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Molecular Modelling and in Vitro Hypoglycemic Examination of Polysubstituted Quinoline Derivatives

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Abstract*: *In the present work in-silico molecular simulations were carried out to find out the binding affinities of synthesized polysubstituted quinolines towards PPARγ protein (2XKW). The results obtained from docking analysis showed that the synthesized polysubstituted quinoline derivatives 1a-g are having stronger binding interactions which was on par to that of standards rosiglitazone and pioglitazone. In addition to this in-vitro hypoglycemic studies were studied through α-amylase and α-glucosidase enzyme inhibition assays. The results showed that compounds 1c and 1d possess good hypoglycemic efficacy with percentage inhibition of 87.94 ± 0.25, 85.90 ± 0.56 towards α-glucosidase and 84.55 ± 1.02, 82.14 ± 0.26 percent inhibition towards α-amylase which was greater than standard rosiglitazone and comparable to standard pioglitazone

Keywords*: *Quinolines, PPARγ, Hypoglycemic

I. INTRODUCTION

Quinolines and their analogues are considered as an important class of bioactive heterocyclic compounds because of its versatile applications in the field of pharmaceuticals and in various biological systems [1-5]. Quinoline scaffolds because of their varied biological activities like antimicrobial, antioxidant, antimalarial (chloroquine and mefloquine), anticancer, antiinflammatory, cytotoxic agents, tyrosine kinase PDGF-RTK inhibitor and topoisomerase I inhibitors have great significance among heterocycles [4-8]. In addition to medicinal applications, quinoline derivatives are found to undergo hierarchical self-assembly into a variety of nano-structures and meso-structures with enhanced electronic and photonic functions [9-12]. In recent years quinoline scaffold was widely used in the design and synthesis of new hypoglycemic agents [13]. Diabetes mellitus (DM) is considered as the world's largest growing metabolic non-communicable disease. Diabetes are at an increased risk of developing chronic complications related to cardiovascular, ophthalmic, neurological, renal and peripheral vascular diseases. Inspite of the releasing various hypoglycemic agents, diabetes and its associated secondary complications continue to be a major problem in the world population. Literature search reveals only little amount of work has been carried out regarding molecular docking analysis of polysubstituted quinoline derivatives towards PPARγ (Peroxisome Proliferator Activated Receptor-Gamma) protein. The purpose of the present investigation was to find out the binding affinity studies of various polysubstituted quinolines with PPARγ protein and its in vitro hypoglycemic studies using α-amylase and glucosidase enzyme inhibition assays

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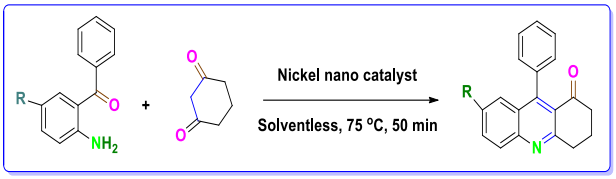
II. MATERIALS AND METHODS

A. Synthesis of Polysubstituted Quinolines

The synthesis of polysubstituted quinolines by the reaction of 2-aminoaryl ketone with enolizable ketone in the presence of nickel nano catalyst was already reported in our previous work [14] (Scheme.1) (Fig.1).



