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Exploring 2-(Furan-2-yl) Quinoline-4-Carboxylic Acid: Synthesis, Characterization, Biological and Electrochemical Analaysis

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KEYWORDS

FQCA. Isatin, Quinoline, Cyclic voltammetry, Glassy carbon electrode, Tuberculosis, MABA.

ABSTRACT:

Employing Isatin as the precursor and 2-acetylfuran within an alkaline medium, the present investigation sought to synthesize a lead-optimized heterocyclic compound, specifically 2-(furan-2-yl) quinoline-4-carboxylic acid. The structural confirmation of the synthesized derivatives was achieved through the application of Mass spectrometry, 13C-NMR, and 1H-NMR spectroscopy. The cyclic voltametric technique was employed to scrutinize the electrochemical characteristics of the aforementioned 2-(furan-2-yl)quinoline-4-carboxylic acid. A glassy carbon electrode facilitated the examination of the impacts of concentration variations and scan rates. The entire electrode process was governed by diffusion control mechanisms. A proposed mechanism for the electrode reaction was formulated.

The in vitro anti-tuberculosis activity was assessed utilizing the Microplate Alamar Blue assay methodology for the synthesized compounds, which exhibited good minimum inhibitory concentration (MIC) comparable to that of the standard antitubercular agents streptomycin, pyrazinamide, and ciprofloxacin; thus, the compound demonstrated promising activity relative to the established standards.

1. Introduction

Quinoline derivatives play a significant role in medicinal and analytical chemistry research, attributed to their wide-ranging pharmacological and electrochemical characteristics. Among these, 2-(furan-2-yl) quinoline-4-carboxylic acid (FQCA) emerges as a distinctive compound with promising applications in biological and electrochemical investigations, owing to its redox-active properties. The comprehensive synthesis, characterization, and interdisciplinary study of FQCA underscore its relevance in both therapeutic and electrochemical fields. [1, 2].

Quinoline, a heterocyclic compound characterized by the molecular formula C9H7N, was first separated from coal tar by Friedlieb Ferdinand Runge in 1834 [3]. The derivatives of this substance are widely recognized for their extensive bioactivities, encompassing anticancer, antibacterial, antifungal, antimalarial, and anti-inflammatory effects [4–6]. The intrinsic structural adaptability of quinoline facilitates comprehensive modifications, fostering the creation of innovative compounds with improved biological and electrochemical properties. Notably, the incorporation of a furan ring and a carboxylic acid group in FQCA enhances its pharmacological efficacy and redox activity, establishing its potential for further exploration [7, 8].

The study details a synthesis protocol for FQCA, which involves the condensation of isatin with 2-acetylfuran, followed by cyclization and acidification. This approach achieves a 71% yield of the desired compound, validated using spectroscopic techniques such as ^{1}H NMR, ^{13}C NMR, and mass spectrometry [9]. Structural characterization of FQCA reveals distinct proton and carbon environments, with peaks indicative of the quinoline, furan, and carboxylic acid functional groups. These detections are essential for confirming the compound's identity and purity, thereby establishing its

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relevance for biological and electrochemical investigations [10].

The electrochemical characterization of FQCA using cyclic voltammetry (CV) offers valuable insights into its redox behaviour and potential applications in catalysis and sensor development. CV, a highly effective electroanalytical technique, measures current as a function of applied potential, offering a huge understanding of the reaction mechanisms of electroactive species and electron transfer processes [11]. Experiments with FQCA conducted on a glassy carbon electrode (GCE) indicate a diffusion-controlled electrode process, exhibiting well-defined oxidation and reduction peaks. Further exploration of the redox kinetics and thermodynamics through scan rate and concentration-dependent studies facilitates hypotheses regarding the electrode mechanism [12]. The enhanced sensitivity observed with modified electrodes, such as SnCuO NPs MGCE, underscores FQCA's potential for advanced electrochemical sensing applications [13].

