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Synthesis, Characterization and Hypoglycemic Efficacy of Isonicotinohydrazide Phenoxy Quinolines: An *in silico* Studies

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Prevention of α-amylase and β-glucosidase to reduce the postprandial blood sugar levels and delays dextrose absorption, the natural inhibitors provide an interesting approach to manage hyperglycemia with type 2 diabetes. The α-amylase and β-glucosidase are important therapeutic targets for type II diabetes. The isonicotinohydrazide phenoxy quinolines (**5a-l**) were synthesized and characterized by mass, ^{1}H & ^{13}C NMR. The characterized compounds are investigated for their *in silico* anti-hyperglycemic efficacy and the compounds shown effective to moderate inhibition against α-amylase and β-glucosidase enzymes. A molecular modelling study was performed for all the synthesized compounds to find the binding interaction of **5a-l** with the α-amylase and β-glucosidase.

Keywords: Isonicotinohydrazide phenoxy quinolines, Antidiabetics, α-Amylase, β-Glucosidase, *in silico* Docking.

INTRODUCTION

In recent days the design of drug molecules mainly consisted of "covalent biotherapy" associated with distinct activity observed by a single molecule. In order to enhance the better activity performance of molecules, dual molecules are coupled into a single hybrid molecule. Modern-day investigation in this field seems to validate hybrid molecules as the next-generation drug aspirants [1-3]. Generally, quinoline is signified as the most important class of nitrogen-containing heterocycle that is present in many natural products like alkaloids [4]; it has various therapeutic activities such as antimalarial [5-7], antibacterial [8,9], anticancer [10-14], anti-inflammatory [15-17], DNA binding properties [18-20] and Alzheimer's disease [21-24]. The quinoline a "privileged substructure" for drug design and its derivatives have been incorporated into various classes of therapeutic drug candidates. Combinations of quinoline core with active pharmacophore exhibit significantly enhanced activity. Hydrazones and azomethine group, continue to attract the attention of the medical researchers [25], since it shows wide-ranging biomedical properties mainly antitumor activities [26,27].

The hybrid compound **A** (Fig. 1) was anticipated to be an antitumor due to the combination of isonicotinohydrazide functionality as well as quinoline structure, since the fragment –CO–NH–N=CH– was found to be responsible for potent anticancer [28] and anti-tuberculosis [29]; based on this literature, as a part of our endeavour towards the improvement of quinoline derivatives, herein we design the heterocyclic derivatives containing various substituted quinoline appended (*E*)-N′-((2-phenoxyquinolin-3-yl)methyl-ene)isonicotinohydrazide (**5a-l**) and trivial efforts have been successfully made to synthesize these molecules and then subjected to *in-silico* and *in-vitro* α-amylase and β-glucosidase inhibitory studies to evaluate the biological efficacy.

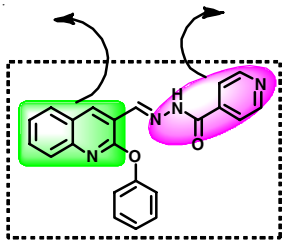


Fig. 1

EXPERIMENTAL

Melting points were recorded in open capillary tubes using Elchem microprocessor-based DT apparatus and are uncorrected. ^{1}H & ^{13}C NMR spectra were recorded using Bruker 400 MHz spectrometer with tetramethylsilane (TMS) as an internal

reference. High-resolution mass spectra were recorded using a Bruker MaXis HR-MS (ESI-Q-TOF–MS) instrument. All the reagents were purchased from Aldrich and used as received. Solvents were removed under a vacuum. Organic extracts were dried with anhydrous Na_2SO_4. Silica gel $60F_{254}$ aluminium sheets were used for analytical thin-layer chromatography (TLC). Visualization of spots on TLC plates was effected by ultraviolet illumination, exposure to iodine vapour, and heating the plates dipped in $KMnO_4$ stain. Silica gel with 230-400 mesh size was used for purification by column chromatography.

***in silico* Docking studies:** Docking study was performed using the Research Collaborators for Structural Bioinformatics Protein Data Bank (RCSB PDB) X-ray structure of α-amylase and β-glucosidase (4GQQ & 3A4A .pdb code); the structures of isonicotinohydrazide phenoxy quinolines, **5a** to **5l** were prepared using Chemdraw 12 software. Docking, and docking analyses were executed with AutoDockTools, AutoDock and PyMOL softwares.

