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INTEGRATED EXPERIMENTAL AND COMPUTATIONAL INVESTIGATION OF A QUINOLINE-2-CARBOXYLIC ACID–3-AMINOACETOPHENONE COMPLEX: SYNTHESIS, CHARACTERIZATION, AND BIOLOGICAL EVALUATION

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ABSTRACT

The present research work deals with Quinoline Carboxylic Acid-3-Aminoacetophenone [QCAP] Complex synthesis and its inhibition against anti-diabetic activity with acarbose was compared. The same complex was characterized by FT-IR, 1H NMR, 13CNMR and UV-visible spectroscopic methods. Molinspiration and pre- ADMET are used to support the drug-likeness and prediction of biological activity. The experimental findings demonstrated promising biological activity, which was further supported by density functional theory (DFT) calculations and molecular docking studies. The computational results provided additional insights into the electronic properties, molecular stability, and ligand–target interactions of QCAP. In particular, the carboxylic acid and carboxylate functional groups appear to play a significant role in mediating molecular interactions with biological targets, thereby contributing to the observed bioactivity. These findings collectively suggest that QCAP possesses favorable structural and electronic characteristics for potential biological applications.

1. INTRODUCTION

3-Aminoacetophenone is one of the aromatic carbonyl compounds which shows high photochemical characteristics and has melting temperature of 96–98 °C. The compound has also been stated to show anesthetic properties. 3′-Aminoacetophenone has been studied for its biological properties, such as HIV inhibition and interaction with the human A2B adenosine receptor [1–5]. It is also said to behave as xenobiotic, photosensitive substance, and animal metabolite. Derivatives of acetophenone have drawn much interest in the field of pharmacology, owing to their multiple biological properties.

The existence of a carboxyl group (-COOH), which comprises carbon, oxygen, and hydrogen atoms, is the characteristic feature that differentiates the carboxylic acid family of organic compounds. Pharmacology and biological systems rely on this particular family of organic compounds. As an example, ibuprofen is one of the common non-aspirin analgesics and anti-inflammatory agents from the carboxylic acid family of compounds. Fatty acids comprise yet another important family of carboxylic acids, which are characterized by long hydrocarbon chains that have a terminal methyl group along with a carboxylic acid functional group. They play vital roles in the biological functions and structures involving lipids and energy storage.

Considering the biological significance of carboxylic acids and 3-aminoacetophenone, the synthesis of new compounds incorporating these functional groups is of considerable interest in the fields of bioactivity and drug discovery [6–11]. The formation of a new molecular complex can result in physicochemical and biological properties that differ significantly from those of the individual parent compounds. Such structural modifications may enhance the pharmacological potential and biological activity of the resulting compound.

In the present study, a quinoline carboxylic acid compound (QCAP) was synthesized from 2-quinaldic acid and 3-aminoacetophenone. FT-IR, UV-visible spectroscopy, 1H NMR, and 13C NMR were used to describe the produced chemical. Its anti-inflammatory and anti-diabetic properties were assessed and contrasted with those of conventional medications. Moreover, α-amylase enzyme (with the PDB ID 1HNY) was used for docking analysis of QCAP in order to evaluate the manner of binding and the most beneficial position of QCAP in the active site of the enzyme.

The optimized molecular structure and electronic characteristics of the synthesized chemical were also examined using density functional theory (DFT) simulations. The Gaussian 09W software tool was used to optimize the molecular shape and examine the electronic factors linked to possible reactive and inhibitory sites. The molecular docking results indicated that QCAP interacts with the α-amylase enzyme through hydrogen bonding and exhibits a favorable binding interaction with the enzyme. The experimental and computational results suggest that QCAP possesses promising antidiabetic activity and may serve as a potential candidate for further investigation in the development of bio-active compounds.

2. MATERIALS AND METHODS

2.1 Materials

The process outlined below was used to synthesize QCAP. Throughout the synthesis and for later biological and associated studies, analytical-grade solvents and double-distilled water were utilized. Thin-layer chromatography (TLC) was used to track the reaction's progress using silica gel 60F254 plates. The reaction spots were visible under ultraviolet (UV) light at 254 and 366 nm.

2.2 Synthesis of QCAP

Ethanol was added as a solvent to a combination of 2-quinaldic acid and 3-aminoacetophenone. To guarantee complete mixing and reaction, the reaction mixture was constantly swirled for thirty minutes. The QCAP product was then obtained by evaporating the solvent. The resulting product was obtained in good yield without further purification and was collected for subsequent characterization and analysis. The Structure of QCAP is shown in Fig. 1.

