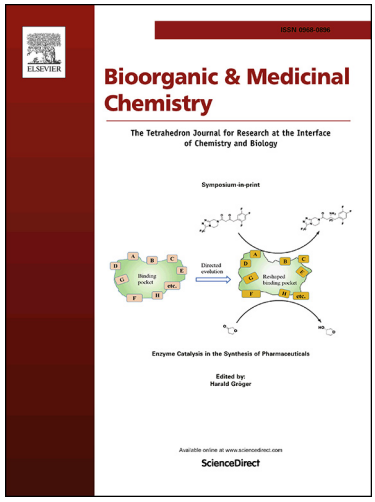

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Synthesis of quinoline derivatives as diabetic *II* inhibitors and molecular docking studies

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Abstract

In searchof the potenttherapeutic agent as an α-glucosidase inhibitor, we have synthesized twenty-five analogs **(1-25)** of quinoline-based Schiff bases as an inhibitoragainst α-glucosidase enzyme under positive control acarbose (IC_{50} = 38.45 ± 0.80 μM). From the activity profile it was foundthat analogs **1**, **2**, **3**, **4**, **11**, **12** and **20**with IC_{50}values 12.40 ± 0.40, 9.40 ± 0.30, 14.10 ± 0.40, 6.20 ± 0.30, 14.40 ± 0.40, 7.40 ± 0.20 and 13.20 ± 0.40 μMrespectively showed most potent inhibition among the series even than standard drug acarbose(IC_{50} = 38.45 ± 0.80 μM). Here in the present study analog **4** (IC_{50} = 6.20 ± 0.30 µM)was found with many folds better α-glucosidase inhibitory activity than the reference drug. Eight analogs like **5**, **7**, **8**, **16**, **17**, **22**, **24** and **25** among the whole series displayed less than 50 % inhibition. The substituents effects on phenyl ring thereby superficially established through SAR study. Binding interactions of analogs and the active site of ligands proteins were confirmed through molecular docking study. Spectroscopic techniques like ^{1}H-NMR, ^{13}C-NMR and ESIMS were used for characterization.

Keywords: quinoline derivatives; Synthesis; diabetic II;α-glucosidase; Molecular docking

1.0. Introduction

Diabetes mellitus is the most common and serious ailment of the 21st century. The survey report of international diabetes federation shows that there are almost 415 million peoples are

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suffering from thisobstacle. It is characterized by a metabolic disorder, where the body cannot produceenough insulin resulting in blood glucose level disturbance. High levels of glucose in blood endorse some severedifficulties to human organs like eyes, nerves, kidneyand heart [1]. In this regard, the basic strategy to control glucose level in blood is delaying the absorption of glucose through inhibiting α-glucose enzyme [2].α-glucosidase is an enzyme that hydrolyzed polysaccharides and disaccharides [3].Dietary carbohydrates are the main reason of the progression of diabetes mellitus and can be controlled by inhibiting of α-glucosidase activityresulting in decline postprandial hyperglycemia [4, 5].

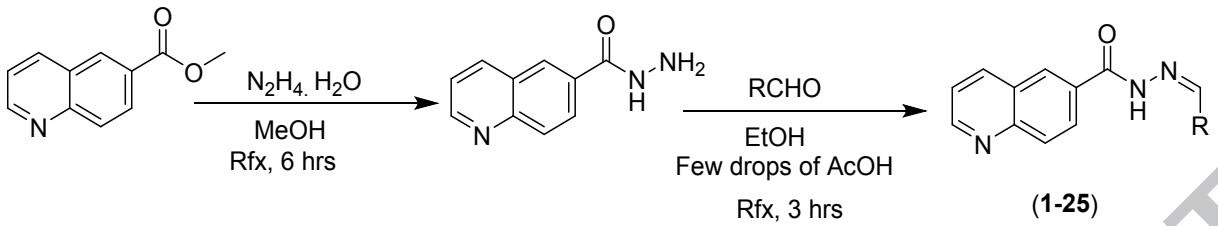
Quinoline and their analogs prove its promising potentials as therapeutic agents like anti-bacterial, anti-fungal [6], anti-cancer [7], anti-convulsant [8], anti-leishmanial [9], anti-malarial [10] anti-Zaka virus [11], anti-plasmodium [12], anti-proliferative [13], proton pump inhibiters [14], anti-ulcer [15], anti-trypanosomal [16], anti-inflammatory [17], anti-diabetes [18] anti-tubercular [19], anti-hypertensive [20] and anti-oxidant agent [21].

In search of lead candidate, our research group has been reported various *N*-containing heterocyclic moieties as a potent inhibitor against urease, thymidine phosphorylase, beta-glucuronidase and α-amylase [25-27]. Our group has already reported quinoline derivatives as α-glucosidase inhibitor [28]. With the hope to further explore the potential ofquinoline as an α-glucosidase inhibitor, here in this study we have synthesized twenty-fiveanalogs **(1-25)** of quinoline-based Schiff base as a potent class of *in vitro*α-glucosidase (*E. coli*) inhibitor.

2.0. Results and Discussion

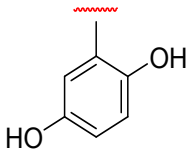
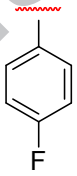
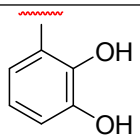
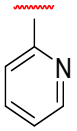
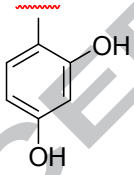
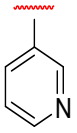
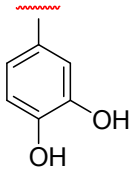
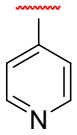
2.1. Chemistry

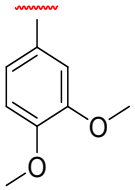
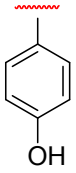
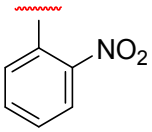
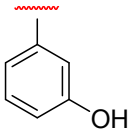
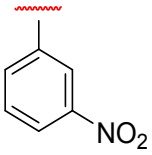
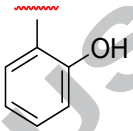
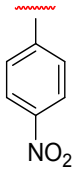
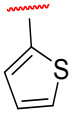
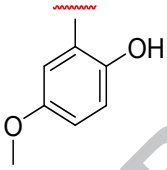
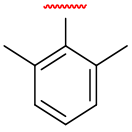
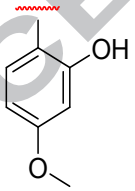
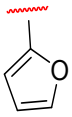
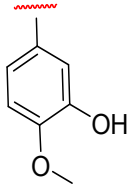
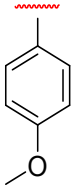
Methyl quinoline-6-carboxylate and hydrazine hydrate were reacted in methanol as solvent and refluxed the reaction mixture for six hrs.To obtained quinoline-6-carbohydarzide. The intermediate quinoline-6-carbohydarzide was then reacted with various aromatic aldehydes in ethanol and the reaction mixture was acidified with few drops of glacial acetic acid and refluxed for 3hrs. to obtained pure product of quinoline-based Schiff base **(1-25). (Scheme-1).** All compounds were confirmed as singal isomer by proton nmr unlike the mixtures of isomer reported [29].

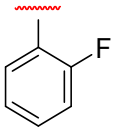
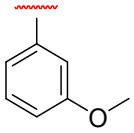
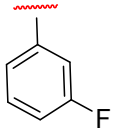


Scheme- 1: Synthesis of quinoline-based Schiff base derivatives **(1-25)**

Table-1: Quinoline based Schiff base derivatives and its α-glucosidase inhibitory activity **(1-25)**

S.NO	R	IC_{50} (μM ± SEM[a])	S.NO	R	IC_{50}(μM ± SEM[a])
1		12.40 ± 0.40	**14**		28.90 ± 0.60
2		9.40 ± 0.30	**15**		38.40 ± 1.00
3		14.10 ± 0.40	**16**		NA[b]
4		6.20 ± 0.30	**17**		NA[b]
5		NA[b]	**18**		23.50 ± 0.60

					
6		37.60 ± 0.80	**19**		48.50 ± 1.30
7		NA[b]	**20**		13.20 ± 0.40
8		NA[b]	**21**		35.70 ± 0.80
9		18.40 ± 0.50	**22**		NA[b]
10		21.60 ± 0.60	**23**		28.60 ± 0.70
11		14.40 ± 0.40	**24**		NA[b]

12		7.40 ± 0.20	**25**		NA[b]
13		48.20 ± 1.10		**Acarbose[c] (Std)**	38.45 ± 0.80μM