Synthesis of compounds (5a-l): An equimolar mixture of 2-phenoxyquinoline-3-carbaldehyde (**3a-l**) (0.004 mol) and isonicotinohydrazide (**4**) (0.004 mol) in 10 mL methanol containing few drops of acetic acid was refluxed at 65 ºC for 30 min. After completion of the reaction checked by TLC, the reaction mixture was extracted with ethyl acetate then the organic layer was separated and evaporated by a rotary evaporator then the compound was purified by column chromatography (**Scheme-I**).

***N′*-((2-Phenoxyquinolin-3-yl)methylene)isonicotinohydrazide (5a):** White coloured solid, yield 95%, m.p.: 250-252 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 8.10 (s, 1H), 8.03 (s, 1H), 7.89 (bs, 1H), 7.22 (d, *J* = 8.0 Hz,1H), 6.97 (d, *J* = 4.4 Hz, 2H), 6.77 (t, *J* = 7.6 Hz,1H), 6.69 (d, *J* = 8.0 Hz, 1H), 6.62-6.56 (m, 4H), 6.41-6.36 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6): δ ppm 166.84, 164.17, 158.45, 155.62, 151.17, 148.28, 145.36, 141.11, 136.33, 134.93, 134.09, 132.01, 132.01, 130.80, 130.72, 130.31, 127.00, 126.82, 123.92. HRMS-ESI (*m/z*) calcd. for $C_{22}H_{16}N_4O_2$ $[M]^+$: 368.1273, found: 368.1270.

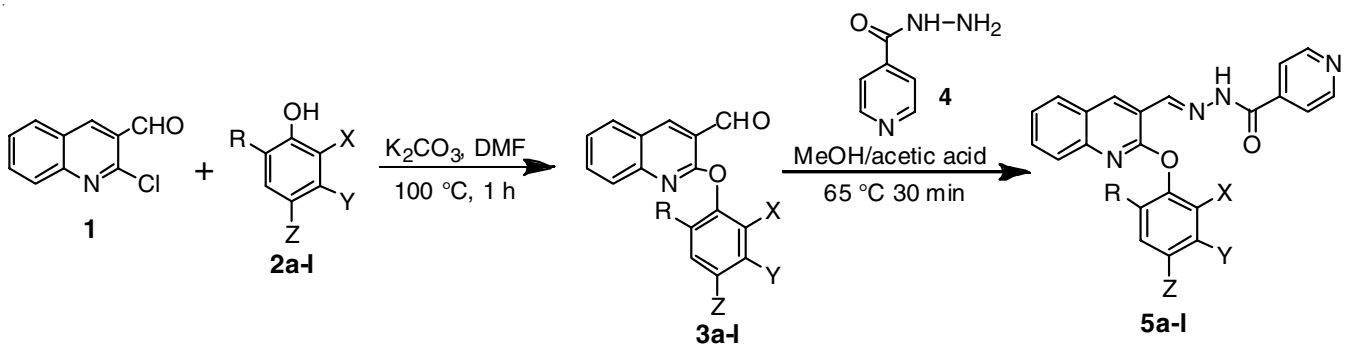
***N′*-((2-(2-Methylphenoxy)quinolin-3-yl)methylene)-isonicotinohydrazide (5b):** White coloured solid, yield 93%, m.p.: 253-255 ºC;^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 12.36 (s, 1H), 9.08 (s, 1H), 8.95 (s, 1H), 8.81 (d, *J* = 4.8 Hz, 2H), 8.71 (d, *J* = 5.6 Hz, 1H), 8.13 (d, *J* = 8.0 Hz, 1H), 7.90 (d, *J* = 4.4 Hz, 1H), 7.74-7.64 (m, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.50 (t, *J* = 7.2 Hz, 1H), 7.38-7.20 (m, 4H), 2.14 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ ppm 164.36, 162.09, 159.09, 151.95, 150.87, 150.67, 146.52, 143.59, 140.73, 140.66, 136.29, 131.66, 129.36, 127.67, 127.21, 125.90, 122.85, 122.02, 121.47, 118.83, 16.56. HRMS-ESI (*m/z*) calcd. for $C_{23}H_{18}N_4O_2$ $[M]^+$: 382.1430, found: 382.1427.