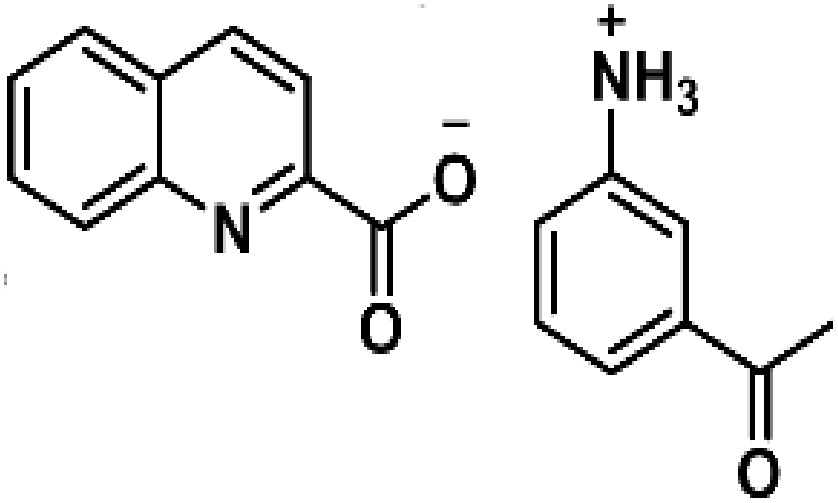

Fig. 1 Structure of QCAP

A mixture containing 1.0 mmol of quinoline-2-carboxylic acid and 3-aminoacetophenone was dissolved in 5.0 mL of ethanol and stirred continuously for approximately 30 min to ensure complete dissolution and homogeneous mixing. In order to promote the development of QCAP, the resultant mixture was left to stand at room temperature for ten minutes. The purified QCAP chemical was then prepared by recrystallization of the crude product using ethanol as the solvent.

3. Result and Discussion

3.1 Spectroscopic Results

The Bruker NMR instrument was used for recording of 1H NMR of 300 MHz and 13C NMR of 75 MHz, with TMS as an internal standard and CDCl3 and DMSO-d6 as solvent and these are shown in Fig. 3 and 4. The Shimadzu UV-1800 UV-Vis spectrophotometer was used to detect UV-Vis absorption (for biological investigations), and a Thermo Scientific Nicolet iS50 FT-IR was utilized to acquire FT-IR spectra and a spectrometer was employed. The following spectrum Fig.2 shows the UV-Vis of QCAP.

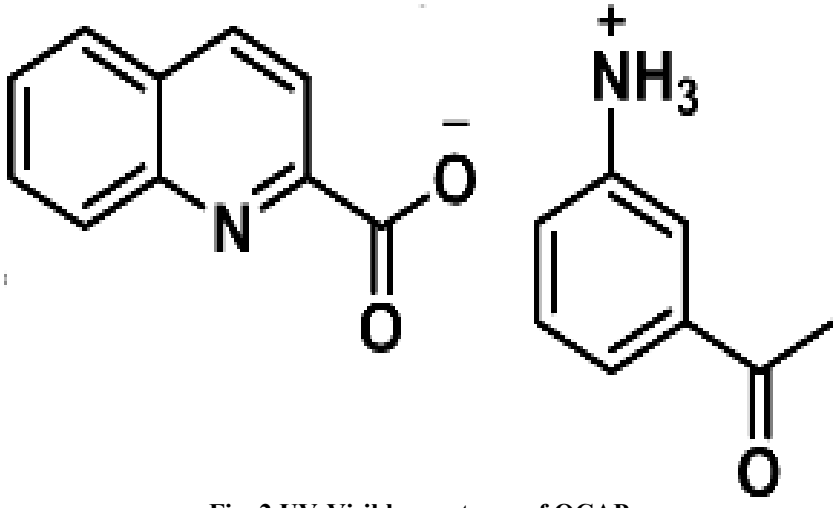

Fig. 2 UV-Visible spectrum of QCAP

1H NMR (300 MHz, CDCl3) δ 8.42 (d, J = 8.3 Hz, 1H), 8.28 (d, J = 8.4 Hz, 1H), 8.17 (d, J = 8.4 Hz, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.85 (t, J = 7.6 Hz, 1H), 7.78 - 7.68 (m, 1H), 7.37 - 7.22 (m, 3H), 6.88 (d, J = 7.7 Hz, 1H), 5.16 (s, 3H), 2.56 (s,

3H) ppm. 13C NMR (75 MHz, CDCl3) δ 198.51, 164.40, 146.62, 145.93, 145.74, 138.84, 138.10, 131.01, 129.85, 129.35, 129.11, 127.82, 119.70, 119.20, 118.85, 114.03, 26.68 ppm is indicated as Fig. 3.