Scheme. 1. Synthesis of polysubstituted quinolines

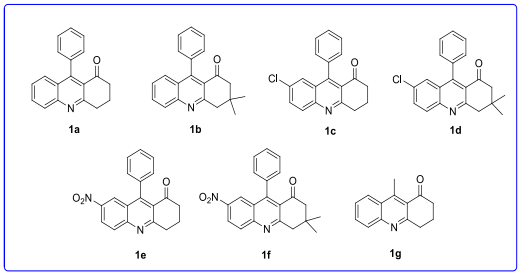


Fig.1.Polysubstituted quinoline analogues

B. Molecular Modelling Studies

The binding affinity of polysubstituted quinoline analogues (1a-g) with PPARγ were analyzed by using Autodock.v.1.5.6. The protein PPARγ was taken from protein data bank (ID: 2XKW). Evaluation of rapid energy was carried out effectively by evaluating atomic affinity potential for individual ligand separately and the energy of interaction of each atom in the ligand was encountered. Finally grid maps were calculated for each ligand separately and docking analysis were carried out by using Lamarckian Genetic Algorithm. In order to predict docking energy for each derivative, Autodock was initiated various times to get several confirmations of docking ligand with the receptor grid. By using Autodock 4.2 scoring functions 5 best confirmations were generated for all ligands. Evaluation of the docking results were done by simultaneously sorting the different complexes with respect to the predicted binding energies.

C. *In Vitro* Hypoglycemic Studies

In vitro hypoglycemic efficacy of the synthesized polysubstituted quinoline derivatives (1a-g) were carried out by using α-amylase and α-glucosidase assays. Patients suffering from type 2 diabetes when treated with drugs that prevent carbohydrate hydrolyzing enzymes has proved to display significant decrease in postprandial blood glucose levels along with increased metabolism of glucose without stimulating secretion of insulin. By using enzyme-starch system the effect of compounds 3a-h on α-amylase activity was studied as per procedure given by Malik and his coworkers [15]. α-glucosidase inhibitors which act as competitive inhibitors of intestinal α-glucosidase can delay the digestion and subsequent absorption of elevated blood glucose levels. A crude enzyme solution of rat intestinal α-glucosidase was employed to assay the α-glucosidase inhibitory activity as per the procedure given by Krishnaveni and her coworkers [16].

- **α-glucosidase inhibition**

A solution containing 1 mL of starch substrate (2 % w/v sucrose or maltose), 0.2 M Tris buffer having pH 8.0 and different concentration of synthesized quinoline products 1a-g were incubated at temperature of 37 °C for a period of 5 min. The reaction was started by the addition of 1 mL α-glucosidase enzyme (1 U/mL) to the above reaction mixture and further incubating at 35 °C for 40 min. After incubation by adding 2 mL of 6 N HCl the reaction was finally terminated. The color intensity developed in the reaction mixture was measured at 540 nm. Then the reaction was terminated by the addition of 2 mL 6 N HCl. The experiment was carried out in triplicate and the percentage inhibition of enzyme activity was calculated as follows

Percentage inhibition (I %) = (Ac-As)/Ac X 100

Where Ac = Absorption of control; As = Absorption of sample

- **α-amylase inhibition**

α-amylase assay was carried out as per the procedure given by Malik and his coworkers by using starch-iodine method. To the reaction mixture various concentration of the synthesized polysubstituted quinoline derivatives 1 a-g (50, 100, 250 µg/ml) was added which initially contains 10 mL of α-amylase solution (0.025 mg/mL), 400 mL of phosphate buffer solution (pH 7.0). After incubation for a period of 10 min at 37 °C, to the reaction mixture 100 mL of starch solution (1 %) was added and further subjected to incubation for 60 min at 37 °C. Later 5 mL distilled water followed by 0.1 mL of 1 % iodine solution was added and the absorbance was recorded at 565 nm. Blank analysis was performed maintaining similar reaction conditions to test solution, reactants and for enzyme α-amylase. The experiment was carried out in triplicate and the percentage inhibition of enzyme activity was calculated as follows

Percentage inhibition (I %) = (As-Ac)/(Ab-Ac) x 100

where, As = absorbance of the sample, Ab = absorbance of blank (without α-amylase) and Ac = absorbance of control (without starch).

III. RESULTS AND DISCUSSION

A. Molecular docking analysis

The protein-ligand based interactions play a crucial role in structural based drug design. The most stable docking conformation of the synthesized polysubstituted quinoline derivatives in complex with PPARγ protein as depicted in Fig.2 evidently specify that the quinoline analogues are having greater binding interactions with the receptor which was compared to that of standards rosiglitazone, and pioglitazone. The results obtained from effective binding interactions of synthesized compounds 1a-g with various amino acids of the protein showed that compound 1c and 1d possess excellent binding interaction towards PPARγ with binding energy of -9.0 k.cal/mol and -8.9 k.cal/mol which was on par to that of standards rosiglitazone (-9.2 k.cal/mol) and pioglitazone (-9.8) whereas compound 1a possess moderate binding interaction with docking score of (-8.7 k.cal/mol) respectively (Table-I). The interaction of compound 1c and 1d with various amino acids of the PPARγ protein was depicted in Fig.3.