SEM[a]is the standard error mean,NA[b]notactive, Acarbose[c] standard drug for α-glucoscidase inhibitory activity

2.2. *In vitroα*-glucosidase activity

The basic goal of our research work is to recognized a lead molecule have a great affinity toward enzyme inhibitions. With this hope, we have synthesized twenty-five analogs of quinoline-based Schiff base **(1-25)** and evaluated for their *in vitroα*-glucosidase inhibitory activity under positive control of reference drug acarbose (IC_{50}= 38.45 ± 0.80 μM).The inhibitory potential of our synthesized analogs with IC_{50} values ranging between (IC_{50}=6.20 ± 0.30 to -48.20 ± 1.10μM). Analogs **1**, **2**, **3**, **4**, **11**, **12**,and **20** with IC_{50} value12.40 ± 0.40, 9.40 ± 0.30, 14.10 ± 0.40, 6.20 ± 0.30, 14.40 ± 0.40, 7.40 ± 0.20 and 13.20 ± 0.40 μM respectively displayed outstanding inhibitory activity many fold better than the standard drug acarbose (IC_{50}= 38.45 ± 0.80 μM). Furthermore analogs **6**,**9**, **10**, **14**, **18**, **21** and **23** with IC_{50} value37.60 ± 0.80, 18.40 ± 0.50, 21.60 ± 0.60, 28.90 ± 0.60, 23.50 ± 0.60, 35.70 ± 0.80 and 28.60 ± 0.70µM respectively were found with good inhibitory activity. Analogs**13**, **15** and **19** (IC_{50}=48.20 ± 1.10, 38.40 ± 1.00 and 48.50 ± 1.30 μM respectively were found in moderate inhibitory potentials, while analogs **5**, **7**, **8**, **16, 17, 22, 24** and **25**were found with potentials less than 50% inhibitions. SAR study was thereby established to know the effects of substituents on the phenyl ring of aldehyde toward enzyme inhibitions.

It was observed that analogs with two OH group on phenyl ring displayed auspiciousinhibitory activity.With this respect analog **4,** a 3,4-dihydroxyanalog (IC_{50} = 6.20 ± 0.30 μM)displayed superior α-glucosidase inhibitory activity among the series. Relocation of OH-groups from 3 and 4-position and their respective existence to each on phenyl ring decline

the inhibitory activity, therefore analog **1,2** and **3** (IC_{50} = 12.40 ± 0.40, 9.40 ± 0.30and 14.10 ± 0.40 μM) were found with less inhibitory potential than analog **4 (Figure 1)**.

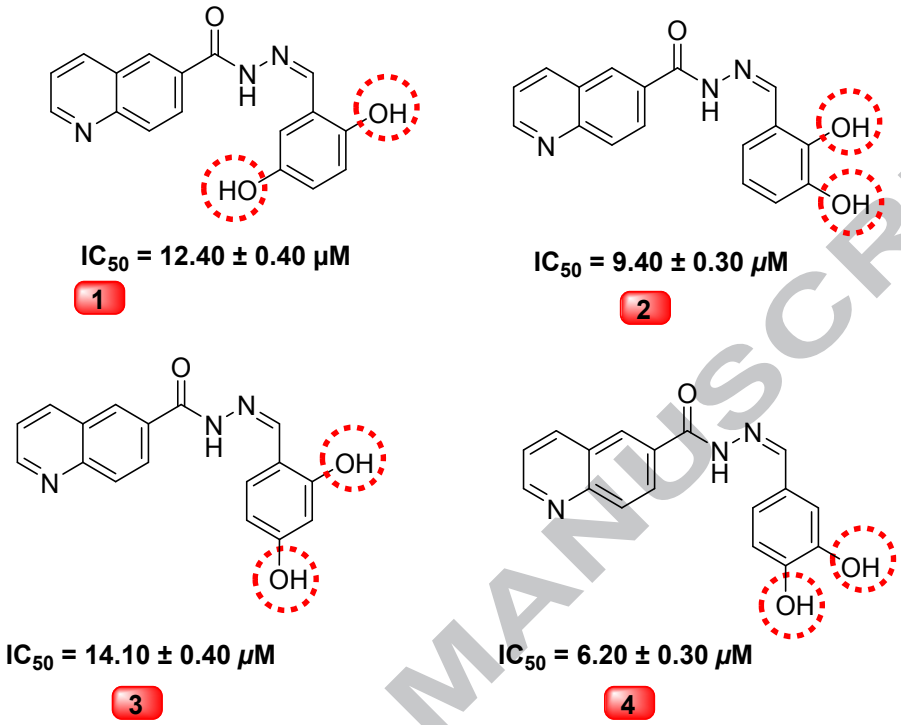


Figure-1:SAR comparison of most potent analogs

If we compared the inhibitory activity of analogs **9, 10** and **11**, all contain methoxy and hydroxyl-group on phenyl ring, but analog **11** (IC_{50}= 14.40 ± 0.40 μM) having OH-group at 3-position and OMe-group at 4-position was found with much better inhibitory potential than analog **9** and **10** (IC_{50}= 18.40 ± 0.50 μM and IC_{50}= 21.60 ± 0.60 μM respectively). It was found out that relocation of one or both groups from 3 and 4-positionon phenyl ring decreases their inhibitory potentials**(Figure 2).**

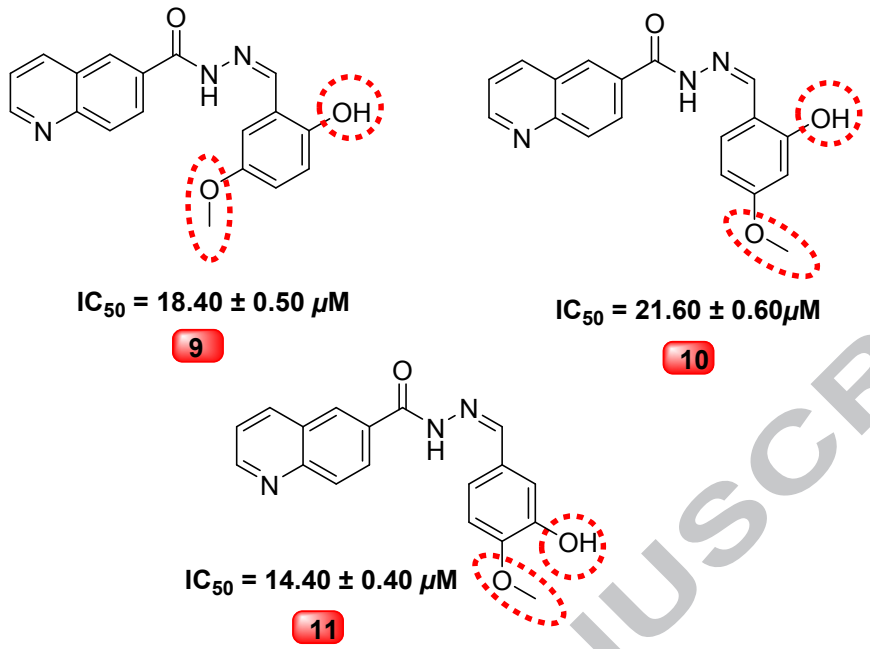


Figure-2:SAR comparison of potent analogs

In compounds **12-14** the polarity of C-F bond which is useful in enzyme inhibition, but the attachment position of fluorine atom on phenyl ring play a significant role to inhibit the enzyme activity. Therefore analog **12** (IC_{50}= 7.40 ± 0.20 μM) have fluorine atom at 2-position on phenyl ring exhibited more significantα-glucosidase inhibitory activity than analogs**13** (IC_{50}= 48.20 ± 1.10 μM) and **14**(IC_{50}= 28.90 ± 0.60 μM) that have fluorine atom at 3 and 4-position on phenyl ring respectively. The more significantα-glucosidase inhibitory activity shown by analog **12** may be due to the position of fluorine atom attached on the phenyl ring.

It was observed through SAR study that isomers of a compound have not equally inhibited the activity because each isomer has a different affinity toward the active site of ligands proteins. In heterocyclic compounds the position of heteroatom changed from one isomer to other isomers directly affects the inhibitory activity. Due to this reason analog **15** (IC_{50}= 38.40 ± 1.00 μM) have nitrogen atom at 2-position on pyridine ring and was found with α-glucosidase inhibitory potential higher than analog **16** and **17** where the position of nitrogen atom in pyridine ring changed from 2 to 3 and 4-position on pyridine ring exhibited α-glucosidase inhibitory activity with less than 50% inhibition.