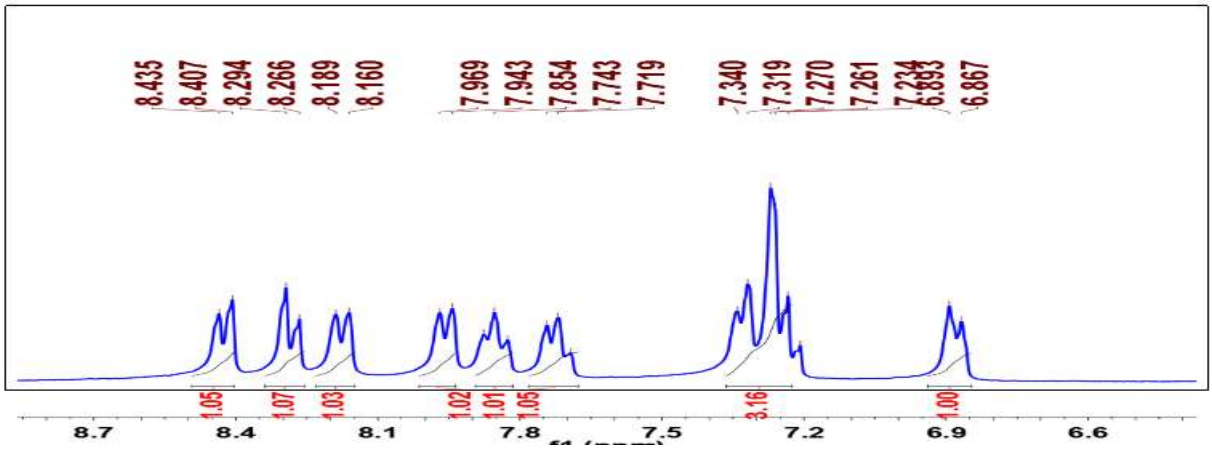

Fig. 3 1H NMR (300MHz, CDCl3) expansion of QCAP

All these signals, especially 7.68, 7.85, 7.96, 8.17, 8.28, and 8.42 ppm, exhibit the occurrence of quinoline units. The 13C NMR signals confirm the molecular structure of the complex. 114.03, 118.85, 119.20, 119.70, 127.82, 129.11, 129.85, 131.01, 138.10, 138.84, 145.74, 146.62, 164.40, 198.51 ppm indicates the existence of a quinoline unit is attached as Fig. 4.

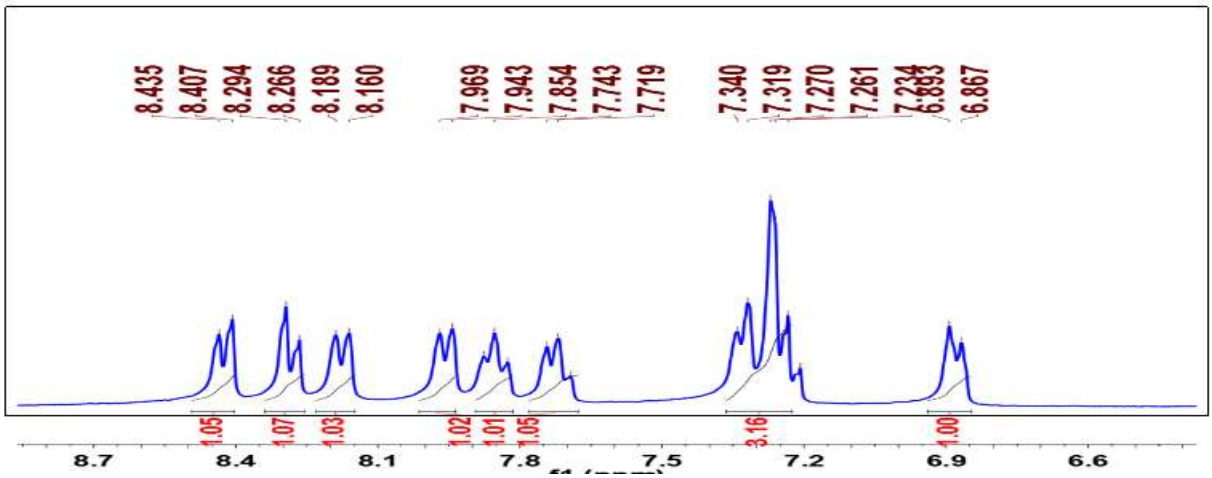

Fig. 4 1C NMR (300MHz, CDCl3) expansion of QCAP

A popular analytical method called Fourier-transform infrared (FT-IR) spectroscopy uses infrared electromagnetic radiation to detect and describe the functional groups in a sample using their distinctive vibrational frequencies is shown in Fig. 5.