***N′*-((2-(4-Methylphenoxy)quinolin-3-yl)methylene)-isonicotinohydrazide (5c):** White coloured solid, yield 88%, m.p.: 254-256 ºC;^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 12.37 (s, 1H), 9.02 (s,1H), 8.92 (s,1H), 8.81 (d, *J* = 5.2 Hz, 1H) 8. 71 (d, *J* = 5.6 Hz, 2H), 8.12 (d, *J* = 8.0 Hz, 1H), 7.90 (d, *J* = 5.6 Hz, 2H), 7.68 (t, *J* = 7.4 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.51 (t, *J* = 7.2 Hz, 1H), 7.28 (d, *J* = 8.0 Hz,2H), 7.20 (d, *J* = 8.4, 2H), 2.36 (s,3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ ppm 164.35, 162.04, 159.58, 151.39, 150.85, 146.47, 143.64, 140.62, 136.14, 134.60, 131.51, 130.53, 129.31, 127.23, 125.93, 122.02, 122.47, 119.13, 20.93. HRMS-ESI (*m/z*) calcd. for $C_{23}H_{18}N_4O_2$ $[M]^+$: 382.1430, found: 382.1428.

***N′*-((2-(2,4-Dimethylphenoxy)quinolin-3-yl)methylene)-isonicotinohydrazide (5d):** White coloured solid, yield 80%, m.p.: 258-261 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 12.33 (s, 1H), 9.06 (s, 1H), 8.93 (s, 1H), 8.81 (d, *J* = 4.0 Hz, 2H), 8.13 (d, *J* = 8.0 Hz,1H), 7.89 (d, *J* = 5.6 Hz, 2H), 7.67 (t, *J* = 7.6 Hz, 1H), 7.57 (t, *J* = 8.4 Hz, 1H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.18 (s, 1H), 7.11 (s, 2H), 2.34 (s, 3H), 2.09 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ ppm 158.84, 150.67, 149.76, 145.90, 139.35, 135.98, 134.76, 134.72, 132.11, 130.85, 130.18, 128.89, 128.05, 127.18, 126.65, 126.04, 125.76, 122.60, 119.49, 112.10, 20.92, 16.52.HRMS-ESI (*m/z*) calcd. for $C_{24}H_{20}N_4O_2$ $[M]^+$: 396.1586, found: 396.1583.

***N′*-((2-(2-Chlorophenoxy)quinolin-3-yl)methylene)-isonicotinohydrazide (5e):** White coloured solid, yield 82%, m.p.: 262-264 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 12.38 (s, 1H), 9.07 (s, 1H), 8.98 (s, 1H), 8.81 (s, 2H), 8.16 (d, *J* = 8.0 Hz, 1H), 7.90 (d, *J* = 4.4 Hz, 2H), 7.74-7.65 (m, 2H), 7.59-7.48 (m, 4H), 7.40-7.35 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ ppm 162.09, 158.67, 150.87, 150.67, 149.35, 146.23, 143.20, 136.53, 131.71, 130.84, 129.42, 129.10, 127.54, 127.27, 126.63, 126.27, 126.10, 125.28, 122.04, 118.63. HRMS-ESI (*m/z*) calcd. for $C_{22}H_{15}ClN_4O_2$ $[M]^+$: 402.0884, found : 402.0881.

***N′*-((2-(3-Chlorophenoxy)quinolin-3-yl)methylene)-isonicotinohydrazide (5f):** White coloured solid, yield 86%, m.p.: 265-268 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 12.39 (s,1H), 9.07 (s,1H), 8.98 (s,1H), 8.82 (s,2H), 8.17 (d, *J* = 8.0 Hz,1H), 7.90 (d, *J* = 4.4 Hz, 2H), 7.67 (t, *J* = 7.6 Hz, 2H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.56-7.48 (m, 3H), 7.38 (t, *J* = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ ppm 172.49, 162.05, 159.10, 154.50, 150.87, 146.26, 143.39, 140.60,



Scheme-I: Synthesized novel heterocyclic quinoline motifs (**5a-l**)

136.42, 133.98, 131.55, 129.35, 127.32, 126.23, 126.14, 125.72, 122.65, 122.01, 121.26, 119.15.HRMS-ESI (m/z) calcd for $C_{22}H_{15}Cl\ N_4O_2$ $[M]^+$= 402.0884, found =402.0882.

