, C = 64.65, H = 3.47, N = 18.10, Found C = 64.67, H = 3.76, N = 18.07; EI MS m/z (% rel. abund.): 464.

4.30. (*E*)-*N'*-(3-nitrobenzylidene)-4-(5-(quinolin-6-yl)-1,3,4-oxadiazol-2-yl)benzohydrazide (30)

Yield: 0.38 g (82%); Yellow solid, M.p. above 285-287°C;^{1}H NMR (500 MHz, DMSO-d_6): δ12.36 (s, 1H, NH), 9.06 (d, 1H, J = 4.0 Hz), 8.93 (s, 1H), 8.66 (d, 1H, J = 8.5 Hz), 8.60 (s, 1H, CH=N-Ar), 8.50 (d, 1H, J = 9.0 Hz), 8.38 (d, 2H, J = 8.5 Hz),), 8.31 (d, 1H, J = 8.0 Hz), 8.26 (d, 1H, J = 9.0 Hz), 8.21 (d, 2H, J = 8.0 Hz), 7.81 (t, 1H, J = 8.0 Hz), 7.72 (dd, 1H, J = 4.0, 4.0 Hz);1) ^{13}C NMR (125 MHz, DMSO-d_6):δ 164.3, 164.3, 163.1, 149.8, 148.4, 148.1, 146.7, 136.3, 134.5, 134.2, 133.6, 132.7, 132.4, 133.4, 130.1, 130.1, 129.6, 129.3, 129.3, 128.2, 127.5, 127.5, 127.1, 126.1, 121.5; Anal. Calcd for $C_{25}H_{16}N_6O_4$, C = 64.65, H = 3.47, N = 18.10, Found C = 64.68, H = 3.77, N = 18.11; EI MS m/z (% rel. abund.): 464.

4.4 Molecular Docking

The crystallographic structure of α-glucosidase enzyme has not been solved yet. However, only few homology models have been reported [36-38] so far. We have built 3D structure of α-glucosidase by comparative homology modeling technique using the same propriety as described [36]. The sequence in fasta format of α-glucosidase was retrieved from UniProt (access code P53341). Template selection

search was performed by means of MOE-Search tools against the PDB-database implemented in MOE 2010.11. The 1.30 Å resolving crystallographic structure of Saccharomyces cerevisiae isomaltase (SCI) (PDB code: 3aj7) [39] with 72.4% was selected as the template for modeling. The 3D structure was built by means of MOE homology modeling tools. The predicted 3D model was subjected to energy minimization up to 0.05 gradients. Before docking simulation, ligands and protein were prepared by means of MOE 2010.11 software. 3D structure of all synthesized compounds was built in MOE of Molecular Builder program. Finally, a database was created in which all the ligands were converted into their particular 3D structures and this database was used as input file MOE-docking. Subsequently, the energy of compounds was minimized up to 0.05 Gradient using MMFF94x force field. Energy minimization of the database was followed by the preparation of protein for docking purposes. Most macromolecular crystal structures contain little or no hydrogen coordinate data due to limited resolution and thus protonation was accomplish prior to docking using Protonate 3D tools implemented in MOE. Protonation was followed by energy minimization up to 0.05 Gradient using Amber99 force field. The database was docked into the active site of protein using the Triangular Matching docking method and 30 conformations of each Ligand protein complex were generated with docking score (S). Each complex was analyzed for interactions and their 3D pose was taken.

4.5. Cytotoxicity assays using 3T3-L1 and CC-1 cell-lines and MTT

In vitro cytotoxicity assays were performed as described by Scholz et al.56, using the 3T3-L1 mouse embryo fibroblast cell line (American Type Culture Collection 'ATCC', Manassas, VA 20108, USA), and CC-1 cells, a rat Wistar hepatocyte cell line (European Collection of Cell Cultures, Salisbury, UK). The CC-1 cells were suspended in Minimum Essential Medium Eagle (MEM) supplemented with 10% FBS, 2 mM glutamine, 1% non-essential amino acids and, 20 mM HEPES. While the 3T3-L1 cells were suspended in Dulbecco's Modified Eagle's Medium (DMEM) formulated with 10% FBS. Using flat bottomed plates, both cell-lines were plated at a concentration of 6 × 104 cells/mL and incubated for 24 h at 37 °C and 5% CO_2 environment. After removal of media, cells were challenged with three different concentrations (1.0, 5.0, and 20 μg/mL) of compounds in triplicates and were then further incubated for 48 h at 37 °C in CO_2 incubator. Following exposure to each compound, cells viability was assessed by using 0.5 mg/mL of MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) for 4 h followed by removal of supernatant and addition of DMSO to solubilize the formazan complex. Plates were read at 540 nm after one minute shaking and readings were processed using MS Excel software. Results were expressed as means ± SD of triplicate readings.