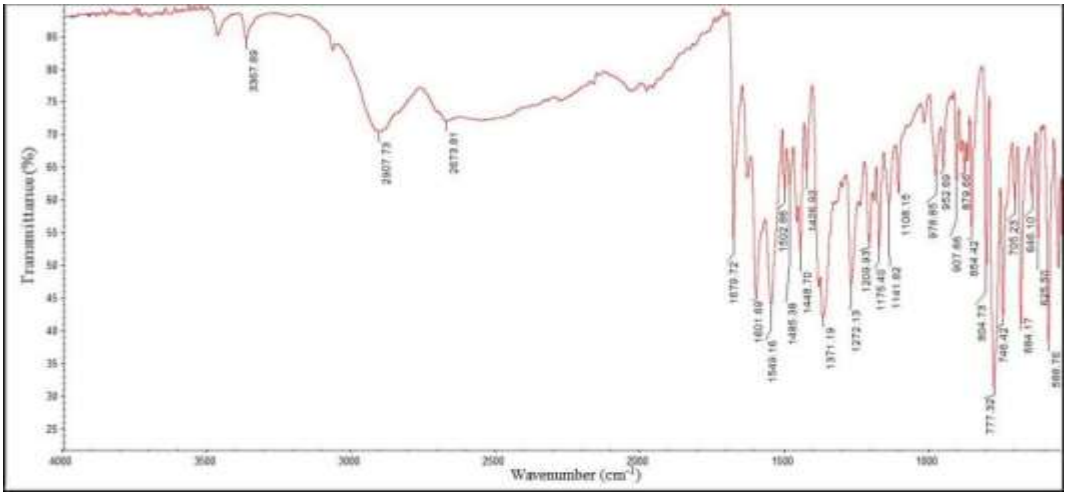

Fig. 5 FT-IR spectrum of QCAP

3.2 Biological Studies

3.2.1 Antidiabetic Activity

α-amylase is a key digestive enzyme which is produced in the pancreas and salivary glands [12]. α-amylase acts on the digestion of food starch to form oligosaccharides such as disaccharides and trisaccharides, which are further broken down to glucose molecules by other digestive enzymes. The glucose thus formed is one of the key sources of energy in the body. In type 1 diabetes mellitus, there is poor insulin production in addition to poor blood glucose regulation owing to the autoimmune destruction of pancreatic β cells. Diabetes mellitus is a common disease affecting a large number of individuals around the world.

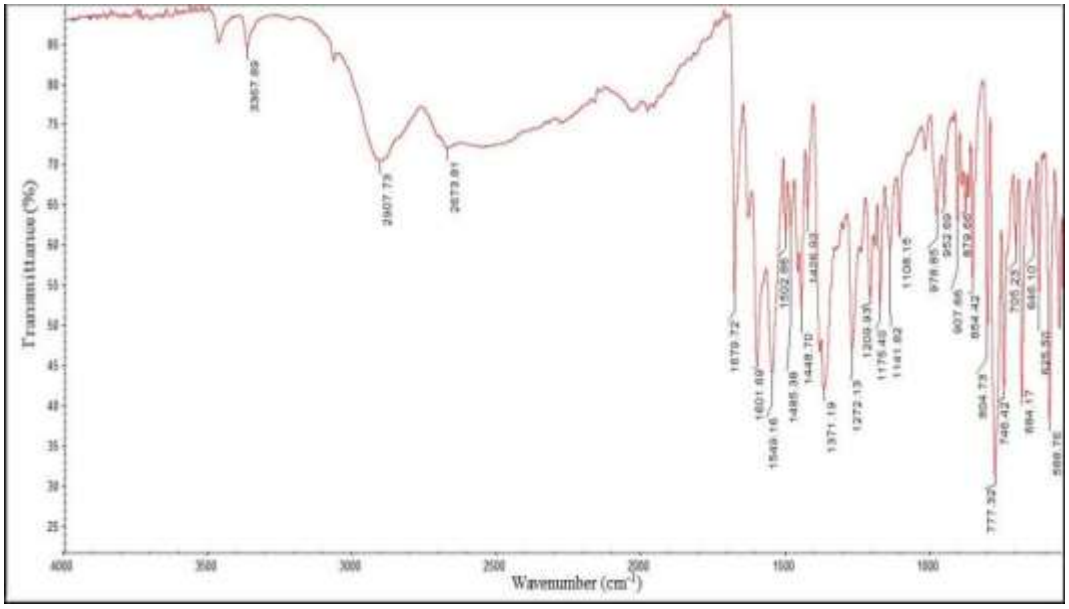

Fig. 6 Antidiabetic activity (α-Amylase inhibitory activity)