2.3. Docking study

The BD approach was performed to explore the possible binding mode of the synthesized inhibitors in the binding site other than the substrate binding site due to the non-competitive type of inhibition of the synthesized derivatives against the α-glucosidase enzyme. Consequently, it was observed that the top-ranked conformations of all the compounds were well accommodated in arbitrary cryptic sites, for example; some compounds accommodated in the site-1 and other wherein site-2 of α-glucosidase enzyme and were involved in various type of interactions with the active site residues of α-glucosidase enzyme. *i.e.,* Lys126, Phe157, Asn241, and Arg137, etc. The detail of docking scores and interactions for all the compounds are listed in **Table 2**. The docking conformation of the most active compound (compound **1-4**) showed four interactions with the active site residues. The oxygen atom of the hydroxyl moiety of the phenyl ring of the compound established hydrogen bond with active site residue Lys126and Glu171 (**Figure 3B**). Whereas the nitrogen and double bonded oxygen atom of quinoline rings of the compound form the second hydrogen bond with active site residue Arg137. This strong bonding network might be one of the reasons for this compound to show the highest activity in the series. If we compare the structure of compound **4** to **2** and **3**, the only difference is the position of hydroxyl moieties at the phenyl ring. The position of hydroxyl moiety plays a role in the activity of these compounds, and the docking results showed that the most favorable positions are the *-para* and *-ortho* positions for the hydroxyl moiety. For example, when the hydroxyl moieties are present in *-para*and *-ortho*positions of the phenyl ring showed more interactions with the active site residues as compared to the compounds (compound **2**) when hydroxyl moieties present at other positions (**Figure 3C**). Like the position, the number of hydroxyl moieties also plays a role in the biological activities of these compounds. For example, when two hydroxyl groups present in the compounds showed good activities (**Table-1**) as well as good interactions as compared to the compounds having a single hydroxyl group (**Table-2**). The docking conformation of a compound having methoxy moiety (compound **11**) instead of hydroxyl moiety (compound **4**) showed fewer interactions with active site residues as well as less activity (**Figure 3D**). In case of a compound having electronegative fluorine-substituted phenyl ring (compound **12**) also showed good biological activity but unexpectedly, this compound showed a smaller number of interactions with active site residues of the enzyme (**Figure 3E**). The good activity of this compound might be due to the strong bonds established by this compound as compared to others (**Table 2**).

Overall the docking results showed that compounds having two OH groups were observed with more activity and good interactions with compounds having single OH substituted phenyl ring. As the number of a hydroxyl group, the position of hydroxyl moiety is also crucial for activity. The electronegative fluorine moiety is favorable for activity whereas the methoxy group is detrimental for activity. Furthermore, a good correlation was observed between biological activities and docking scores of these compounds (**Table-1** and **2**).

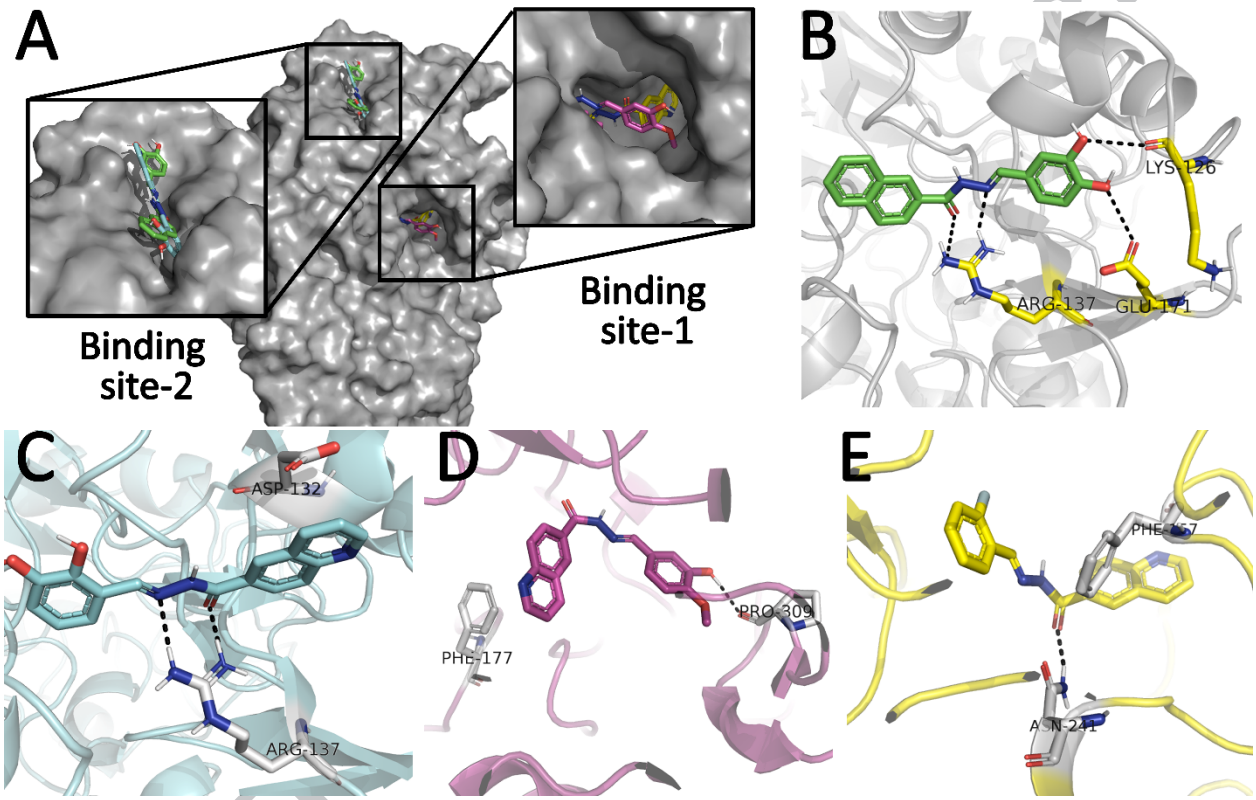


Figure-3: The Blind Docked conformations of most active compounds.(**A**) The surface representation of the enzyme including two cryptic sites (site-1 & site-2) due to the non-competitive behavior of the synthesized derivatives. (**B**)the 3D binding mode of compound **4**,(**C**)for compound **2**, (**D**) for compound **11** and (**E**) for compound **12** against the α-glucosidase enzyme.

Table 2:Docking scores and report of predicted interactions of docked conformations.

Comp. No.	D.scores (S)	Interaction Report				
		Ligand	**Receptor**	**Interaction**	**Distance**	**E(kcal/mol)**
1	-11.8252	O 33 N 1 6-ring	O ASP 349 ND2 ASN 241 N ARG 312	H-donor H-acceptor pi-H	3.28 3.25 4.35	-1.3 -0.8 -0.7
2	-12.8423	6-ring O 33 O 33	ASP 132 N ARG 137 N ARG 137	pi-H H-donor H-donor	4.44 3.1 2.3	-1.0 -0.8 -0.9
3	-11.8883	O 33 6-ring	O ASP 349 CB ARG 312	H-donor pi-H	3.10 4.46	-1.6 -1.0
4	-11.9182	O 26 O 25 O 14 O14	CG LYS 126 CG GLU`171 NH2ARG 137 NH2 ARG 137	H-acceptor H- donor H-donor H-donor	3.3 3.5 3.4 2.4	-0.9 -1.8 -0.5 -1.7
5	NA					
6	-11.5449	O 35 6-ring	NE2 HIS 348 6-ring PHE300	H-acceptor pi-pi	3.34 3.68	-1.4 -0.0
7	NA					
8	NA					
9	-11.5208	O 18 6-ring	CD ARG 439 N ARG 312	H-acceptor pi-H	3.30 4.56	-0.9 -0.9
10	-11.8106	N 19	OD2 ASP408	H-donor	3.40	-0.5
11	-11.3226	O 25 6-ring	O PRO CA PHE 177	H-donor pi-H	2.3 pi-H	-1.6 -1.4
12	-10.7830	0 13 6-ring	ND2 ASN241 CA PHE 157	H-acceptor H-pi	2.2 4.58	-2.4 -0.5
13	-10.9461	6-ring	6-ring PHE300	pi-pi	3.59	-0.0
14	-11.1485	N 1 6-ring	ND2 ASN347 6-ring PHE157	H-acceptor H-acceptor	2.99 3.54	-4.1 -0.0

15	-10.1818	6-ring	6-ring PHE157	pi-pi	3.89	-0.0
16	NA					
17	NA					
18	-11.8110	N 1 6-ring	ND2 ASN241 6-ringPHE1570	H-acceptor pi-pi	3.15 3.55	-2.3 -0.0
19	-9.3442	N 1	ND2 ASN241	H-acceptor	3.42	-1.1
20	-10.4988	O 34 6-ring	OD2 ASP349 6-ring PHE300	H-donor pi-pi	3.17 3.74	-1.6 -0.0
21	-10.4347	5-ring	6-ring PHE300	pi-pi	3.58	-0.0
22	NA					
23	-10.5880	N 19 5-ring	OD2 ASP349 6-ring PHE300	H-donor pi-pi	3.64 3.58	-1.0 -0.0
24	NA					
25	NA					

3.0. Conclusion

Twenty five analogs (**1-25**) of quinoline based schiff bases have been synthesized and evaluated for their *in vitroα*-glucosidase inhibitory activity in the presence of reference drug acarbsoe. All analogs displayed inhibitory actvity in range beween 6.20 ± 0.30 to 48.50 ± 1.30 μM. Here in the present study analogs **4** with two OH-groups and analog **12** with F-group as substituents emerged the most potent analogs among the series. The substitution effect on aromatic residue of aldehyde was estimated through SAR study. Ligands Protein and analogs binding interaction was confirmed through molecular docking study.

