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Synthesis and Molecular Docking of Quinazoline Derivatives as Potential DPP-4 Inhibitors for Type 2 Diabetes Mellitus

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Abstract

Quinazoline derivatives are heterocyclic compounds with significant therapeutic potential, especially as dipeptidyl peptidase-4 (DPP-4) inhibitors, a target for managing Type 2 Diabetes Mellitus (T2DM). This study reports the synthesis of novel quinazoline derivatives through a three-step process involving benzoxazinone precursors and Schiff base formation. The compounds were characterized using infrared (IR) spectroscopy, nuclear magnetic resonance (NMR), and mass spectrometry. Molecular docking studies were performed using AutoDock Vina to evaluate their potential as DPP-4 inhibitors, comparing the binding affinities and interactions of the synthesized compounds with those of sitagliptin, a known DPP-4 inhibitor. Docking results demonstrated favorable binding affinities, with some compounds showing interactions comparable to sitagliptin. These findings indicate that quinazoline derivatives hold promise as therapeutic agents for the treatment of T2DM.

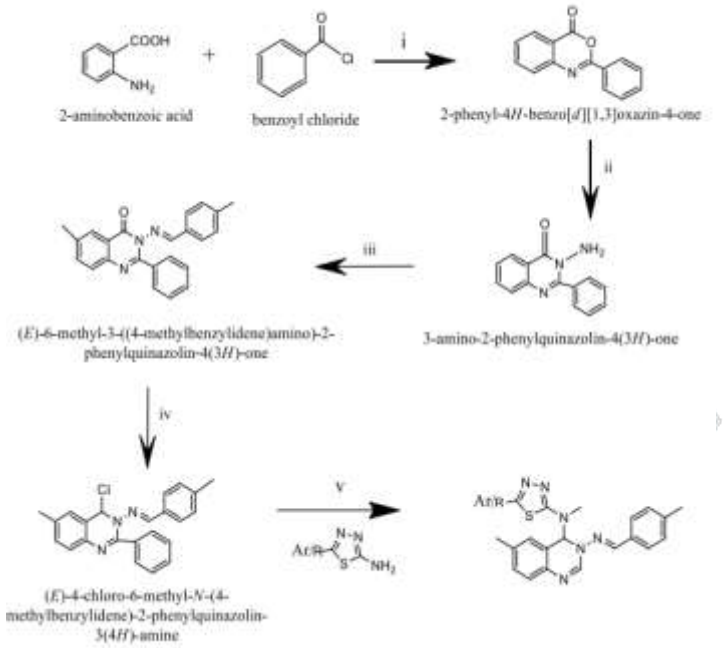
Keywords: quinazoline, heterocyclic compounds, DPP-4 inhibitors, Type 2 Diabetes Mellitus, molecular docking, sitagliptin

1. Introduction

Quinazoline derivatives have been widely studied in medicinal chemistry for their versatile biological activities, including anticancer, antibacterial, and anti-inflammatory properties. In recent years, these heterocyclic compounds have gained attention as potential dipeptidyl peptidase-4 (DPP-4) inhibitors, which are vital in the regulation of blood glucose levels and the management of Type 2 Diabetes Mellitus (T2DM).[1] DPP-4 plays a critical role in glucose homeostasis by degrading incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). Inhibition of DPP-4 prolongs incretin hormone activity, enhancing insulin secretion and reducing blood glucose levels.