The α-amylase enzyme is frequently used via the inhibition approach to assess the in vitro anti-diabetes efficacy of bioactive molecules or plant extracts. Despite the current effectiveness of antidiabetic drugs, especially α-glucosidase (GLS) inhibitors, in managing postprandial hyperglycemia, their strong and non-specific inhibition of the pancreatic α-amylase could potentially cause gastrointestinal side effects that would limit the clinical application of such drugs [13-15]. As a result, much effort has been made to develop safer and selective antidiabetic drugs. Apart from the traditional treatment approaches, antioxidant and antiglycation drugs have been explored for their possible role in the treatment of diabetes mellitus and its complications [16]. Curcuma longa (turmeric), one of the natural sources, has shown promising antidiabetic and preventive properties against diabetes mellitus [17,18].

3.2.1.1 α-Amylase inhibitory activity

The pancreatic α-amylase enzyme hydrolyzes starch into small molecules, which are later converted into glucose. The inhibition of α-amylase is known to decrease the rate of starch hydrolysis and lower postprandial blood glucose concentration. The α-amylase inhibition test was employed to determine the antidiabetic properties of the synthesized QCAP compound in vitro. The acarbose drug, an already clinically approved α-glucosidase inhibitor, was selected as the reference standard treatment [19].

The percent inhibition shown by QCAP has been compared with the standard drug acarbose, and the results have been shown in Fig. 6. QCAP showed considerable inhibition against α-amylase at various concentrations, and it is possible to use this compound as a potential anti-diabetic drug. This activity was further supported by the molecular docking results which showed favorable binding of QCAP with the α-amylase active site. The carboxylic acid/carboxylate capabilities may increase hydrogen bonding interactions with amino acid residues in the enzyme-binding pocket.

The in vitro α-amylase inhibition assay involved pre-incubating α-amylase (0.5 mg/mL) with the test drug or standard acarbose for 10 minutes at 25 °C. The process was conducted in a 20 mM sodium phosphate buffer (pH 6.9) [20]. After pre-incubation, 1 mL of 1% starch solution was introduced into the reaction mixture and incubated, in 25 °C temperature for 30 minutes. Enzymatic activity was quenched by introducing 1 mL of DNSA reagent and heating in boiling water for 15 minutes to generate the characteristic color [21]. Then, the reaction mixture was allowed to cool down to room temperature, and absorbance was measured using UV-Vis spectrophotometer at 266 nm, indicating the presence of Aromatic group and 540 nm shows Aminoacetophenone. Absorbance values for the test samples were compared to that of control, and percentage inhibition of α-amylase activity was determined.

3.3 Computational Studies

3.3.1 Drug-likeness: ADME Calculation

Using the ADME calculation, we can determine whether the synthesized compound can be used for the primary stage of drug discovery. All the parameters are satisfying as per Lipinski's rule (Ro5) for the synthesized QCAP. Next, the hydrogen-bond donor or acceptor counts are 1 and 5, respectively. The molecular weight is 308.33, and there is only one

rotatable bond. So, it shows the structure is stable. Then, Log P and TPSA are 2.24 and 97.2 Å2. All the violations for the compounds are obtained as zero. Also, the number of atoms is less than 70.
The physicochemical profile of the quinoline-2-carboxylic acid–3-aminoacetophenone (QCAP) complex was evaluated using a bioavailability radar based on six important molecular properties: lipophilicity, molecular size, polarity, water solubility, saturation, and molecular flexibility. The resulting radar profile was predominantly located within the optimal region, indicating a favorable balance among these physicochemical parameters. This profile indicates that QCAP is a promising drug like compound and might have good oral bioavailability. However, all these assumptions have been made by using computational physicochemical properties and need to be tested experimentally.

LIPO (X log P3)	: Optimal range −0.7 to +5.0
SIZE (MW)	: 150–500 g/mol
POLAR (TPSA)	: 20–130 Å²
SOLUBILITY (log S)	: Not poorly soluble
FLEX (Rotatable bonds)	: ≤ 9
SATURATION (Fraction Csp³)	: ≥ 0.25

The QCAP complex shows partial ionic behavior due to the presence of ionizable carboxyl and protonated amine groups. This could increase the solubility of the complex in water and help with pH-stability. The predicted solubility profile of the complex at mildly acidic to physiological pH values indicates that the complex will have good aqueous behavior, which would favor oral availability. However, experimental results will be necessary for confirmation.