4.0 General Method

All nuclear magnetic resonance experiments had been carried out using on Avance Bruker 500 MHz. Elemental analysis was performed on Carlo Erba Strumentazion-Mod-1106, Italy. Electron impact mass spectra (EI-MS) were recorded on a Finnigan MAT-311A, Germany. Thin layer chromatography (TLC) was performed on pre-coated silica gel aluminum plates (Kieselgel 60, 254, E. Merck, Germany). Chromatograms were visualized by UV at 254 and 365 nm.

4.1. Syntheis of quinoline-6-carbohydrazide

Methyl quinoline-6-carboxylate (20 mmoL) were refluxed with excess amount of hydrazine hydrate in absolute methano for six hrs to achieved quinoline-6-carbohydrazide. The reaction completion was monitored by TLC. After completion of the reaction the reaction mixture in round bottom flask placed in cold water till to crystals formation and then filtered to obatained pure product.

4.2. Syntheis of N'-benzylidenequinoline-6-carbohydrazides

Quinoline-6-carbohydrazide (1 mmoL) were reacted with different substitueted aromatic aldehydes (1 mmoL) in absolute ethanole (20 mL) as solvent. After complete dissolution of reactants, the solution was acidified by few drops of glacial acetic acid and then refluxed the reaction mixture for three hrs. After completion of the reaction solvent was evaporated through rotavapour and the pure products **(1-25)** were crytalized from methanol.

4.2.1 *N*'-(2,5-dihydroxybenzylidene)quinoline-6-carbohydrazide (1)

^{1}H NMR (500 MHz, DMSO-d_6): δ12.22 (s, 1H, NH), 10.35 (s, 1H, OH), 9.03 (dd, 1H, J = 1.5, J = 4.0 Hz), 8.99 (s, 1H, OH), 8.65 (s, 1H, CH=N), 8.63 (d, 1H, J = 1.0 Hz), 8.54 (d, 1H, J = 8.0 Hz), 8.27 (dd, 1H, J = 2.0, J = 9.0 Hz), 8.17 (d, 1H, J = 8.5 Hz), 7.67 (dd, 1H, J = 4.0, J = 8.0 Hz), 7.04 (d, 1H, J = 2.5 Hz), 6.80 - 6.76 (m, 2H); ^{13}C NMR (150 MHz, DMSO-d_6):163.1, 153.4, 152.1, 151.0, 146.9, 146.0, 137.5, 134.2, 130.1, 129.3, 129.1, 127.5, 122.1, 120.1, 119.6, 119.3, 116.1. HR-ESI-MS: m/z calcd for $C_{17}H_{13}N_3O_3$, $[M+ H]^+$ 308.1035; Found 308.1417. Anal. Calcd for $C_{17}H_{13}N_3O_3$, C = 66.44, H = 4.26, N = 13.67, O = 15.62, found C = 66.47, H = 4.27, N = 13.68.

4.2.2. *N*'-(2,3-dihydroxybenzylidene)quinoline-6-carbohydrazide (2)

^{1}H NMR (500 MHz, DMSO-d_6): δ12.35 (s, 1H, NH), 11.11 (s, 1H, OH), 9.25 (s, 1H, OH), 9.04 (dd, 1H, J = 1.5, J = 4.0 Hz), 8.67 (s, 1H, CH=N), 8.64 (d, 1H, J = 1.0 Hz), 8.56 (d, 1H, J = 8.0 Hz), 8.27 (dd, 1H, J = 1.5, J = 8.5 Hz), 8.18 (d, 1H, J = 8.5 Hz), 7.67 (dd, 1H, J = 4.0, J = 8.0 Hz), 7.03 (d, 1H, J = 7.0 Hz), 6.90(d, 1H, J = 7.5 Hz), 6.79 (t, 1H, J = 8.0, J = 15.5 Hz); ^{13}C

NMR (150 MHz, DMSO -d_6):163.2, 152.2, 151.5, 147.3, 146.3, 146.1, 137.4, 134.3, 130.2, 129.4, 129.1, 127.4, 124.4, 122.5, 122.1, 119.5, 119.4. HR-ESI-MS: m/z calcd for $C_{17}H_{13}N_3O_3$, $[M+H]^+$ 308.1035; Found 308.1173. Anal. Calcd for $C_{17}H_{13}N_3O_3$, C = 66.44, H = 4.26, N = 13.67, O = 15.62, found C = 66.48, H = 4.25, N = 13.69.

4.2.3 *N'*-(2,4-dihydroxybenzylidene)quinoline-6-carbohydrazide (3)

^{1}H NMR (500 MHz, DMSO-d_6): δ12.15 (s, 1H, NH), 11.44 (s, 1H, OH), 9.99 (s, 1H, OH), 9.03 (dd, 1H, J = 1.5, J = 4.0 Hz), 8.61 (d, 1H, J = 1.0 Hz), 8.57 (s, 1H, CH=N), 8.54 (d, 1H, J = 8.0 Hz), 8.25 (dd, 1H, J = 2.0, J = 9.0 Hz), 8.16 (d, 1H, J = 9.0 Hz), 7.67 (dd, 1H, J = 4.5, J = 8.5 Hz), 7.37 (d, 1H, J = 8.5 Hz), 6.40 (dd, 1H, J = 2.0, J = 8.5 Hz), 6.35 (d, 1H, J = 2.0 Hz); ^{13}C NMR (150 MHz, DMSO -d_6):163.3, 162.3, 162.1, 152.1, 147.2, 146.0, 137.6, 134.5, 133.4, 130.3, 129.3, 129.2, 127.3, 122.3, 110.9, 108.3, 103.5. HR-ESI-MS: m/z calcd for $C_{17}H_{13}N_3O_3$, $[M+H]^+$ 308.1035; Found 308.1131. Anal. Calcd for $C_{17}H_{13}N_3O_3$, C = 66.44, H = 4.26, N = 13.67, O = 15.62, found C = 66.45, H = 4.28, N = 13.67.

4.2.4 *N'*-(3,4-dihydroxybenzylidene)quinoline-6-carbohydrazide (4)

^{1}H NMR (500 MHz, DMSO-d_6): δ11.85 (s, 1H, NH), 9.34 (s, 2H, 2 x OH), 9.02 (dd, 1H, J = 1.5, J = 4.0 Hz), 8.58 (d, 1H, J = 1.5 Hz), 8.54 (dd, 1H, J = 1.5, J = 8.5 Hz), 8.32 (s, 1H, CH=N), 8.23 (dd, 1H, J = 1.5, J = 8.5 Hz), 8.15 (d, 1H, J = 8.5 Hz), 7.66 (dd, 1H, J = 4.0, J = 3.0 Hz), 7.29 (d, 1H, J = 2.0 Hz), 6.99 (dd, 1H, J = 2.0, J = 8.0 Hz), 6.82 (d, 1H, J = 8.0 Hz). ^{13}C NMR (150 MHz, DMSO -d_6):163.2, 152.3, 149.4, 147.4, 146.5, 146.2, 137.5, 134.3, 131.1, 130.2, 129.4, 129.0, 127.5, 123.1, 122.2, 117.2, 116.1; HR-ESI-MS: m/z calcd for $C_{17}H_{13}N_3O_3$, $[M+H]^+$ 308.1035; Found 308.1400. Anal. Calcd for $C_{17}H_{13}N_3O_3$, C = 66.44, H = 4.26, N = 13.67, O = 15.62, found C = 66.45, H = 4.28, N = 13.68.