***N′*-((2-(4-Chlorophenoxy)quinolin-3-yl)methylene)-isonicotinohydrazide (5g):** White coloured solid, yield 89%, m.p.: 263-265 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 12.34 (s,1H), 9.00 (s,1H), 8.95 (s,1H), 8.81 (d, *J* = 4.8 Hz, 2H), 8.15 (d, *J* = 8.0 Hz,1H), 7.89 (d, *J* = 5.2 Hz, 2H), 7.70 (t, *J* = 7.2 Hz, 1H), 7.63 (d, *J* = 8.0 Hz,1H), 7.57-7.52 (m, 3H), 7.39 (d, *J* = 8.0 Hz, 2H).^{13}C NMR (100 MHz, DMSO-d_6): δ ppm 162.05, 159.22, 152.45, 150.88, 146.28, 143.45, 140.61, 136.37, 131.64, 130.08, 129.64, 129.36, 127.28, 126.17, 126.07, 124.30, 122.01, 119.10. HRMS-ESI (*m/z*) calcd. for $C_{22}H_{15}ClN_4O_2$ $[M]^+$: 402.0884, found: 402.0880.

***N′*-((2-(2,4-Dichlorophenoxy)quinolin-3-yl)methylene)isonicotinohydrazide (5h):** White coloured solid, yield 81%, m.p.: 268-271 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 12.39 (s, 1H), 9.04 (s, 1H), 8.98 (s, 1H), 8.16 (d, *J* = 7.6 Hz, 1H), 7.91 (s, 2H), 7.85 (s, 1H), 7.70 (t, *J* = 7.4 Hz, 1H), 7.61-7.52 (m, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ ppm 172.51, 162.15, 158.44, 150.88, 148.43, 146.10, 143.07, 136.68, 131.81, 130.86, 130.32, 129.43, 129.21, 127.93, 127.28, 126.66, 126.36, 126.16, 118.55. HRMS-ESI (*m/z*) calcd. for $C_{22}H_{14}Cl_2N_4O_2$ $[M]^+$: 436.0494, found: 436.0491.

***N′*-((2-(4-Bromophenoxy)quinolin-3-yl)methylene)-isonicotinohydrazide (5i):** White coloured solid, yield 90%, m.p.; 275-278 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 12.35 (s, 1H), 9.00 (s, 1H), 8.95 (s, 1H), 8.81 (d, *J* = 4.4 Hz, 2H), 8.16 (d, *J* = 8.0 Hz, 1H), 7.89 (d, *J* = 5.2 Hz, 2H), 7.73-7.62 (m, 4H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.33 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ ppm 162.04, 159.15, 152.95, 150.88, 146.28, 143.44, 140.61, 136.38, 133.02, 131.65, 129.37, 127.28, 126.18, 126.08, 124.73, 122.01, 119.12, 117.74. HRMS-ESI (*m/z*) calcd. for $C_{22}H_{15}BrN_4O_2$ $[M]^+$: 446.0378, found: 446.0375.

***N′*-((2-(4-(*tert*-Butyl)phenoxy)quinolin-3-yl)methylene)-isonicotinohydrazide (5j):** White coloured solid, yield 84%, m.p.: 259-262 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 8.96 (s, 1H), 8.90 (s,1H), 8.77 (d, *J* = 4.8 Hz, 2H), 8.09 (d, *J* = 8.0 Hz, 1H), 7.85 (d, *J* = 4.8 Hz, 2H), 7.65 (t, *J* = 7.6 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.50-7.44 (m, 4H), 7.19 (d, *J* = 8.4 Hz, 2H), 1.30 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6): δ ppm 177.25, 166.84, 164.16, 156.14, 155.69, 152.41, 151.22, 145.40, 136.29, 134.09, 131.99, 131.56, 131.12, 130.74, 126.77, 126.26, 123.98, 119.86, 39.45, 36.51.HRMS-ESI (*m/z*) calcd. for $C_{26}H_{24}N_4O_2$ $[M]^+$: 424.1899, found: 424.1896.