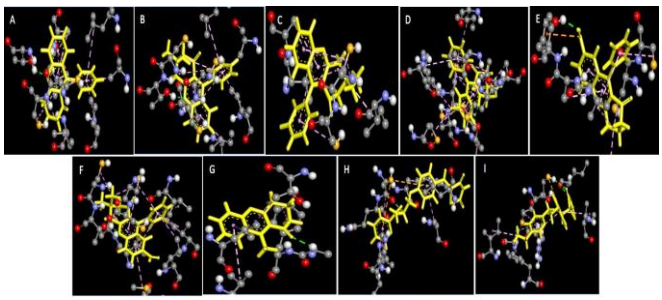


Fig.2. Binding interactions of 1a-g with PPARγ protein [A] Interaction of compound 1a [B] Interaction of compound 1b [C] Interaction of compound 1c [D] Interaction of compound 1d [E] Interaction of compound 1e [F] Interaction of compound 1f [G] Interaction of compound 1g [H] Interaction of standard rosiglitazone [I] Interaction of standard pioglitazone

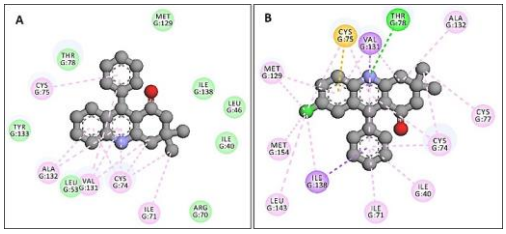


Fig.3. Binding interactions of 1c and 1d with various aminoacids of PPARγ [A] Compound 1c interactions [B] Compound 1d interactions

Table-I: *In silico* molecular docking analysis for hypoglycemic efficacy of the synthesized polysubstituted quinoline derivatives, 1a-g and standards

S.No	Ligand	Autodock Score
1	1a	-8.7
2	1b	-8.5
3	1c	-9.0
5	1d	-8.9
6	1e	-8.1
7	1f	-7.8
8	1g	-8.0
9	Std[a]	-9.2
10	Std[b]	-9.8

[a] Rosiglitazone, [b] Pioglitazone

B. *In Vitro* Hypoglycemic Studies

From *in-vitro* enzyme inhibition analysis towards hypoglycemic activity out of the synthesized quinoline derivatives 1a-g compounds 1c and 1d showed 87.94 ± 0.25 and 85.90 ± 0.56 percent inhibition towards α-glucosidase, 84.55 ± 1.02 and 82.14 ± 0.26 percent inhibition towards α-amylase which was greater than standard rosiglitazone (74.06 ± 0.07, 72.91 ± 0.24) and comparable to pioglitazone (89.28 ± 0.82, 85.36 ± 0.47), Acarbose (91.60 ± 0.18, 87.19 ± 0.55) (see Table-II and Table-III, Fig.3 and Fig.4).

Table-II: α-glucosidase inhibitory efficacy of polysubstituted quinoline derivatives (1a-g)

S.No	Compound	Concentration (µg/ml)		
		50	100	250
1	1a	34.18 ± 0.42	53.29 ± 0.14	85.21 ± 0.62
2	1b	32.16 ± 0.45	51.33 ± 0.69	81.58 ± 0.42
3	1c	35.67 ± 0.30	56.29 ± 0.10	87.94 ± 0.25
4	1d	34.79 ± 0.40	54.75 ± 0.12	85.90 ± 0.56
5	1e	31.20 ± 0.05	50.22 ± 0.72	78.12 ± 0.15
6	1f	30.44 ± 0.95	49.14 ± 0.68	77.43 ± 0.80
7	1g	28.40 ± 0.20	46.55 ± 0.71	73.28 ± 0.10
8	Std1[a]	29.64 ± 0.19	47.24 ± 0.18	74.06 ± 0.07
9	Std2[b]	37.22 ± 0.10	56.78 ± 1.22	89.28 ± 0.82
10	Std3[c]	38.95 ± 0.22	58.10 ± 0.55	91.60 ± 0.18