This study aims to explore the synthesis of quinazoline derivatives and their potential as DPP-4 inhibitors through molecular docking simulations. By comparing the binding affinities of these derivatives with sitagliptin, a clinically approved DPP-4 inhibitor, we seek to assess their potential for the treatment of T2DM.[2]

2. Materials and Methods



2.1. Synthesis of Quinazoline Derivatives

Step 1: Synthesis of 2-Phenyl-4H-Benzoxazin-4-One

Anthranilic acid (0.1 mol) was dissolved in pyridine (30 mL), and benzoyl chloride (0.02 mol) was added dropwise while stirring at 2-8°C for 1 hour. The reaction mixture was stirred further at room temperature, treated with aqueous sodium bicarbonate to remove unreacted acid, and the resulting solid was filtered, washed, and recrystallized from ethanol.[3]

Physical Properties:

- Molecular formula: C14H9NO2
- Molecular weight: 223.23 g/mol
- Yield: 71%
- Melting point: 124°C
- Solubility: Ethanol, acetone

Step 2: Synthesis of 3-Amino-2-Phenyl-Quinazolin-4(3H)-One

The synthesized 2-phenyl-4H-3,1-benzoxazin-4-one (6.8 g) was refluxed with hydrazine monohydrate (5 mL) in ethanol (60 mL) for 6-7 hours. The solid product was washed with water, filtered, dried, and recrystallized from ethanol.[4]

Physical Properties:

- Molecular formula: C14H11N3O
- Molecular weight: 237.26 g/mol
- Yield: 69%
- Melting point: 159°C
- Solubility: Ethanol, acetone, chloroform

Step 3: Synthesis of Schiff Base Quinazoline Derivatives

The 3-amino-2-phenyl-quinazolin-4-one was reacted with various aromatic aldehydes in ethanol, using glacial acetic acid as a catalyst. The reaction mixture was refluxed for 10 hours, and the solid product was filtered, washed, dried, and recrystallized from ethanol.[5]

Physical Properties of Selected Schiff Base Derivatives:

Compound Code	Substituent (R)	Molecular Formula	Molecular Weight (g/mol)	Yield (%)	Melting Point (°C)
2-a	3-NO2	C21H14N4O3	370.36	71	250-266
2-b	4-Cl	C21H14ClN30	359.81	70	166-170
2-c	H	C21H15N3O	325.36	73	200-205
2-d	4-OH	C21H15N3O2	341.36	75	163-169
2-e	4-N(CH3)2	C23H20N4O	368.43	72	180-185

2.2. Characterization of Synthesized Compounds

The synthesized compounds were characterized using various analytical techniques:

- **Infrared Spectroscopy (IR):** Identified functional groups such as C=O (1600-1430 cm^{-1}), H-C=N (1645-1605 cm^{-1}), NO2 (1527.16 cm^{-1}), and C-Cl (1091.57 cm^{-1}).
- **Nuclear Magnetic Resonance (NMR):** Proton and carbon NMR spectra confirmed the molecular structure of the quinazoline derivatives.
- **Mass Spectrometry (MS):** Molecular weights were confirmed via mass spectrometry.

3. Molecular Docking Studies

3.1. Molecular Docking Methodology

Molecular docking simulations were performed using AutoDock Vina in PyRx to assess the binding affinity of the quinazoline derivatives to DPP-4. The 3D structure of DPP-4 (PDB ID: 1X70) was retrieved from the RCSB Protein Data Bank, and the binding site was identified based on the ligand interactions observed in the crystal structure.[6]

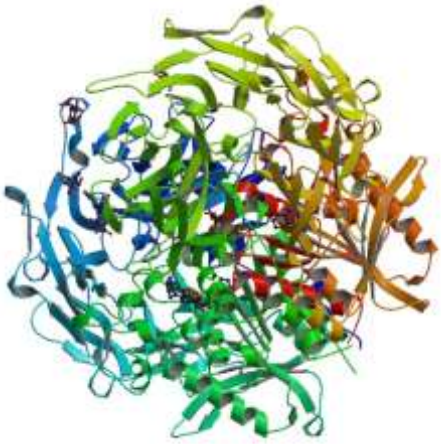


Fig-1. PDB structure of Dipeptidyl peptidase- 4

3.2. Protein and Ligand Preparation

The crystallographic ligand (sitagliptin) was removed from the protein, and water molecules were excluded using AutoDock Tools. Polar hydrogens were added to the protein, and a grid box was centered on the active site. The synthesized ligands were drawn using ChemDraw, minimized in PyRx, and saved in .pdbqt format for docking.[7]