***N′*-((2-(3-Methylphenoxy)quinolin-3-yl)methylene)-isonicotinohydrazide (5k):** White coloured solid, yield 79%, m.p.: 252-254 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 12.36 (s,1H), 9.08 (s, 1H), 8.95 (s,1H), 8.81 (d, *J* = 4.8 Hz, 2H), 8.71 (d, *J* = 5.6 Hz,1H), 8.13 (d, *J* = 8.0 Hz, 1H), 7.90 (d, *J* = 4.4 Hz, 1H), 7.67 (d, *J* = 7.4 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.51 (t, *J* = 7.4 Hz,1H), 7.38 (d, *J* = 7.2 Hz, 1H), 7.32 (t, *J* = 7.2 Hz, 1H), 7.26-7.20 (m, 2H), 2.14 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ ppm 164.36, 162.09, 159.09, 151.95, 150.87, 150.67, 146.42, 143.59, 140.73, 140.66, 136.29, 131.66, 129.36, 127.67, 127.21, 125.90, 122.85, 122.02, 121.47, 118.83, 16.56. HRMS-ESI (*m/z*) calcd. for $C_{23}H_{18}N_4O_2$ $[M]^+$: 382.1430, found: 382.1428.

***N′*-((2-(2,6-Dimethoxyphenoxy)quinolin-3-yl)-methylene)isonicotinohydrazide (5l):** White coloured solid, yield 85%, m.p.: 260-263 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 11.67 (s, 1H), 8.90 (s, 1H), 8.59 (s, 1H), 8.20 (d, *J* = 8.8 Hz,1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.49-7.44 (m, 2H), 7.30-7.17 (m, 3H), 6.83 (d, *J* = 8.0 Hz, 1H), 6.80 (d, *J* = 8.4 Hz, 1H), 3.70 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ ppm 158.80, 158.44, 153.05, 150.70, 145.97, 139.37, 137.53, 136.14, 134.42, 130.57, 128.89, 127.15, 126.97, 126.64, 126.16, 125.59, 119.13, 112.13, 106.18, 106.02, 56.52, 56,47. HRMS-ESI (*m/z*) calcd. for $C_{24}H_{20}N_4O_4$ $[M]^+$: 428.1485, found: 428.1483.

RESULTS AND DISCUSSION

Initially, the required 2-chloro-3-formyl quinoline (**1**) has been synthesized according to the procedure available in the literature [30], which in turn reacted with phenol derivatives **2a-l** in the presence of K_2CO_3/DMF at 100 ºC for an h to afford substituted 2-phenoxyquinoline-3-carbaldehyde (**3a-l**), which upon reacts with isonicotinohydrazide (in methanol containing acetic acid at 65 ºC for 30 min) afford corresponding *N′*-((2-phenoxyquinolin-3-yl)methylene)isonicotinohydrazide (**5a-l**). Then the product was extracted with ethyl acetate and the separated organic layer was evaporated using the rotary evaporator, obtained crude product was purified using the column chromatography. All the synthesized compounds were characterized by their physical and spectral data (^{1}H, ^{13}C, HR-MS). The melting point and ^{1}H and ^{13}C NMR spectral data of compounds (**3a-l**) were found to be in concurrence with the literature. Whose disappearance confirmed the conversion of **3a-l** into **5a-l** (**Scheme-I**), which is further characterized by ^{1}H & ^{13}C NMR and HRMS (ESI) spectral analysis. Compound *N′*-((2-phenoxyquinolin-3-yl)methylene)isonicotinohydrazide (**5a**) has been taken as the representative sample and its spectral characterization is discussed. Compound **5a** exhibited the following chemical shifts in the aromatic region δ ppm 8.10 (s, 1H), 8.03 (s, 1H), 7.89 (bs, 1H), 7.22 (d, *J* = 8.0 Hz, 1H), 6.97 (d, *J* = 4.4 Hz, 2H), 6.77 (t, *J* = 7.6 Hz, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 6.62-6.56 (m, 4H), 6.41-6.36 (m, 4H). The examination of the above signals clearly illustrated that the signals at δ 8.10 (s, 1H) is for the amide hydrogen, δ 8.03 (s, 1H) is for C_4 hydrogen, δ 7.89 (s, 1H) is for the emine hydrogen (emine hydrogen present near to the 3º amine so the peak is broad) remaining chemical shifts all in aromatic region. The ^{13}C NMR spectrum exhibited the following signals δ 166.84, 164.17, 158.45, 155.62, 151.17, 148.28, 145.36, 141.11, 136.33, 134.93, 134.09, 132.01, 132.01, 130.80, 130.72, 130.31, 127.00, 126.82, 123.92 ppm; the extreme downfield signal at δ 166.84 ppm was assigned to the carbonyl carbon at isoniazid ring. All other signals are due to the aryl carbons of phenoxyquinoline isonicotinohydrazide.