The biological assessment of FQCA, particularly its anti-tuberculosis (anti-TB) potential, represents a pivotal aspect of this investigation. Tuberculosis (TB), caused by Mycobacterium tuberculosis, remains a persistent global health concern, involving the identification of novel therapeutic agents [14]. The inhibitory effects of FQCA against M. tuberculosis are evaluated using the microplate Alamar blue assay (MABA), with its efficacy compared to established drugs such as streptomycin, pyrazinamide, and ciprofloxacin [15]. Findings reveal that FQCA demonstrates comparable activity to these standards, with a minimum inhibitory concentration (MIC) ranging from 3.12 to 6.25 µg/mL. This encouraging anti-TB activity highlights FQCA's potential as a lead compound for further stages of drug development [16].

Molecular docking studies provide a theoretical perspective on FQCA's interactions with target proteins. Simulations indicate that FQCA forms stable complexes with selective amino acids in M. tuberculosis enzyme binding sites through hydrogen bonding, π-alkyl stacking interactions, and van der Waals forces [17]. The compound's high binding affinity and specificity, reflected in a binding energy of -9.3 kcal/mol, further corroborate its promise as an anti-TB agent [18].

This research adopts an integrated approach by combining synthetic chemistry, spectroscopic characterization, electrochemical evaluation, and biological assessment to develop a compound with both therapeutic potential and applications in electrochemical devices and sensors [19]. FQCA's dual role as a bioactive compound and an electroactive species underscores its versatility and broadens its interdisciplinary research relevance [20]..

In summary, this study emphasizes the significance of quinoline derivatives, particularly FQCA, in enriching the fields of medicine and electrochemistry. It establishes a robust foundation for forthcoming investigations to refine FQCA's properties and applications, thereby contributing to the expanding understanding of heterocyclic compounds and their capacity to bridge biological activity and electrochemical functionality [21–22].

2. Materials and Methods

Experimental Work

2.1 Synthesis of 2-(furan-2yl) quinoline – 4 carboxylic acids

MATERIALS: Isatin, 2-acetyl furan were received from Sri Durga Laboratory Equipment Supplies, Mangalore, India, Sodium hydroxide, Ethanol and were obtained from Bharat Scientific world, Kodigehalli Bangalore, India. TLC plate also received from Bharat Scientific world, Kodigehalli– Bangalore, India.

The chemicals, reagents and solvents used for the synthesis are bought from Sigma Aldrich, SD-fine, The Hi-Media Company provides synthetic grade solvents that have been purified before use.

Procedure

A detailed synthesis procedure for FQCA is outlined as follows: 2.5 grams of Isatin was introduced into a two-necked round-bottom flask and dissolved in 15 mL of distilled water under continuous stirring. Simultaneously, a solution of 2.5 grams of NaOH in 10–15 mL of distilled water was prepared in a separate container. The NaOH solution was gradually added to the flask, followed by stirring for approximately 10–15 minutes. Subsequently, an additional 5–10 mL of water