4.6. Conclusion: Current study resulted in the synthesis of new series of quinoline derivatives **6-30** bearing an oxadiazole ring, characterized by EI-MS, ^{1}HNMR and CHN and evaluated for yeast α-glucosidase inhibitory potential. Among the series, twenty three (**23**) analogs showed α-glucosidase inhibitory potential with IC_{50} values ranging between 2.60 to 102.12 μM when compared with the standard acarbose (IC_{50}, 38.25 ± 0.12 μM). Among the series compounds **21**, **9**, **15**, **16**, **22, 26, 23, 24, 17, 19, 10, 11, 20, 25, 28, 30,** and **27** showed potent inhibitory potential many fold better than standard inhibitor acarbose. All other analogs except **12** and **13** also displayed good enzyme inhibition. The binding interactions of these compounds were confirmed through molecular docking. Docking studies revealed that potent inhibitory activities were achieved by the active compounds (**24** and **27**) through formation of hydrogen and arene-arene bonds between quinoline, oxadiazole and methylacetamide with residues of the active site such as Phe-177, Asp-214, His-279, Phe-157 and Gly-306. All the compounds were tested for cytotoxicity but none of them was toxic.

Acknowledgment:

The authors would like to acknowledge Universiti Teknologi MARA for the financial support under the Research Intensive Faculty grant scheme with reference number UiTM 600-RMI/DANA 5/3/RIF (347/2012).

References and notes

1. American Diabetes Association. Diabetes care 2008, 31, S55.
2. D. Edmont, R. Richard, P. Christophe, C. Jacques, Bioorg. Med.Chem. Lett. 10, (2000), 1831.
3. G.I. Bell, Diabetes 40, (1991), 413.
4. J.M. Chehade, D.M.A Arshag, Drugs 60, (2000), 95.
5. K.G.M.M. Alberti, P. Z. Zimmet, Diabetic med. 15, (1998), 535.
6. Y.D. Kim, K.G. Park, Y. S. Lee, Y.Y. Park, D. K. Kim, B. Nedumaran, H. S. Choi, Diabetes 57, (2008), 306.
7. H. Gin, V. Rigalleau, Diabetes Metab. 26, (2000), 265.
8. K. Yasuda, K. Shimowada, M. Uno, H. Odaka, T. Adachi, N. Shihara, Y. Seino, Diabetes Res. Clin. Pr. 59, (2003), 113.
9. A.L. Notkins, J.Biol. Chem. 277, (2002), 43545.
10. R. Musiol, J. Jampilek, V. Buchta, L. Silva, H. Niedbal, B. Podeszwa, J. Polanski, Bioorg. Med. Chem. 14, (2006), 3592.
11. R. Musiol, M. Serda, S. Hensel-Bielowka, J. Polanski, Curr. Med. Chem. 17, (2010), 1960.

12. M. Foley, L. Tilley, Pharmacol. Therapeut. 79, (1998), 55.
13. J.P. Sanchez, M.D. John, E.H. Susan, L.H. Carl, P.H. Marland, B.N. Jeffry, K.T. Ashok, J. Med. Chem. 31, (1988), 983.
14. R.J. Alaimo, F.S. Claude, B.S. James, J. S. Ronald, J.H. Christopher, E.K. Robert, J. Med. Chem. 21, (1978), 298.
15. S. Rossiter, J. Péron, P.J. Whitfield, K. Jones, Med. Chem.Lett. 15, (2005), 4806.
16. Y. Chen, H. Hsien-Ming, C. Lu, K. Li, C. Tzeng, Bioorg. Med. Chem. 12, (2004), 6539.
17. L.D. Via, O. Gia, V. Gasparotto, M.G. Ferlin, Eur. J. Med. Chem. 43, (2008), 429.
18. Z. Xie, K. Chai, H. Piao, K. Kwak, Z. Quan, Bioorg. Med. Chem.Lett. 15, (2005), 4803.
19. A.A. Bekhit, O.A. El-Sayed, E. Aboulmagd, J. Y. Park, Eur. J. Med. Chem. 39, (2004), 249.
20. K. M. Boini, D. Graf, D. Kuhl, D. Häussinger, F. Lang, Eur. J. Physiol. 457, (2009), 955.
21. M. Kidwai, N. Negi, Chem. Mon. 128, (1997), 85.
22. B.R. Baker, R. B. Ray, J. Med. Chem. 15, (1972), 233.
23. N.Maeda,Tamagawa,T.;Niki,I.;Miura,H.;Ozawa,K.;Watanabe,G.;Nonogaki,K.;Uemura,K.;Iguchi, A. Brit. J. Pharmacol. 117, (1996), 372.
24. R. Holmes, K. Macchiano, S.S. Jhangiani, N. R. Agarwal, J. A. Savino, Am. J.Nurs. 87, (1987), 1301.
25. P. E. Cryer, L. Axelrod, A. B. Grossman, S. R. Heller, V.M. Montori, E. R. Seaquist, F. J. Service, J. Clin.Endocr.Metab. 94, (2009), 709.
26. P. H. Bouchard, P. Sai, G. Reach, I. Caubarrere, D. Ganeval, R. Assan, Diabetes 31, (1982), 40.
27. a) M. Taha, N.H. Ismail, M.S. Baharudin, S. Lalani, S. Mehboob, K.M. Khan, S. Siddiqui, F. Rahim, M.I. Choudhary. Med. Chem. Res. 24 (2015) 1310-1324; b) M. Taha, N. H. Ismail, S. Imran, M. Q. B. Rokei, S. M. Saad, K. M. Khan. Inhibitors. Bioorg. Med chem. **2015**, *23*, 4155; c) M. Taha, H. Naz, S. Rasheed, N.H. Ismail, A.A. Rahman, S. Yousuf, and M.I. Choudhary. Molecules 19 (2014) 1286.
28. H. W. Lee, J. Y. Yang, H. S. Lee. J. Korean Soc. Appl. Bio. Chem., 57 (2014) 441.
29. a) M. Taha, N. H. Ismail, W. Jamil, K. M. Khan, U. Salar, S. M. Kashif, F. Rahim, Y. Latif. Med.Chem. Res. 24 (2015) 3166; b) M. Taha, N. H. Ismail, W. Jamil , H. Rashwan, S. M. Kashif, A. A. Sain, M. I. Adenan, E. H.Anouar, M. Ali, F. Rahim, K. M. Khan. Eur J Med Chem. 84 (2014) 731; c) Z.S. Saify, A. Kamil, S. Akhtar, M. Taha, A. Khan, K.M. Khan, S. Jahan, F. Rahim, S. Perveen, M.I.Choudhary. *Med. Chem. Res.,* **2014**, 23, 4447; d) N. K. N. Z., Abdullah, M. Taha, N. Ahmat, A. Wadood, N. H. Ismail, F. Rahim, M. Ali, N. Abdullah, K. M. Khan. Bioorg. Med. Chem. 23 (2015) 3119; e) M. Taha, N. H. Ismail, A. Khan, S. A. A. Shah, A. Anwar, S. A. Halim, M. Q. Fatmi, S. Imran, F. Rahim K. M. Khan. Bioorg. Med Chem Lett. 25