3.3.2 Molecular Docking Studies
Computer-aided techniques are becoming an integral part of drug discovery, where they are usually termed in silico techniques, in order to assist in the identification and optimization of possible candidates for drug molecules. Computational methods allow one to predict the interaction between the protein and the ligand molecule even before conducting any

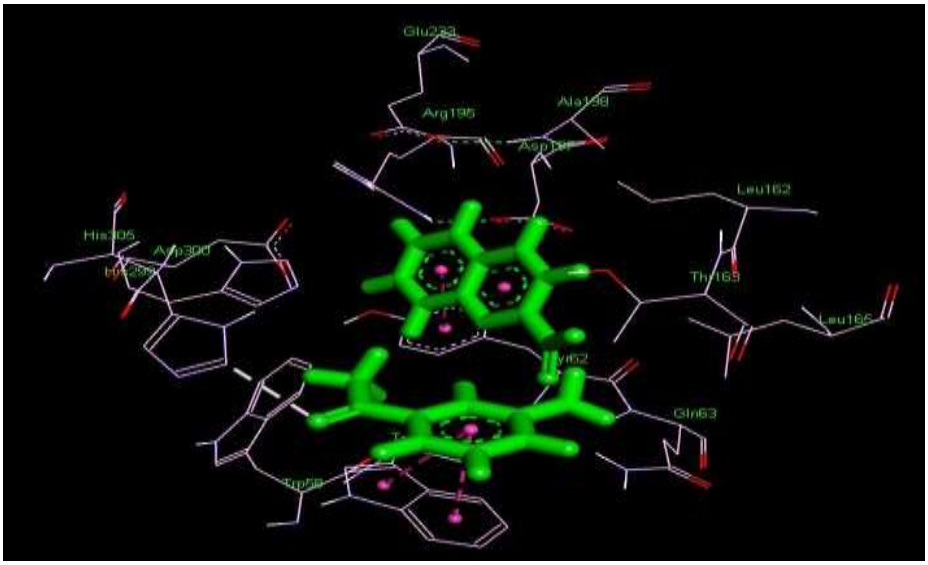

Fig. 7 Interaction of QCAP with 1HNY

experiment (Stroud & Finer-Moore, 2007). Consequently, computational drug-design techniques have become an important component of contemporary and emerging drug-discovery pipelines, particularly in the investigation of complex diseases such as HIV infection, cancer, tuberculosis, malaria, and other infectious and non-communicable diseases.
Hex 8.0 software was used to dock the generated compound with the α- amylase enzyme [22]. ChemDraw 12 (MMFF94, 5000 interactions) efficiently minimizes the 3-dimensional structure employed in the docking procedure. A three-dimensional crystal structure of α-amylase enzyme (1HNY.pdb) was obtained from the Protein Data Bank (pdb). The docking step involved substituting polar hydrogen and removing ligand-bound water from the enzyme. The three-dimensional structure of the enzyme α-amylase was obtained from the Protein Data Bank. (1HNY.pdb). During docking, the polar hydrogen was swapped out, and all ligand-bound water was subsequently removed from the enzyme.
Drug discovery using computer-aided methods is one of the popular methods in drug design [23]. We know that the ligand with the biomolecule of the known 3D structure was used to predict the primary binding modes. The α-amylase (1HNY.pdb) was docked [24] to the optimal molecular configuration and 3D structure. The compound has a -288.60 kJ/mol binding energy. The carbon hydrogen bonding interface with Imidazole CH of HIS305 was found and shown in Fig. 7. The bonding distance is determined as 3.20 Å.
Molecular docking research showed that QCAP interacts well with amino acids present in the active region of the 1HNY protein. A carbon-hydrogen (C-H···O) contact was found between the ligand's oxygen atom and the imidazole C-H group

of HIS305. This connection helped stabilize the ligand-protein complex. QCAP's aromatic rings and TRP59's indole ring exhibited π-π stacking interactions at distances of 4.58 and 4.64 Å, respectively. Further aromatic stacking was identified between the quinoline ring of QCAP and the phenyl ring of TYR63, with a π–π interaction distance of approximately 4.44 Å. These hydrogen-bonding and aromatic interactions may contribute to the favorable binding orientation and stability of QCAP within the active site of the 1HNY protein.

3.3.3 Computational Calculations using Density Functional Theory (DFT)

The Gaussian 09W program was used in Density Functional Theory for HOMO and LUMO calculations. The DFT method is used to calculate the complex method to optimize the chemical structure of the QCAP using B3LYP/6-311 G basis set. So, to view the computed HOMO and LUMO structures, and Molecular Electrostatic Potential (MEP), Gauss view software was used.

The complex has strong chemical stability while maintaining enough reactivity for enzyme interaction, as indicated by the moderate HOMO–LUMO energy gap and global hardness values. These findings are consistent with the established inhibitory actions of α-amylase.

In this case, Table 1 provided the binding energy, hydrogen bonds, and hydrogen-bonded amino acid residue. Fig. 8 shows the Optimized structure of QCA.