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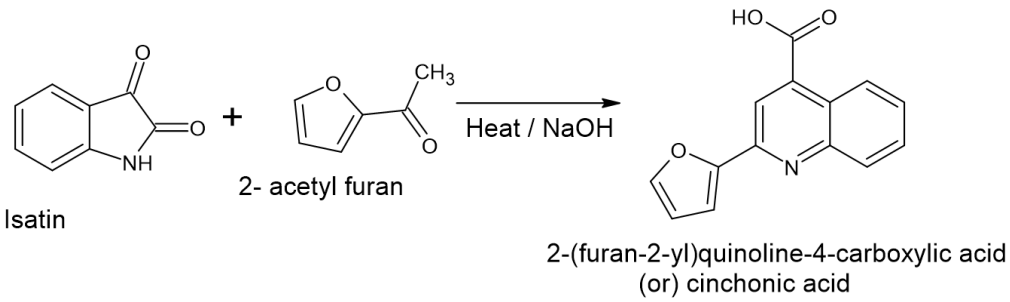
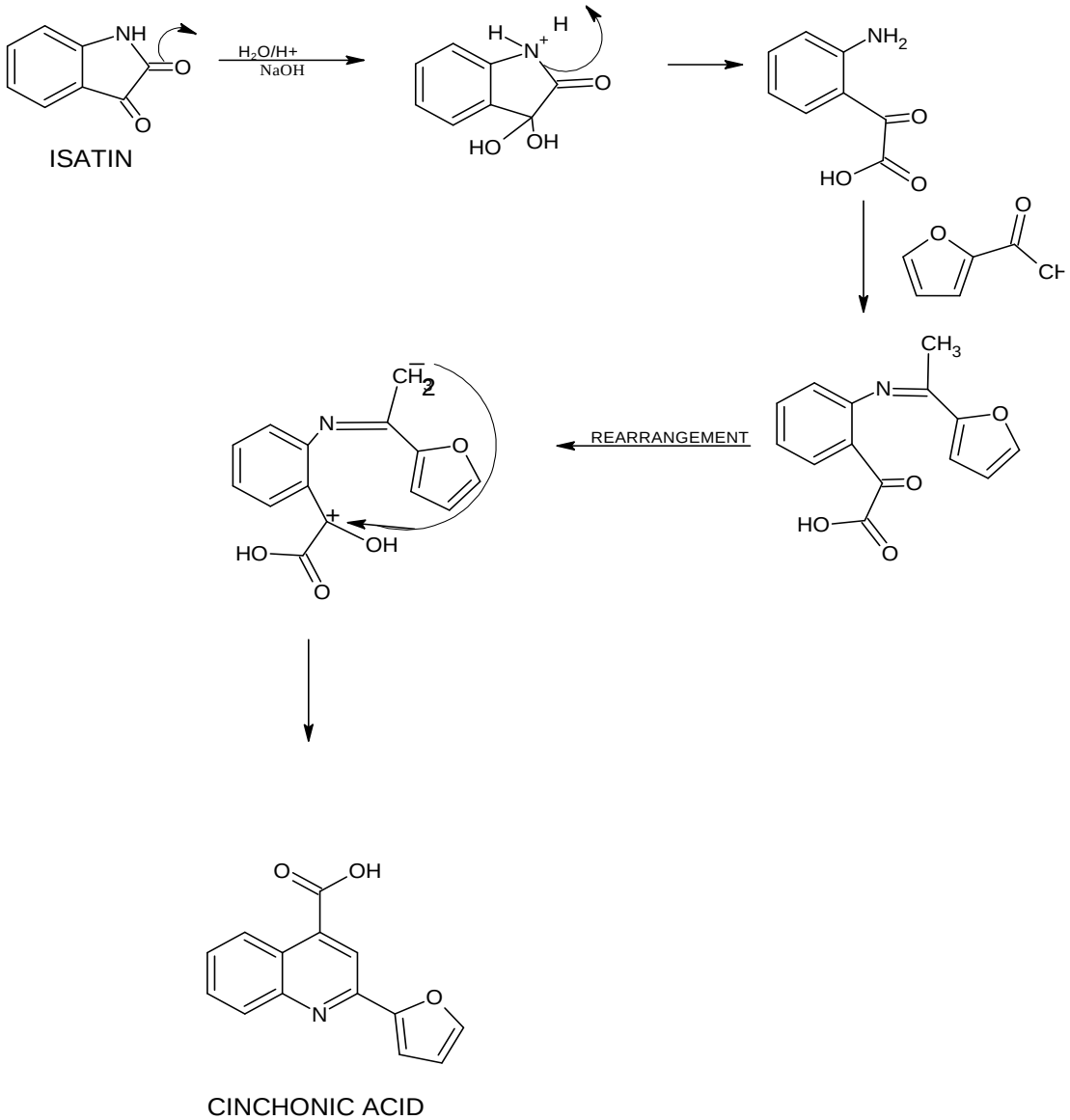
Scheme



Mechanism:



was incorporated, and the reaction mixture was subjected to refluxing at 60–70°C for 45 minutes using a water bath.