The *m/z* observed at 368.1270 in the mass spectrum also confirmed the formation of the desired molecule [HRMS-ESI (*m/z*) calculated for $C_{22}H_{16}N_4O_2$ $[M]^+$ = 368.1273, found = 368.1270]. In a similar fashion, the spectral characterization of remaining compounds in the series has also been done mentioned.

Protein ligand interactions: To find the binding method and potential interactions of compounds **5a-l** with target

enzymes (α-amylase and β-glucosidase), docking analyses were performed. The 3D simulations of target enzymes were initiated *via* the Swiss model type (Fig. 2). Fig. 3 represents the electrostatic potential surface simulations of enzymes, 3D picture exposes the distribution of charged and uncharged residues, which concludes the binding sites for the activators/inhibitors. *In silco* docking studies were performed with the compounds **5a-l** against the active site of 4GQQ and 3A4A enzymes. When the inhibitors and protein are docked together, Autodock tools are revealed for the suitable confirmation of the protein-ligand complex with the highest stability and least binding energy. In this technique, it gives the best docking score of **5a** and **5c** ligands show potential effect among the compounds **5a-l** with diverse binding affinities in kcal/mol.

The validation which is classified **5a** and **5c** has the least binding energy and is assumed the best plausible orientation that can be achieved in docking. The ligand binding interaction with 4GQQ and 3A4A: **5a-l** ligands have the binding affinity of α-amylase -9.36, -8.85, -9.46, -9.12, -9.24, -6.76, -8.90, -8.67, -6.87, -9.07, -8.33, -8.75 and β-glucosidase -8.59, -6.41, -8.57, -7.06, -7.07, -6.86, -6.79, -4.96, -6.07, -6.99, -5.69 and -5.78 kcal/mol, respectively (Table-1). The least binding energy of compounds **5a** and **5c** with the affinity -9.36 and -9.46 (α-amylase), -8.59 and -8.57 kcal/mol (β-glucosidase) will be selected for the further analysis Besides 12 compounds were docked against the active sites of 4GQQ and 3A4A and out of these compounds, **5a** and **5c** showed the highest binding interaction with both 4GQQ and 3A4A having the best docking affinity of -9.36 and -9.46 (α-amylase), -8.59 and -8.57 kcal/mol.

When the highest binding energy ligand was combined with the "PDB" (Protein Data Bank) file format of the protein (α-amylase and β-glucosidase) and opened in the Ligplot$^+$ software, we get to observe different interactions between each compound and amino acid residues in and around the active site of the protein. In each of the protein-ligand interactions,