4.2.5 *N'*-(3,4-dimethoxybenzylidene)quinoline-6-carbohydrazide (5)

^{1}H NMR (500 MHz, DMSO-d_6): δ11.97 (s, 1H, NH), 9.03 (t, 1H, J = 3.0, J = 4.0 Hz), 8.59 (s, 1H, CH=N), 8.55 (d, 1H, J = 8.0 Hz), 8.44 (s, 1H), 8.24 (d, 1H, J = 9.5 Hz), 8.16 (d, 1H, J = 9.0 Hz), 7.66 (dd, 1H, J = 4.5, J = 8.5 Hz), 7.39 (s, 1H), 7.26 (d, 1H, J = 8.0 Hz), 7.07 (d, 1H, J = 8.5 Hz), 3.85 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3); ^{13}C NMR (150 MHz, DMSO -d_6):163.4, 152.3, 152.1, 149.5, 146.5, 147.1, 137.4, 134.3, 130.3, 130.2, 129.3, 129.1, 127.5, 122.4, 122.2,

111.5, 108.9, 55.9, 55.9. HR-ESI-MS: m/z calcd for $C_{19}H_{17}N_3O_3$, $[M+H]^+$ 336.3645; Found 336.1498. Anal. Calcd for $C_{19}H_{17}N_3O_3$, C = 68.05, H = 5.11, N = 12.53, O = 14.31, found C = 68.07, H = 5.12, N = 12.55.

4.2.6 *N*'-(2-nitrobenzylidene)quinoline-6-carbohydrazide (6)

^{1}H NMR (500 MHz, DMSO-d_6): δ12.45 (s, 1H, NH), 9.04 (d, 1H, J = 3.0 Hz), 8.94 (s, 1H, CH=N), 8.65 (s, 1H), 8.56 (dd, 1H, J = 1.5, J = 8.5 Hz), 8.27 (d, 1H, J = 9.0 Hz), 8.20 (dd, 2H, J = 8.0, J = 12.5 Hz), 8.12 (d, 1H, J = 7.5 Hz), 7.88 (t, 1H, J = 7.0, J = 14.5 Hz), 7.73 (t, 1H, J = 7.0, J = 15.0 Hz), 7.68 (dd, 1H, J = 4.0, J = 8.0 Hz); ^{13}C NMR(150 MHz, DMSO -d_6):163.2, 152.2, 147.5, 147.3, 143.1, 137.5, 134.4, 134.3, 131.7, 130.2, 130.1, 129.3, 129.1, 128.1, 127.4, 123.9, 122.1. HR-ESI-MS: m/z calcd for $C_{17}H_{12}N_4O_3$, $[M+H]^+$ 321.0988; Found 320.1247. Anal. Calcd for $C_{17}H_{12}N_4O_3$, C = 63.75, H = 3.78, N = 17.49, O = 14.98, found C = 63.76, H = 3.79, N = 17.50.

4.2.7 *N*'-(3-nitrobenzylidene)quinoline-6-carbohydrazide (7)

^{1}H NMR (500 MHz, DMSO-d_6): δ12.36 (s, 1H, NH), 9.04 (dd, 1H, J = 1.5 J = 4.0 Hz), 8.63 (s, 1H, CH=N), 8.60 (s, 2H), 8.56 (t, 1H, J = 1.0, J = 8.5 Hz), 8.30 - 8.20 (m, 3H), 8.18 (d, 1H, J = 8.5 Hz), 7.81 (t, 1H, J = 8.0, J = 16.0 Hz), 7.67 (dd, 1H, J = 4.0, J = 8.0 Hz); ^{13}C NMR (150 MHz, DMSO -d_6):163.4, 152.1, 148.3, 147.2, 146.4, 137.5, 134.3, 134.2, 132.3, 130.1, 129.5, 129.3, 129.1, 127.4, 126.1, 122.2, 121.3. HR-ESI-MS: m/z calcd for $C_{17}H_{12}N_4O_3$, $[M+H]^+$ 321.0988; Found 321.1098. Anal. Calcd for $C_{17}H_{12}N_4O_3$, C = 63.75, H = 3.78, N = 17.49, O = 14.98, found C = 63.78, H = 3.79, N = 17.48.

4.2.8 *N*'-(4-nitrobenzylidene)quinoline-6-carbohydrazide (8)

^{1}H NMR (500 MHz, DMSO-d_6): δ12.36 (s, 1H, NH), 9.04 (dd, 1H, J = 1.5 J = 4.0 Hz), 8.63 (s, 1H, CH=N), 8.60 (s, 2H), 8.56 (t, 1H, J = 1.0, J = 8.5 Hz), 8.30 - 8.20 (m, 3H), 8.18 (d, 1H, J = 8.5 Hz), 7.81 (t, 1H, J = 8.0, J = 16.0 Hz), 7.67 (dd, 1H, J = 4.0, J = 8.0 Hz); ^{13}C NMR(150 MHz, DMSO -d_6):163.3, 152.3, 149.9, 147.1, 146.5, 138.9, 137.6, 134.2, 130.1, 129.2, 129.1, 127.4, 123.9, 123.9, 123.7, 127.7, 122.1. HR-ESI-MS: m/z calcd for $C_{17}H_{12}N_4O_3$, $[M+2H]^+$ 322.1066; Found 322.11584. Anal. Calcd for $C_{17}H_{12}N_4O_3$, C = 63.75, H = 3.78, N = 17.49, O = 14.98, found C = 63.76, H = 3.79, N = 17.49.

4.2.9 *N*'-(2-hydroxy-5-methoxybenzylidene)quinoline-6-carbohydrazide (9)

^{1}H NMR (500 MHz, DMSO-d_6): δ12.31 (s, 1H, NH), 10.66 (s, 1H, OH), 9.04 (dd, 1H, J = 1.5, J = 4.0 Hz), 8.70 (s, 1H, CH=N), 8.63 (d, 1H, J = 1.0 Hz), 8.55 (d, 1H, J = 8.0 Hz), 8.27 (dd, 1H, J = 1.5, J = 8.5 Hz), 8.17 (d, 1H, J = 9.0 Hz), 7.67 (dd, 1H, J = 4.0, J = 8.0 Hz), 7.18 (d, 1H, J = 3.0 Hz), 6.95 (dd, 1H, J = 2.5, J = 8.5 Hz), 6.90 (d, 1H, J = 9.0 Hz), 3.76 (s, 3H, OCH_3); ^{13}C NMR(150 MHz, DMSO -d_6):163.2, 153.5, 153.1, 152.2, 147.3, 146.2, 137.4, 134.3, 130.2, 129.3, 129.1, 127.5, 122.2, 118.9, 118.3, 117.2, 113.1, 55.8. HR-ESI-MS: m/z calcd for $C_{18}H_{15}N_3O_3$, [M+ H]$^+$ 322.1192; Found 322.1334. Anal. Calcd for $C_{18}H_{15}N_3O_3$, C = 67.28, H = 4.71, N = 13.08, O = 14.94, found C = 67.30, H = 4.72, N = 13.09.

4.2.10 *N*'-(2-hydroxy-4-methoxybenzylidene)quinoline-6-carbohydrazide (10)

^{1}H NMR (500 MHz, DMSO-d_6): δ12.23 (s, 1H, NH), 11.59 (s, 1H, OH), 9.04 (dd, 1H, J = 1.5, J = 4.5 Hz), 8.62 (s, 2H, CH=N, H-6), 8.55 (d, 1H, J = 8.0 Hz), 8.26 (dd, 1H, J = 2.0, J = 9.0 Hz), 8.17 (d, 1H, J = 8.5 Hz), 7.67 (dd, 1H, J = 4.0, J = 8.5 Hz), 7.49 (d, 1H, J = 8.5 Hz), 6.57 (dd, 1H, J = 2.0, J = 8.5 Hz), 6.53 (d, 1H, J = 2.0 Hz), 3.80 (s, 3H, OCH_3); ^{13}C NMR (150 MHz, DMSO -d_6):164.4, 163.3, 162.1, 152.3, 147.1, 146.0, 137.5, 134.4, 133.3, 130.1, 129.4, 129.2, 127.3, 122.1, 109.9, 106.8, 103.1, 55.8. HR-ESI-MS: m/z calcd for $C_{18}H_{15}N_3O_3$, [M+ H]$^+$ 322.1192; Found 321.1379. Anal. Calcd for $C_{18}H_{15}N_3O_3$, C = 67.28, H = 4.71, N = 13.08, O = 14.94, found C = 67.29, H = 4.73, N = 13.10.