[a] Pioglitazone; [b] Rosiglitazone; [c] Acarbose

Table-III: α-amylase inhibitory efficacy of polysubstituted quinoline derivatives (1a-g)

S.No	Compound	Concentration (µg/ml)		
		50	100	250
1	1a	32.19 ± 0.62	52.46 ± 1.44	80.11 ± 0.26
2	1b	32.69 ± 0.15	48.72 ± 0.73	78.24 ± 0.18
3	1c	34.47 ± 0.90	53.18 ± 0.85	845.5 ± 1.02
4	1d	34.08 ± 0.23	52.95 ± 0.56	82.14 ± 0.26
5	1e	32.97 ± 0.25	50.02 ± 0.76	79.85 ± 0.17
6	1f	31.76 ± 0.81	48.92 ± 0.10	73.15 ± 0.29
7	1g	31.05 ± 0.62	46.97 ± 0.24	75.31 ± 1.04
8	Std1[a]	28.00 ± 0.68	46.78 ± 0.22	72.91 ± 0.24
9	Std2[b]	34.92 ± 0.55	54.25 ± 1.35	85.36 ± 0.47
10	Std3[c]	36.15 ± 0.28	57.10 ± 0.74	87.19 ± 0.55

[a] Pioglitazone; [b] Rosiglitazone; [c] Acarbose

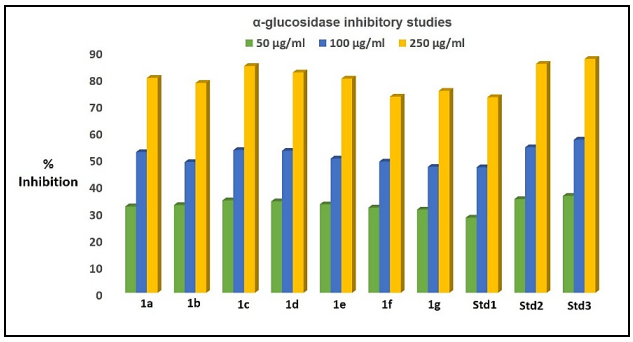


Fig.4. α-glucosidase inhibitory efficacy of polysubstituted quinolines

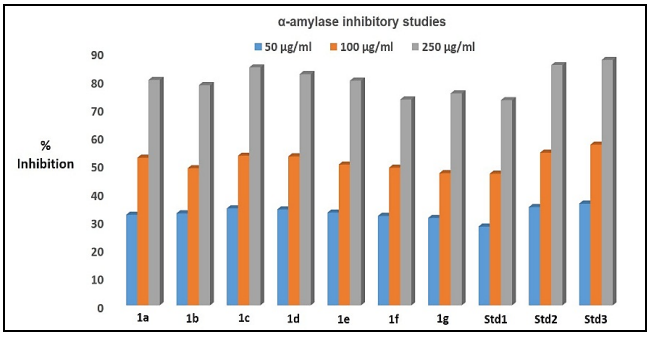


Fig.5. α-amylase inhibitory efficacy of polysubstituted quinolines

IV. CONCLUSION

The pharmacological role of polysubstituted quinolines towards PPARγ was successfully explored for their hypoglycemic efficacy. The results obtained from molecular modelling studies were consistent with in vitro hypoglycemic enzyme assays. In the present generation there is a growing need for effective therapies to achieve optimal glycemic control in the treatment of diabetes. Therefore the results obtained in the present work can be utilized for finding effective therapeutic agents in the management of diabetes.

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