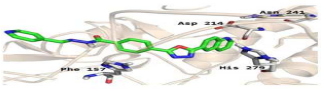
(2015) 3285; f) M. Taha, N. H. Ismail, S. Imran, M. Selvaraj, H. Rashwan, F. U. Farhanah, F. Rahim, K. K. Selvarajane, M. Ali. Bioorg. Chem. 61 (2015) 61, 36.

30. M. Taha, N. H. Ismail, S. Lalani, M.Q. Fatmi, Atia-tul-Wahab, S. Siddiqui, K.M. Khan, S. Imran, M.I. Choudhary. Eur J. Med. Chem. 92 (2015) 387.
31. Khan K. M.; Rahim, F. Wadood, A.; Kosar, N.; Taha, M.; Khan, A.; Fakhri, M. I.; Junaid, M.; Rehman, W.; Khan, M.; Perveen, S.; Abid, O.; Mohammad, B.; Sajid, M.; Choudhary, M. I. *Eur J Med Chem.* 81 (2014), 245.
32. F. Rahim, F. Malik, H. Ullah, A. Wadood, F. Khan, M. T. Javid, M. Taha, W. Rehman, A. U. Rehman, K. M. Khan. *Bioorg. Chem.* **2015**, *60,* 42.
33. S. B. Ferreira, A. C. Sodero, M. F. Cardoso, E. S. Lima, C. R. Kaiser, F. P. Silva, V. F. Jr Ferreira, J. Med. Chem. 53 (2010) 2364.
34. a) F. Rahim, K. Ullah, H. Ullah, A. Wadood, M. Taha, A. U. Rehman, I. uddin, M. Ashraf, A. Shaukat, W. Rehman, S. Hussain, K. M. Khan. Bioorg. Chem. 58 (2015) 81;b) F. Rahim, H. Ullah, M. T. Javid, A. Wadood, M. Taha, M. Ashraf, A. Shaukat, M. Junaid, S. Hussain, W. Rehman, R. Mehmood, M. Sajid, M. N. Khan, K. M. Khan. Bioorg. Chem. 62 (2015) 15.
35. M. Taha, N. H. Ismail, S. Imran, K. M. Khan. *Molbank* (2014) M826.
36. L. R. Guerreiro, E. P. Carreiro, L. Fernandes, T. A. Cardote, R. Moreira, A. T. Caldeira, R. C. Guedes, A. Burke, Bioorg. Med. Chem. 21 (2013) 1911.
37. J. Park, S. Ko, H. Park, Bull, Korean Chem. Soc. 29 (2008) 921.
38. A. Roujeinikova, C. Raasch, S. Sedelnikova, W. Liebl, D. W. Rice, J. Mol. biol. 321 (2002) 149.
39. K. Yamamoto, H. Miyake, M. Kusunoki, S. Osaki, FEBS J. 277 (2010) 4205.

A table of contents entry

Novel Quinoline Derivatives as Potent *In Vitro* α-Glucosidase Inhibitors: *In Silico* Studies and SAR Predictions

Muhammad Taha, Nor Hadiani Ismail, Syahrul Imran, Abdul Wadood, Fazal Rahim, Muhammad Ali, and Ashfaq Ur Rehman



A new series of exceptionally potent quinoline derivatives **6-30** as α-glucosidase inhibitors was identified.