Afterward, 1.50 grams of 2-acetylfuran was added dropwise to the reaction mixture, with observable color changes during the addition. The reaction mixture was

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refluxed at 60–70°C for 4.5 hours under continuous stirring. Thin-layer chromatography (TLC) was employed to monitor the progress of the reaction. Upon completion, the reaction mixture was poured into ice-cold water, resulting in precipitation. The precipitate was collected from filtration using a suction pump and Buchner funnel, followed by rinsing with cold water.

To assess the alkalinity of the solution, litmus paper was utilized, confirming a basic pH. Glacial acetic acid was subsequently added to adjust the pH to acidic conditions, which led to the formation of a yellow solid that was left to stand at room temperature. The precipitate was filtered, dried, and recrystallized using ethyl acetate. Reaction progress was monitored by using TLC, while structural elucidation was carried out using NMR, IR, and mass spectroscopy techniques. The purified compound, obtained as a yellow crystalline powder, exhibited a yield of 71% and a melting point of 226°C.

3. Results and Discussion

3.1 Docking studies:

General procedure for molecular docking:

Molecular docking studies were conducted utilizing AutoDock Tools (AutoDock 4.2 and AutoDock Vina), supplemented by additional software such as ChemSketch, Open Babel GUI, and Discovery Studio Visualizer. The structure of 2-(furan-2-yl) quinoline-4-carboxylic acid was initially drawn using ChemSketch and saved in. mol format. Open Babel GUI was then employed to convert the mol file into .pdb format. Additionally, the protein file 3M0O was accessed from the Protein Data Bank in .pdb format.

The target protein file was processed in Discovery Studio Visualizer, where water molecules, metal ions, salts, and pre-docked ligands were removed, resulting in a cleaned file saved in .pdb format. Subsequently, the target file was prepared in AutoDock Tools by adding polar hydrogen atoms and performing energy minimization, after which it was saved in .pdbqt format. Binding site dimensions were determined and configured using the GRID option for docking studies. The structure of 2-(furan-2-yl) quinoline-4-carboxylic acid underwent similar preparation in AutoDock Tools, including energy minimization, identification of rotatable bonds, and saving in .pdbqt format.

Table 01: Key interactions identified:

Binding Site Definitions	Types of Interactions	No of Interactions
ARG A:49, TYR A:317, GLY A:344, HIS A:345, GLY A:346, PHE A:347	Conventional Hydrogen Bond, Pi-Donor Hydrogen Bond, Van der Waals, Amide-Pi stacked, Pi-Alkyl	07

Molecular docking was carried out using Auto Dock Vina through the command prompt, and the docked pose output was saved as .pdbqt files, with binding energy values recorded in log files. Visualization of the docked poses was carried out using Discovery Studio Visualizer, yielding both 2D and 3D images (1a, 1b) for analysis, and the binding pockets were identified and characterized.

Molecular Docking Results:

The analysis of the molecular docking pose illustrates the interaction between 2-(furan-2-yl) quinoline-4-carboxylic acid and specific amino acid residues within the binding site of the target protein. The docking pose evaluation identifies various interaction types that enhance the binding affinity and specificity of 2-(furan-2-yl) quinoline-4-carboxylic acid, with a calculated binding energy of -9.3 kcal/mol.