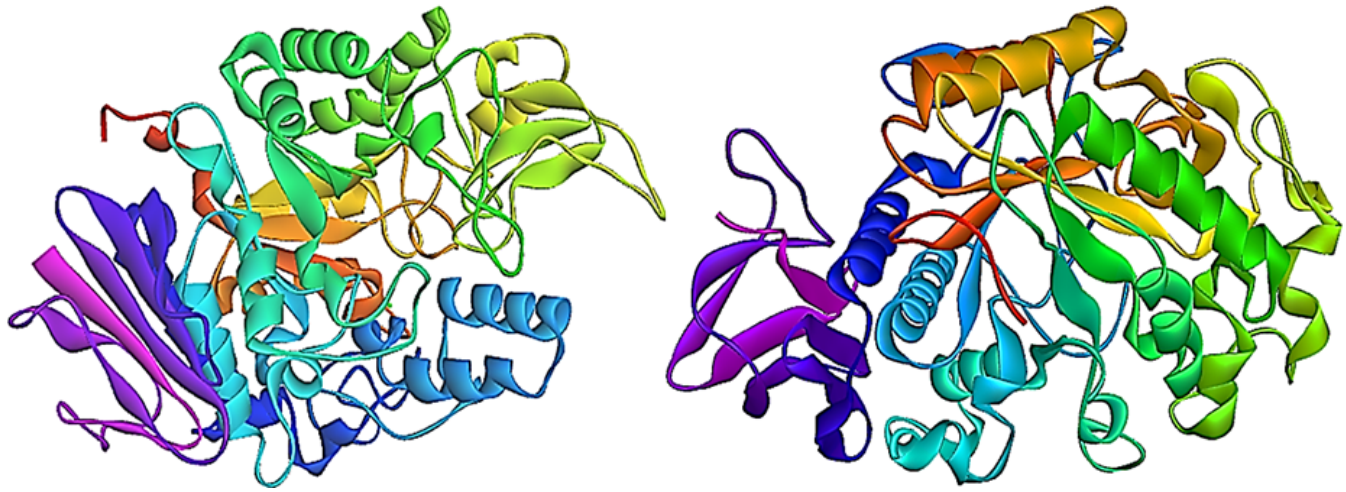


Fig. 2. 3D image of α-amylase and α-glucosidase enzymes

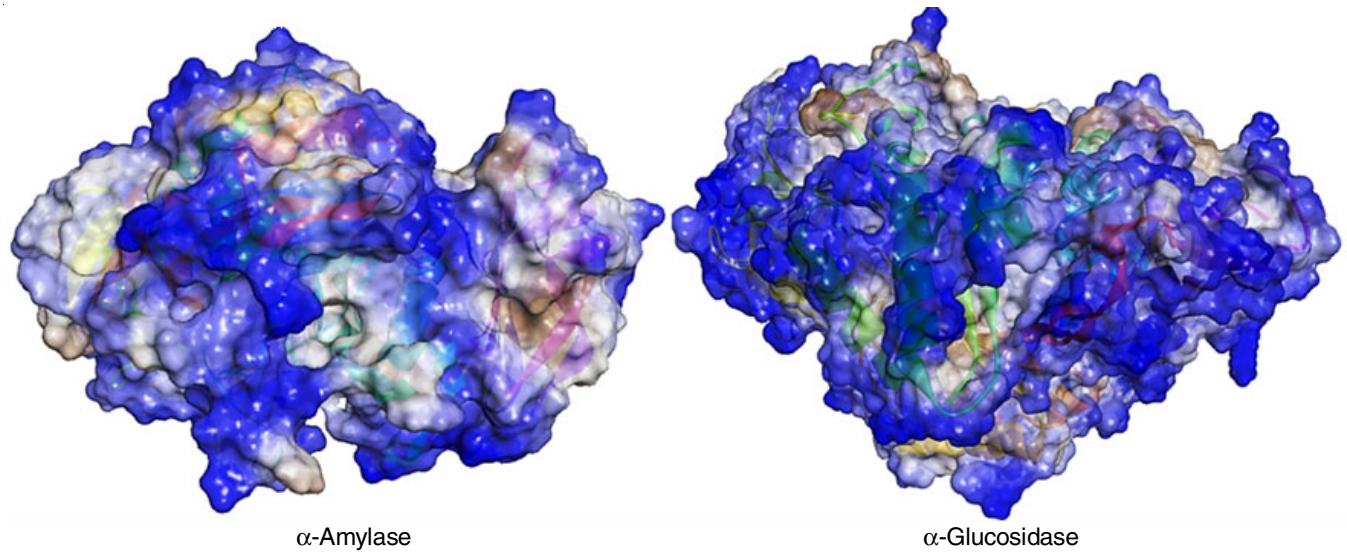


Fig. 3. Electrostatic potential surface models of α-amylase and α- glucosidase enzymes of the rat. Colours on the surface representation of the compound buildings are based on electrostatic possibilities of positive (brown) and negative (blue) charged residues

TABLE-1
In silco DOCKING SCORE α-AMYLASE AND α-GLUCOSIDASE

Compd.	X	Y	Z	R	Binding score	
					α-Amylase	α-Glucosidase
5a	H	H	H	H	-9.36	-8.59
5b	CH_3	H	H	H	-8.85	-6.41
5c	H	H	CH_3	H	-9.46	-8.57
5d	CH_3	H	CH_3	H	-9.12	-7.06
5e	Cl	H	H	H	-9.24	-7.07
5f	H	Cl	H	H	-6.76	-6.86
5g	H	H	Cl	H	-8.90	-6.79
5h	Cl	H	Cl	H	-8.67	-4.96
5i	H	H	Br	H	-6.87	-6.07
5j	H	H	*t*-Bt	H	-9.07	-6.99
5k	H	CH_3	H	H	-8.33	-5.69
5l	OCH_3	H	H	OCH_3	-8.75	-5.78