Table 1 Molecular docking interaction of QCAP against α-Amylase

Compound Name	1HNY		
	Binding Energy (kJ/mol)	Number of hydrogen bonding	Hydrogen bonded amino acid residue
QCAP	-288.6	1	HIS305 (3.20 Å)

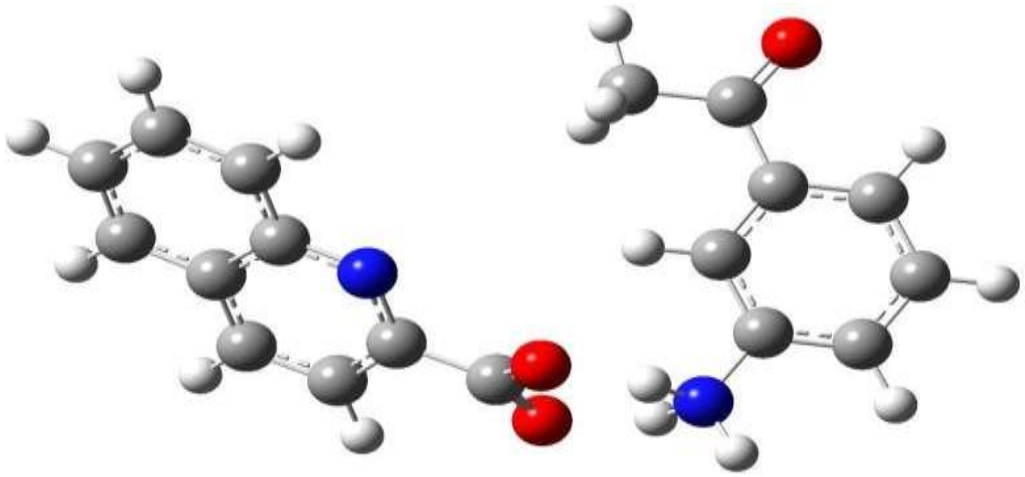

Fig. 8 Optimized structure of QCAP

3.3.4 Molecular Electrostatic Potential (MEP)

While illustrating MEP, various charges are represented by distinct colours [25]. The positive potential as represented in blue can attract proton. Negative potential is ready to repel the proton, which is shown in red, and the green represents zero potential. The ligand and biomolecule interactions were determined by the MEP. MEP's negative potential plays a significant role in hydrogen bonding with proteins [26]. Figure 9 depicts the molecular electrostatic potential of QCAP.

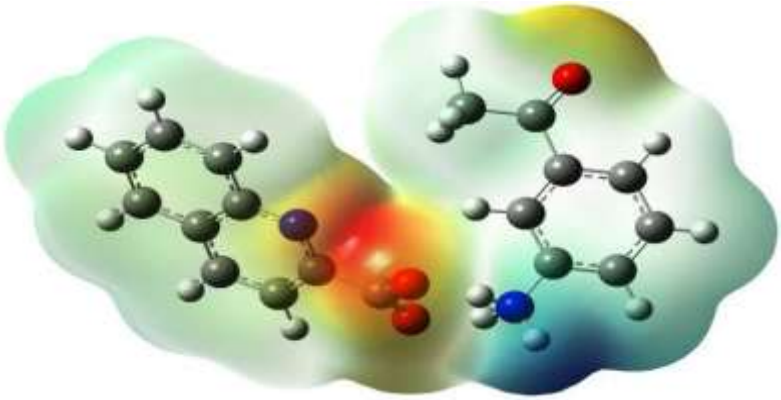

Fig. 9 Molecular Electrostatic Potential of QCAP

Carboxylate and carboxylic acids have a negative potential (red) and interact with biomolecules thru hydrogen bonding [27-28]. The molecular docking data also show hydrogen bond interactions.

3.3.5 Frontier Molecular Orbital (FMO)

In the process of producing stability and reactivity in the complex, the HOMO and LUMO have a vital role. The HOMO energy gives the electron-donating ability, whereas LUMO energy helps with electron- withdrawing ability [29]. The QCAP optimized structure is exhibited in Fig. 8.

There is no regular alteration regarding the electron contribution- donating nature of the complex. In the quinoline portion of QCAP, the HOMO has more electron concentration, whereas the LUMO has more electron concentration in the carboxylate unit [18], as shown in Fig. 10. So, in the QCAP complex, higher electron concentrations are observed in the area of the carboxylate unit and carboxylic acid moiety. Due to high negativity, both the carboxylate and carboxylic acid regions form hydrogen bonding linkages with a biomolecule. Because the carboxylic acid and carboxylate moieties aid in improving the α-amylase enzyme and hydrogen bond interaction, similar results are obtained during molecular docking studies.