4.2.11 *N*'-(3-hydroxy-4-methoxybenzylidene)quinoline-6-carbohydrazide (11)

^{1}H NMR (500 MHz, DMSO-d_6): δ11.91 (s, 1H, NH), 9.32 (s, 1H, OH), 9.03 (dd, 1H, J = 1.5, J = 4.0 Hz), 8.59 (s, 1H, CH=N), 8.54 (t, 1H, J = 7.5, J = 8.0 Hz), 8.36 (s, 1H), 8.24 (dd, 1H, J = 1.0, J = 8.5 Hz), 8.15 (d, 1H, J = 9.0 Hz), 7.66 (dd, 1H, J = 4.0, J = 8.5 Hz), 7.32 (s, 1H), 7.11 (t, 1H, J = 6.5, J = 8.0 Hz), 7.01 (d, 1H, J = 8.5 Hz), 3.83 (s, 3H, OCH_3); ^{13}C NMR (150 MHz, DMSO -d_6):163.4, 152.2, 152.1, 147.3, 147.1, 146.5, 137.6, 134.2, 131.0, 130.1, 129.3, 129.2, 127.2, 122.5, 122.1, 115.6, 112.1, 55.9. HR-ESI-MS: m/z calcd for $C_{18}H_{15}N_3O_3$, [M+ H]$^+$ 322.1192; Found 322.1319. Anal. Calcd for $C_{18}H_{15}N_3O_3$, C = 67.28, H = 4.71, N = 13.08, O = 14.94, found C = 67.27, H = 4.73, N = 13.09.

4.2.12 *N*'-(2-fluorobenzylidene)quinoline-6-carbohydrazide (12)

^{1}H NMR (500 MHz, DMSO-d_6): δ12.22 (s, 1H, NH), 9.04 (dd, 1H, J = 1.5, J = 4.0 Hz), 8.77 (s, 1H, CH=N), 8.63 (s, 1H), 8.55 (t, 1H, J = 7.5, J = 8.5 Hz), 8.26 (d, 1H, J = 8.5 Hz), 8.17 (d, 1H, J = 9.0 Hz), 8.02 (t, 1H, J = 7.0, J = 14.0 Hz), 7.67 (dd, 1H, J = 4.5, J = 8.5 Hz), 7.55 (dd, 1H, J = 6.5, J = 13.5 Hz), 7.35 (dd, 2H, J = 7.0, J = 11.0 Hz). ^{13}C NMR (150 MHz, DMSO -d_6):163.3, 159.3, 152.3, 147.1, 143.5, 137.4, 134.3, 132.2, 130.6, 130.3, 129.3, 129.1, 127.4, 123.7, 122.3, 117.9, 115.2. HR-ESI-MS: m/z calcd for $C_{17}H_{12}FN_3O$, $[M+H]^+$294.1043; Found 294.1504. Anal. Calcd for $C_{17}H_{12}FN_3O$, C = 69.62, H = 4.12, F = 6.48, N = 14.33, O = 5.45, found C = 69.65, H = 4.14, N = 14.35.

4.2.13 *N*'-(3-fluorobenzylidene)quinoline-6-carbohydrazide (13)

^{1}H NMR (500 MHz, DMSO-d_6): δ12.21 (s, 1H, NH), 9.04 (dd, 1H, J = 1.5, J = 4.0 Hz), 8.62 (s, 1H, CH=N), 8.56 (dd, 1H, J = 1.5, J = 8.5 Hz), 8.52 (s, 1H), 8.25 (d, 1H, J = 8.5 Hz), 8.17 (d, 1H, J = 9.0 Hz), 7.67 (dd, 1H, J = 4.0, J = 8.5 Hz), 7.63 (d, 1H, J = 7.5 Hz), 7.59 (d, 1H, J = 10.5 Hz), 7.55 (t, 1H, J = 6.5, J = 13.5 Hz), 7.32 (t, 1H, J = 7.5, J = 15.5 Hz); ^{13}C NMR (150 MHz, DMSO -d_6):163.3, 163.1, 152.2, 147.4, 146.5, 137.3, 134.9, 134.3, 130.1, 130.1, 129.2, 128.9, 127.5, 124.3, 122.1, 117.6, 113.9. HR-ESI-MS: m/z calcd for $C_{17}H_{12}FN_3O$, $[M+H]^+$294.1043; Found 294.1277. Anal. Calcd for $C_{17}H_{12}FN_3O$, C = 69.62, H = 4.12, F = 6.48, N = 14.33, O = 5.45, found C = 69.64, H = 4.15, N = 14.34.

4.2.14 *N*'-(4-fluorobenzylidene)quinoline-6-carbohydrazide (14)

^{1}H NMR (500 MHz, DMSO-d_6): δ12.11 (s, 1H, NH), 9.03 (dd, 1H, J = 1.5, J = 4.0 Hz), 8.61 (s, 1H, CH=N), 8.54 (d, 1H, J = 1.0 Hz), 8.53 (d, 1H, J = 3.5 Hz), 8.25 (d, 1H, J = 8.5 Hz), 8.16 (d, 1H, J = 8.5 Hz), 7.85 (t, 2H, J = 7.5, J = 13.5 Hz), 7.66 (dd, 1H, J = 4.0, J = 8.0 Hz), 7.34 (t, 2H, J = 9.0, J = 17.5 Hz); ^{13}C NMR (150 MHz, DMSO -d_6):164.9, 163.1, 152.1, 145.4, 142.9, 136.8, 134.3, 130.6, 130.3, 130.3, 129.1, 129.0, 128.9, 127.6, 122.2, 115.3, 115.2. HR-ESI-MS: m/z calcd for $C_{17}H_{12}FN_3O$, $[M+H]^+$294.1043; Found 294.1329. Anal. Calcd for $C_{17}H_{12}FN_3O$, C = 69.62, H = 4.12, F = 6.48, N = 14.33, O = 5.45, found C = 69.63, H = 4.13, N = 14.36.

4.2.15 *N*'-(pyridin-2-ylmethylene)quinoline-6-carbohydrazide (15)

^{1}H NMR (500 MHz, DMSO-d_6): δ12.30 (s, 1H, NH), 9.04 (dd, 1H, J = 1.0, J = 4.0 Hz), 8.64 (s, 2H, CH=N, H-6),8.57 (d, 2H, J = 10.0 Hz), 8.26 (d, 1H, J = 8.5 Hz), 8.18 (d, 1H, J = 9.0 Hz), 8.04 (d, 1H, J = 7.5 Hz), 7.93 (t, 1H, J = 7.5, J = 15.0 Hz), 7.67 (dd, 1H, J = 4.0, J = 8.5 Hz), 7.46 (t, 1H, J = 6.0, J = 11.5 Hz). ^{13}C NMR (150 MHz, DMSO -d_6):163.2, 153.3, 152.2, 148.9, 145.3, 138.8,137.5, 136.1, 134.3, 130.1, 129.2, 129.1, 127.4, 125.8, 123.5, 122.3. . HR-ESI-MS: m/z calcd for $C_{16}H_{12}N_4O$, $[M+H]^+$ 277.1089; Found 277.1041. Anal. Calcd for $C_{16}H_{12}N_4O$, C = 69.55, H = 4.38, N = 20.28, O = 5.79, found C = 69.59, H = 4.39, N = 20.30.

4.2.16 *N*'-(pyridin-3-ylmethylene)quinoline-6-carbohydrazide (16)

^{1}H NMR (500 MHz, DMSO-d_6): δ12.26 (s, 1H, NH), 9.03 (dd, 1H, J = 1.5, J = 4.5 Hz), 8.91 (s, 1H, CH=N),8.65 (d, 1H, J = 4.0 Hz), 8.62 (s, 1H), 8.57 (s, 1H), 8.55 (dd, 1H, J = 1.0, J = 8.0 Hz), 8.25 (d, 1H, J = 8.5 Hz), 8.20 (dd, 2H, J = 7.5, J = 16.0 Hz), 7.66 (dd, 1H, J = 4.0, J = 8.0 Hz), 7.53 (dd, 1H, J = 5.0, J = 7.0 Hz); ^{13}C NMR (150 MHz, DMSO -d_6):163.2, 152.2, 152.0, 150.9, 145.3, 142.9, 137.5, 137.3, 134.2, 130.2, 130.1, 129.3, 129.1, 127.4, 123.9, 122.3. HR-ESI-MS: m/z calcd for $C_{16}H_{12}N_4O$, $[M+H]^+$ 277.1089; Found. 277.1098. Anal. Calcd for $C_{16}H_{12}N_4O$, C = 69.55, H = 4.38, N = 20.28, O = 5.79, found C = 69.57, H = 4.41, N = 20.29.