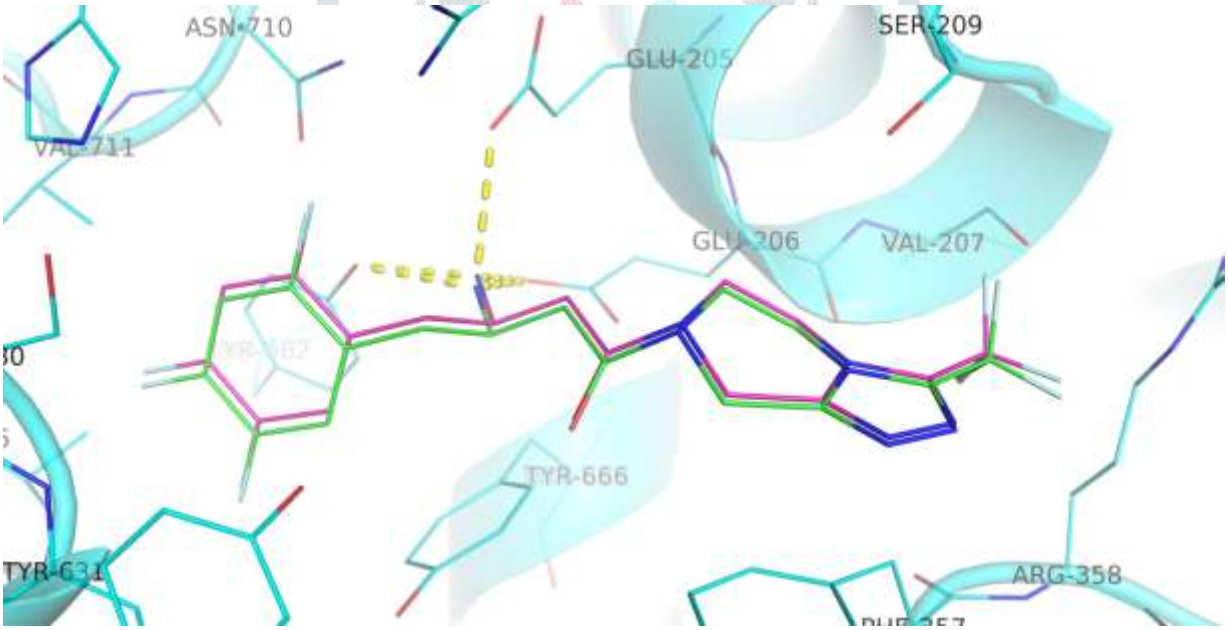


FIG.2. Validation of docking protocol: The interactions of crystallographic ligand (violet carbons) were mimicked by docking of ligand structure (green carbons) in Autodock Vina.

3.3. Docking Procedure

The docking procedure involved placing the ligands in the DPP-4 active site to evaluate their interactions. Multiple conformers were generated for each ligand, and binding energies were recorded.

4. Results and Discussion

4.1. Docking Results

The docking simulations revealed that all quinazoline derivatives displayed favorable binding affinities to the DPP-4 active site. Table 1 summarizes the docking results, showing the binding energies and key interactions for each compound compared to sitagliptin.

Table 1: Docking Results of Quinazoline Derivatives

Ligand	Binding Energy (kcal/mol)	Key Interactions
Compound 2	-8.3	HIS740, ASN710, TYR666
Compound 2a	-8.6	GLU205, HIS740, ASN710, TYR666
Compound 2b	-9.0	TYR666, GLU205, ASN710, HIS740
Compound 2c	-8.8	HIS740, ASN710, GLU205, TYR666
Compound 2d	-8.5	ASN710, GLU205, TYR666, HIS740
Compound 2e	-8.7	GLU205, ASN710, TYR666, HIS740
Sitagliptin	**-9.9**	ASN710, GLU205, TYR666, HIS740