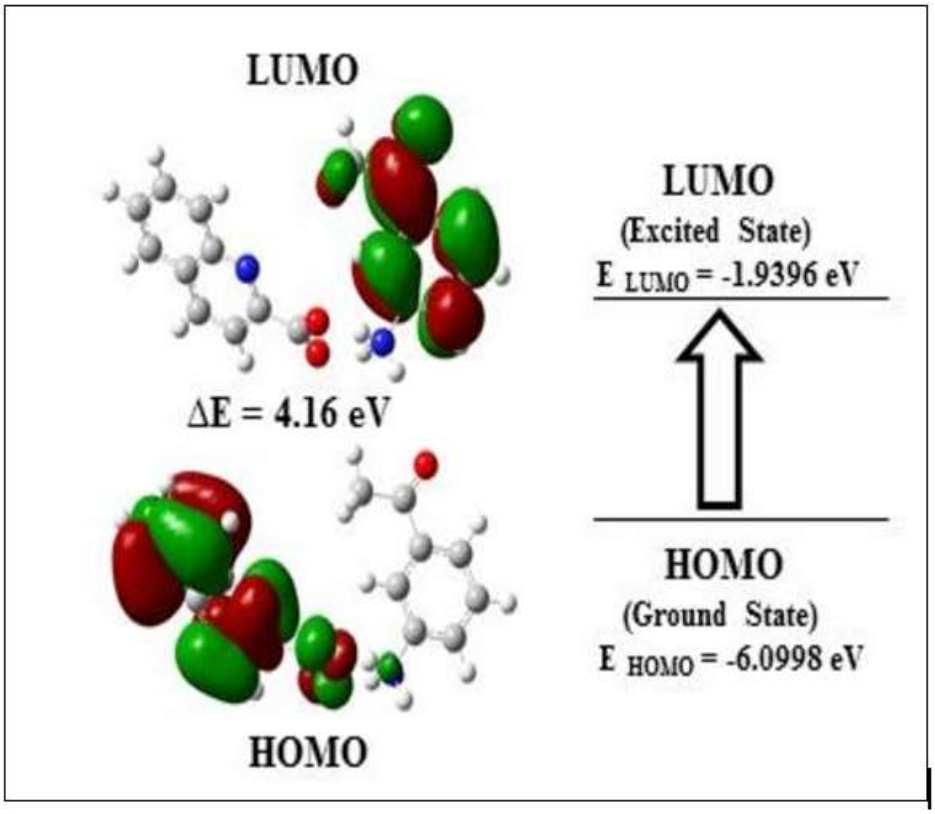

Fig. 10 Frontier Molecular Orbital of QCAP

The stability and chemical reactivity of the molecule is now determined by bandgap (ΔE). The bandgap and the reactivity of the molecule are inversely proportional to each other [30]. Here, the complex bandgap value is measured to be higher (4.160 eV) and hence the complex can be considered as a less reactive molecule with considerable biological activity. Also, using the bandgap, the parameters like electrophilicity index, chemical hardness, and chemical softness are determined [31-32]. The binding capacity and stability of biomolecules can be explained through these parameters. Global softness, global hardness, and global chemical potential lie within a range of -4.0197, 2.0800, and 0.2403, respectively.

An electron is attracted from the environment through the electrophilicity index. The molecules with a higher electrophilicity index [33] tend to interact more with biomolecules. The QCAP has a good electrophilicity index value (3.8840). In molecular docking experiments, the QCAP makes a significant number of interactions with the α-amylase enzyme, as expected [34]. The synthesized QCAP Frontier Molecular Orbitals are shown in Fig. 10.

4 CONCLUSIONS

The QCAP compound was successfully synthesized and comprehensively characterized using spectroscopic techniques. The experiment results showed 65% inhibition by QCAP in comparison to the control drug acarbose which clearly demonstrates that there is a high in-vitro antidiabetic potential. The predicted ADME properties were in accordance with Lipinski's rule of five.

The computational studies have confirmed the results obtained from the experiments. The electrical behavior and reactivity of QCAP is explained by DFT analysis and molecular docking study reveals the great interactions between drug

and target protein. The molecular and electronic properties are represented by the calculated binding energy (−288.6 kcal/mol) and the HOMO-LUMO energy gap (4.160 eV).
Overall, the results suggest that carboxylic acid/carboxylate functional groups are involved in the molecular interaction of QCAP. The combined results of the experiment and the calculations suggest that QCAP could be a good candidate for further testing and evaluation as a potential drug for diabetes and inflammation. Nevertheless, further biochemical and pharmacological evaluations should be performed.

Declaration of Competing Interest
No funds, grants, or other support was received.

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