4.2.17 *N'*-(pyridin-4-ylmethylene)quinoline-6-carbohydrazide (17)

^{1}H NMR (500 MHz, DMSO-d_6): δ12.37 (s, 1H, NH), 9.04 (dd, 1H, J = 1.5, J = 4.0 Hz), 8.68 (s, 2H), 8.63 (s, 1H, CH=N),8.56 (d, 1H, J = 8.0 Hz), 8.51 (s, 1H), 8.25 (d, 1H, J = 8.5 Hz), 8.17 (d, 1H, J = 9.0 Hz), 7.72 (s, 2H), 7.67 (dd, 1H, J = 4.0, J = 8.5 Hz); ^{13}C NMR (150 MHz, DMSO -d_6):163.0, 152.3, 149.5, 149.5, 145.6, 144.3, 143.0, 137.8, 134.6, 130.3, 129.6, 129.2, 127.7, 124.1, 124.1, 122.2. HR-ESI-MS: m/z calcd for $C_{16}H_{12}N_4O$, $[M+H]^+$ 277.1089; Found 276.1009. Anal. Calcd for $C_{16}H_{12}N_4O$, C = 69.55, H = 4.38, N = 20.28, O = 5.79, found C = 69.58, H = 4.40, N = 20.31.

4.2. 18 *N*'-(4-hydroxybenzylidene)quinoline-6-carbohydrazide (18)

^{1}H NMR (500 MHz, DMSO-d_6): δ11.91 (s, 1H, NH), 9.97 (s, 1H, OH), 9.02 (t, 1H, J = 2.5, J = 4.0 Hz), 8.59 (s, 1H, CH=N), 8.53 (d, 1H, J = 8.0 Hz), 8.42 (s, 1H), 8.24 (t, 1H, J = 8.0, J = 9.0 Hz), 8.15 (d, 1H, J = 8.5 Hz), 7.65 (dd, 1H, J = 4.0, J = 8.0 Hz), 7.62 (d, 2H, J = 8.5 Hz), 6.88(d, 2H, J = 8.5 Hz)**;** ^{13}C NMR (150 MHz, DMSO -d_6):163.3, 160.5, 152.1, 145.3, 142.9, 137.3,

134.2, 130.3, 130.2, 130.0, 129.2, 129.1, 127.5, 126.3, 122.1, 115.9, 115.9. HR-ESI-MS: m/z calcd for $C_{17}H_{13}N_3O_2$, $[M+H]^+$ 292.1086; Found 292.1468. Anal. Calcd for $C_{17}H_{13}N_3O_2$, C = 70.09, H = 4.50, N = 14.42, O = 10.98, found C = 70.11, H = 4.51, N = 14.44.

4.2.19 *N*'-(3-hydroxybenzylidene)quinoline-6-carbohydrazide (19)

^{1}H NMR (500 MHz, DMSO-d_6): δ12.04 (s, 1H, NH), 9.66 (s, 1H, OH), 9.03 (dd, 1H, J = 1.5, J = 4.0 Hz), 8.61 (s, 1H, CH=N), 8.54 (d, 1H, J = 8.0 Hz), 8.43 (s, 1H), 8.25 (d, 1H, J = 9.0 Hz), 8.16 (d, 1H, J = 9.0 Hz), 7.66 (dd, 1H, J = 4.0, J = 8.0 Hz), 7.30 (d, 1H, J = 7.5 Hz), 7.27 (d, 1H, J = 5.0 Hz), 7.15 (d, 1H, J = 7.5 Hz), 6.87(d, 1H, J = 7.0 Hz); ^{13}C NMR (150 MHz, DMSO -d_6):163.3, 158.3, 152.2, 145.2, 142.8, 137.5, 134.9, 134.3, 130.4, 130.2, 129.1, 129.0, 127.4, 122.0, 121.5, 117.9, 114.8. HR-ESI-MS: m/z calcd for $C_{17}H_{13}N_3O_2$, $[M+H]^+$ 292.1086;Found 292.1528. Anal. Calcd for $C_{17}H_{13}N_3O_2$, C = 70.09, H = 4.50, N = 14.42, O = 10.98, found C = 70.10, H = 4.52, N = 14.43.

4.2.20 *N*'-(2-hydroxybenzylidene)quinoline-6-carbohydrazide (20)

^{1}H NMR (500 MHz, DMSO-d_6): δ12.30 (s, 1H, NH),11.26 (s, 1H, OH), 9.04 (dd, 1H, J = 1.5, J = 4.0 Hz), 8.72 (s, 1H, CH=N), 8.64 (s, 1H), 8.55 (d, 1H, J = 8.0 Hz), 8.27 (dd, 1H, J = 1.5, J = 8.5 Hz), 8.18 (d, 1H, J = 9.0 Hz), 7.67 (dd, 1H, J = 4.0, J = 8.0 Hz), 7.61 (d, 1H, J = 7.5 Hz), 7.35 (dd, 1H, J = 1.0, J = 8.0 Hz), 6.98 (dd, 2H, J = 8.0, J = 13.5 Hz); ^{13}C NMR (150 MHz, DMSO -d_6):163.2, 160.9, 152.2, 145.3, 142.7, 137.4, 134.3, 132.2, 130.3, 130.1, 129.3, 129.1, 127.5, 122.1, 121.2, 118.3, 115.8. HR-ESI-MS: m/z calcd for $C_{17}H_{13}N_3O_2$, $[M+H]^+$ 292.1086; Found 292.1334. Anal. Calcd for $C_{17}H_{13}N_3O_2$, C = 70.09, H = 4.50, N = 14.42, O = 10.98, found C = 70.10, H = 4.52, N = 14.45.

4.2.21 *N*'-(thiophen-2-ylmethylene)quinoline-6-carbohydrazide (21)

^{1}H NMR (500 MHz, DMSO-d_6): δ12.05 (s, 1H, NH), 9.02 (t, 1H, J = 2.5, J = 4.0 Hz), 8.72 (s, 1H, CH=N), 8.58 (s, 1H),8.54 (d, 1H, J = 8.0 Hz), 8.23 (d, 1H, J = 9.0 Hz), 8.16 (d, 1H, J = 9.0 Hz), 7.71 (d, 1H, J = 4.5 Hz), 7.66 (dd, 1H, J = 4.0, J = 8.0 Hz), 7.52 (d, 1H, J = 2.5 Hz), 7.18 (t, 1H, J = 4.5, J = 8.0 Hz); ^{13}C NMR (150 MHz, DMSO -d_6):163.4, 152.4, 145.2, 144.1, 137.6, 134.2, 130.1, 129.2, 129.0, 127.3, 127.1, 127.1, 125.3, 125.1, 122.2. HR-ESI-MS: m/z calcd for

$C_{15}H_{11}N_3OS$, $[M+H]^+$ 282.0701; Found 282.0889. Anal. Calcd for $C_{15}H_{11}N_3OS$, C = 64.04, H = 3.94, N = 14.94, O = 5.69, S = 11.40 found C = 64.05, H = 3.96, N = 14.97.

4.2.22 *N*'-(2,6-dimethylbenzylidene)quinoline-6-carbohydrazide (22)

^{1}H NMR (500 MHz, DMSO-d_6): δ12.03 (s, 1H, NH), 9.03 (d, 1H, J = 3.0 Hz), 8.85 (s, 1H, CH=N), 8.62 (s, 1H), 8.56 (d, 1H, J = 8.0 Hz), 8.26 (t, 1H, J = 7.5, J = 9.0 Hz), 8.17 (d, 1H, J = 8.5 Hz), 7.67 (dd, 1H, J = 4.0, J = 8.5 Hz), 7.23 (t, 1H, J = 7.5, J = 15.0 Hz), 7.14 (d, 2H, J = 7.5 Hz), 2.52 (s, 3H, CH_3), 2.49 (s, 3H, CH_3); ^{13}C NMR (150 MHz, DMSO -d_6):163.3, 152.2, 145.2, 142.9, 138.4, 138.2, 137.5, 134.3, 130.5, 130.1, 129.4, 129.1, 127.4, 125.8, 125.3, 125.2, 122.1, 17.8, 17.8. HR-ESI-MS: m/z calcd for $C_{19}H_{17}N_3O$, $[M+H]^+$304.1450; Found 304.1634. Anal. Calcd for $C_{19}H_{17}N_3O$, C = 75.23, H = 5.65, N = 13.85, O = 5.27 found C = 75.26, H = 5.67, N = 13.86.