the ligand is described as purple in colour, the hydrophobic interactions are illustrated as a semi-circled structure and the amino acids residues are in red and hydrophilic interactions of the amino acid residues are specified in green colour. Although exhibits the bond length between the nitrogen atoms. Compound **5a** and **5c** being the best inhibitor among the 12 exhibited and α-amylase protein hydrophilic interactions with **5a** and **5c**: His303 and Arg195, Aso297, Asp300; hydrophobic interactions: Try65, Asp197, Glu233, Ile235, Asp300, Gly306, Ala307and His15, Phe17, Gln41, Trp58, Tyr62, Asp96, Ile235, Phe256, Phe295, Asn298, His299, Gly306, Ala307, Arg337 (Fig. 4). The β-glucosidase protein hydrophilic interactions with **5a** and **5c**: Arg442, Gln279, Gln353 and Gln279; hydrophobic interactions: Try158, Phe159, Phe178, Glu277, His280, Phe303, Asp307, Pro312, Arg315, Asp352, Glc601 and Try158, Phe159, Phe178, Asp242, His280, Phe303, Asp307, Pro312, Asp352, Gln353, Glu411, Arg442, Glc601 (Fig. 5). From the docking results, compounds **5a** and **5c** showed the best binding interaction affinity than the remaining molecules with both proteins, respectively. In present studies, all the synthesized compounds were examined for an active hydrogen bond to interact with active residues of α-amylase and β-glucosidase proteins. The active site residues of α-amylase and β-glucosidase have contributed to hydrogen bonding with all synthesized inhibitors (**5a-l**) investigated in the existing study. The

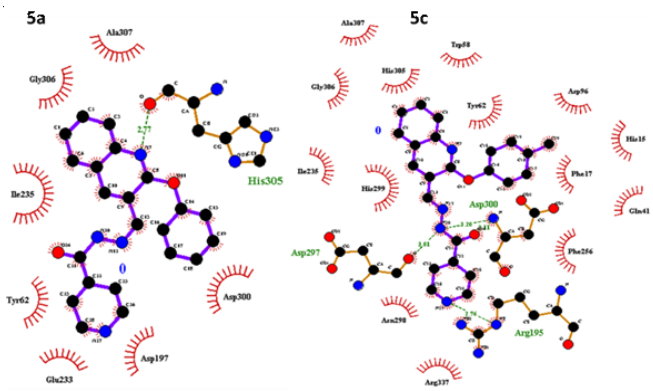


Fig. 4. Ligplot showing the 4GQQ-ligand interactions of **5a** and **5c** ligands, based on energy score (hydrogen bonding and hydrophobic), prepared by Ligplot program

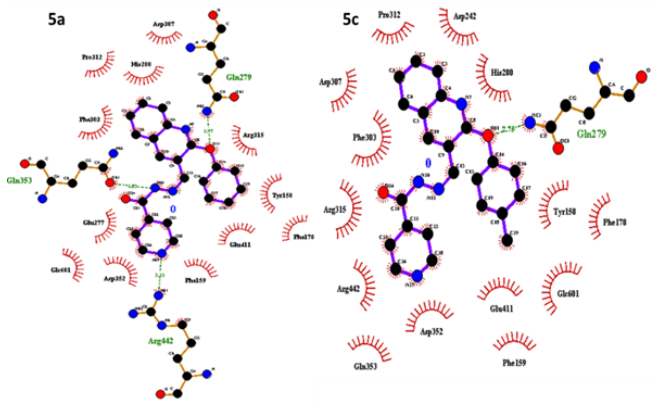


Fig. 5. Ligplot showing the 3A4A-ligand interactions of **5a** and **5c** ligands, based on energy score (hydrogen bonding and hydrophobic), prepared by Ligplot program

interaction was revealed that inhibitors molecules may inhibit/prevent the activity of enzymes in disease conditions.

Conclusion

Isonicotinohydrazide phenoxy quinolines (**5a–l**) were synthesized and investigated for α-amylase and β-glucosidase inhibition and found to exhibit moral inhibition against α-amylase and β-glucosidase. The *in silico* molecular docking studies determined the types of binding interactions, which facilitated the characteristic compounds to interact within the active site of α-amylase and β-glucosidase. Therefore, this study identified several lead molecules particularly **5a** and **5c** that can act as potential antidiabetic agents.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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