4.2. Interpretation of Results

The strongest binding affinity was observed for compound 2b (-9.0 kcal/mol), with interactions similar to those of sitagliptin (-9.9 kcal/mol), which suggests that compound 2b could be a promising DPP-4 inhibitor. The key interactions between the quinazoline derivatives and DPP-4 involved hydrogen bonding and hydrophobic interactions with critical residues, including GLU205, HIS740, ASN710, and TYR666.[8]

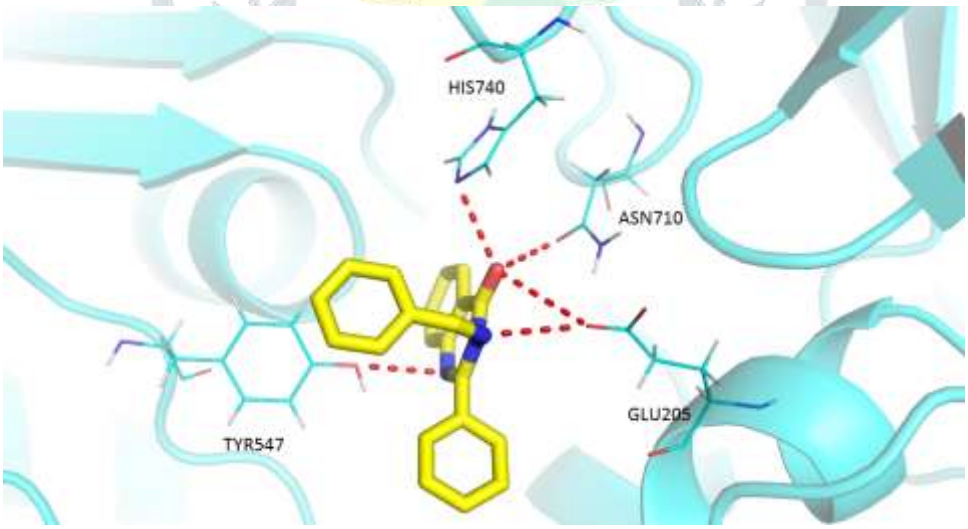


FIG.3:Compound-02 (B) Interactions with amino acid residues in the active site (B) Alignment with the crystallographic ligand (Sitagliptin) in the active site

5. Conclusion

In this study, a series of novel quinazoline derivatives were successfully synthesized and characterized through various analytical techniques. The reaction of anthranilic acid with benzoyl chloride yielded 2-phenyl-4H-3,1-benzoxazin-4-one via an N-acylation and

dehydrative cyclization mechanism. This intermediate was subsequently converted to 2-phenyl-3-aminoquinazolin-4(3H)-one using hydrazine hydrate. The final products, 3-(benzylidene amino)-2-phenylquinazolin-4(3H)-one derivatives, were synthesized by reacting 2-phenyl-3-aminoquinazolin-4(3H)-one with various substituted aromatic aldehydes, resulting in a series of 2,3-disubstituted quinazoline derivatives.

The compounds were purified through recrystallization in ethanol, and their purity was confirmed using thin-layer chromatography. Characterization was carried out using IR and NMR spectroscopy, where IR analysis showed peaks corresponding to functional groups such as C=O (1600-1430 cm^{-1}), Ar-C-H bending (684.76 cm^{-1}), C-H aliphatic (2976-2850 cm^{-1}), NO2 (1527.16 cm^{-1}), and C-Cl (1091.57 cm^{-1}). The NMR spectra confirmed the quinazoline core with characteristic peaks, including N=C-N (9.04 ppm) and aromatic protons (7.57-8.15 ppm).

The molecular docking studies demonstrated favorable binding affinities of these quinazoline derivatives with the DPP-4 enzyme, indicating their potential as inhibitors for managing Type 2 Diabetes Mellitus. In particular, compound 2b exhibited the highest binding affinity, comparable to that of sitagliptin, a known DPP-4 inhibitor.

6. Conflict of interest:

The authors have no conflicts of interest regarding this investigation.

7. Acknowledgement:

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