4.2.23 *N'*-(furan-2-ylmethylene)quinoline-6-carbohydrazide (23)

^{1}H NMR (500 MHz, DMSO-d_6): δ12.04 (s, 1H, NH), 9.03 (t, 1H, J = 2.5, J = 4.0 Hz), 8.59 (s, 1H, CH=N), 8.54 (d, 1H, J = 8.0 Hz), 8.40 (s, 1H),8.23 (d, 1H, J = 8.5 Hz), 8.16 (d, 1H, J = 8.5 Hz), 7.88 (s, 1H), 7.66 (dd, 1H, J = 4.0, J = 8.0 Hz), 6.99 (d, 1H, J = 2.5 Hz), 6.67 (s, 1H); ^{13}C NMR (150 MHz, DMSO -d_6):163.2, 152.1, 148.8, 145.4, 143.6, 137.4, 134.3, 134.2, 130.1, 129.2, 129.1, 127.3, 122.3, 109.5, 109.2. HR-ESI-MS: m/z calcd for $C_{15}H_{11}N_3O_2$, $[M+H]^+$ 266.093; Found 266.1123. Anal. Calcd for $C_{15}H_{11}N_3O_2$, C = 67.92, H = 4.18, N = 15.85, O = 12.06, found C = 67.94, H = 4.20, N = 15.88.

4.2.24 *N'*-(4-methoxybenzylidene)quinoline-6-carbohydrazide (24)

^{1}H NMR (500 MHz, DMSO-d_6): δ11.96 (s, 1H, NH), 9.03 (dd, 1H, J = 1.5, J = 4.0 Hz), 8.59 (s, 1H, CH=N), 8.54 (t, 1H, J = 7.0, J = 8.5 Hz), 8.46 (s, 1H), 8.24 (d, 1H, J = 8.5 Hz), 8.16 (d, 1H, J = 9.0 Hz), 7.73 (d, 1H, J = 8.5 Hz), 7.66 (dd, 1H, J = 4.0, J = 8.0 Hz), 7.06 (d, 1H, J = 8.5 Hz), 3.83 (s, 3H, OCH_3); ^{13}C NMR (150 MHz, DMSO -d_6):163.3, 163.1, 152.3, 145.5, 142.9, 137.6, 134.3, 130.4, 130.1, 130.0, 129.2, 129.1, 127.4, 125.8, 122.0, 114.1, 114.1, 55.9. HR-ESI-MS: m/z calcd for $C_{18}H_{15}N_3O_2$, $[M+H]^+$306.1243; Found 306.1432. Anal. Calcd for $C_{18}H_{15}N_3O_2$, C = 70.81, H = 4.95, N = 13.76, O = 10.48, found C = 70.84, H = 4.96, N = 13.78.

4.2.25 *N*'-(3-methoxybenzylidene)quinoline-6-carbohydrazide (25)

^{1}H NMR (500 MHz, DMSO-d_6): δ12.11 (s, 1H, NH), 9.03 (dd, 1H, J = 1.5, J = 4.0 Hz), 8.61 (s, 1H, CH=N), 8.55 (dd, 1H, J = 1.5, J = 8.5 Hz), 8.49 (s, 1H), 8.25 (d, 1H, J = 9.0 Hz), 8.16 (d, 1H, J = 8.5 Hz), 7.67 (dd, 1H, J = 4.0, J = 8.0 Hz), 7.43 (t, 1H, J = 8.0, J = 16.0 Hz), 7.34 (d, 2H, J = 6.0 Hz), 7.05 (d, 1H, J = 7.0 Hz), 3.84 (s, 3H, OCH_3); ^{13}C NMR (150 MHz, DMSO -d_6):163.3, 160.4, 152.3, 145.3, 142.8, 137.5 , 134.5, 134.4, 130.1, 129.4, 129.2,129.1, 127.3, 122.1, 121.2, 116.3, 113.1, 55.9. HR-ESI-MS: m/z calcd for $C_{18}H_{15}N_3O_2$, $[M+ H]^+$ 306.1243; Found 306.1450. Anal. Calcd for $C_{18}H_{15}N_3O_2$, C = 70.81, H = 4.95, N = 13.76, O = 10.48, found C = 70.83, H = 4.97, N = 13.77.

4.3. *α*-glucosidase assay

The a-glucosidase inhibition assay had been carried out using Baker's yeast a-glucosidase (EC 3.2.1.20) and p-nitrophenyl-α-D-glucopyranoside. The samples (5 mg/mL) were prepared by dissolving all compounds **(1–25)** in DMSO. Test samples (10 mL) which had been prepared were reconstituted in 100 mL of phosphate buffer (100 mM) at pH 6.8 in 96-well micro-plate and incubated with 50 mL of Baker's yeast a-glucosidase for 5 min before 50 mL of p-nitrophenyl-a-D-glucopyranoside (5 mM) was added. After incubating for 5 min, the absorbance was measured at 405 nm using Spectra Max plus384 (Molecular Devices Corporation, Sunnyvale, CA, USA). Blank in which the substrate was changed with 50 mL of buffer were analyzed to accurately determine the background absorbance. Positive control sample (acarbose) was prepared to contain 10 mL DMSO instead of test samples.

4.4. Molecular docking

Blind docking (BD) approach was performed using MOE-dock module implemented in Molecular Operating Environment (MOE) software packageof all the non-competitive type synthesized derivatives against α-glucosidase enzyme. Due to the unavailability of

crystallographic structure of the corresponding enzyme, we used the homology modelling structural coordinates described by **Taha M** *et al* [28]for α-glucosidase enzyme. Next, the whole protein was considered as a binding site for the purpose of BD. Briefly, the homology model was subjected for 3D protonation and energy minimization up to 0.05 Gradient using MMFF94s forcefield implemented in MOE software. The 3D structures were built by using Molecular Builder Module in MOE. All the derivatives were then docked using the whole protein as a binding site and total 50 different conformations for each inhibitor allowed to generate. The ligands be flexible during docking, so that to obtain minimal energy complex. Later, the docked complexes were ranked based on the docking scores (S). Finally, the predicted ligand-protein complexes were analyzed for molecular interactions using**PyMol** v 1.7.

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Synthesis of quinoline derivatives as diabetic *II* inhibitors and molecular docking studies

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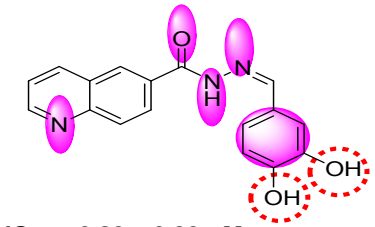
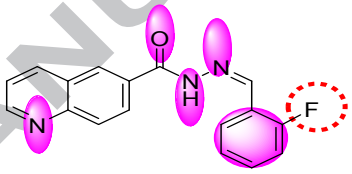


IC_{50} = 6.20 ± 0.30 μM

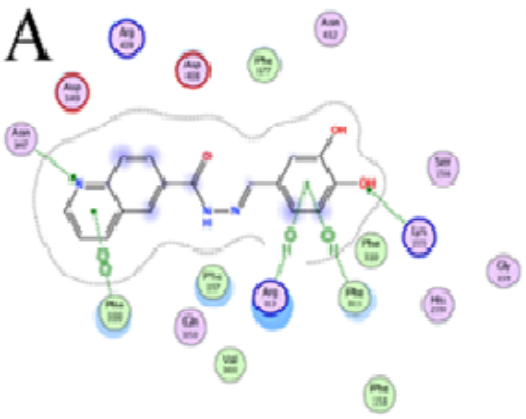
Compound 4
FigA

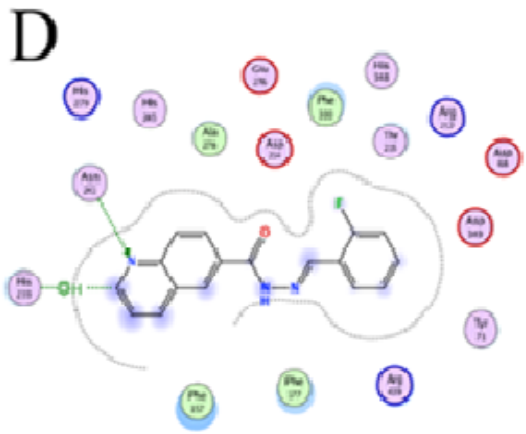


IC_{50} = 7.40 ± 0.20 μM

Compund 12
FigD

Acarbose (Std) IC_{50} = 38.45 ± 0.80µM





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