3.2 Spectral Characterization of Synthesized Compound

Spectral information of 2-(furan-2-yl) quinoline-4-carboxylic acid

Yield: 80%. M. Pt. 248-250 o C; 1H NMR (DMSO-d6, 400 MHz): 14.15 (s, 1H, COOH), 8.70-8.72 (d, J=8, 1H Ar-H), 8.52 (s, 1H quinoline 3C-H), 8.18-8.20 (d, J=8.4, 1H, Ar-H), 7.88-7.94 (q, 2H, Ar-H),7.73-7.82(m, 3H, Ar-H), 7.45-7.48 (t, 1H, Ar-H), 7.34-7.38 (t, 1H, Ar-H). Calculated mass: 239.80 g/mol, M/Z (molecular ion peak) =240, M+1=241, Base peak =240

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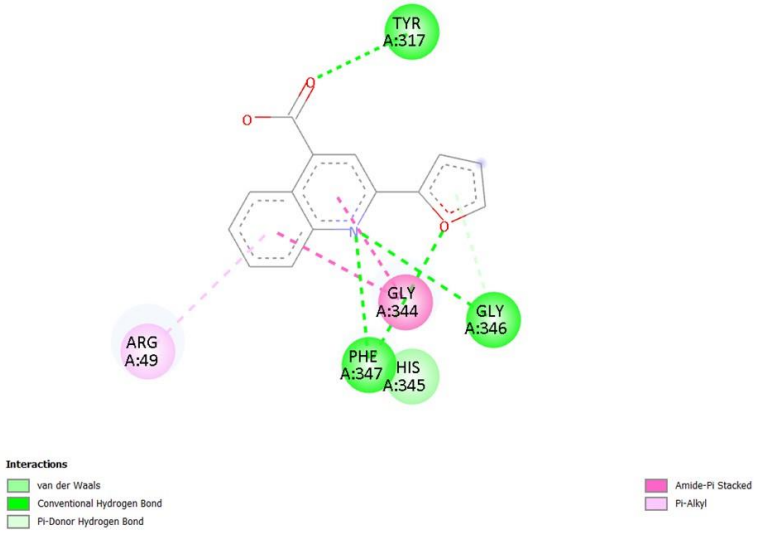

Fig 1a, 2D image FQCA-3M0O complex

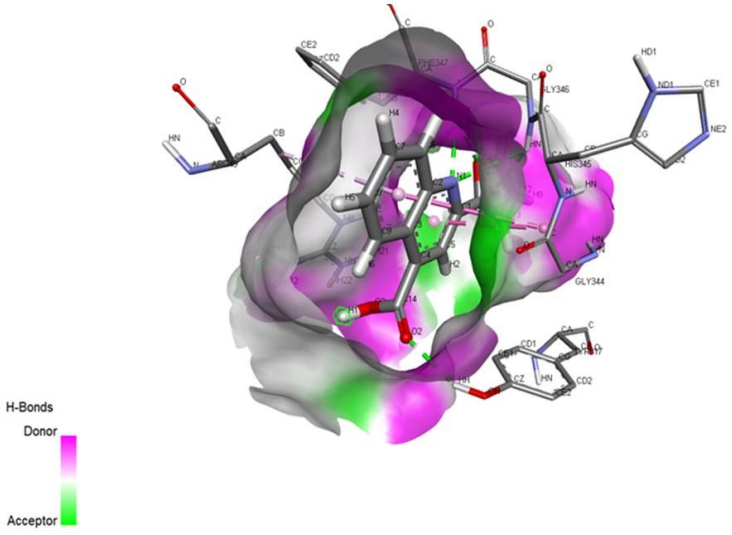

Fig 1b 3D image FQCA-3M0O complex

3.3 Electrochemical Characterization

3.3a Electrochemical behaviour of 2-(furan-2-yl) quinoline-4-carboxylic acid at SnCuO NPs MGCE

The electrochemical behaviour of analyte FQCA was investigated in 0.2 m PBS at SnCuO NPs MGCE using a cyclic voltammetric technique, fig 2(a) shows the cyclic voltammogram of 2.5 mM FQCA at bare GCE red curve and fig 2(b) represents the cyclic voltammogram of analyte at SnCuO NPs MGCE, above studies showed that analyte oxidation peak at of -0.246 V potential with peak current of 4.35 µA at BGCE where as no peak was observed at BGCE in PBS without analyte, in the potential range -1 to +1 volts, no reduction peak was observed in the revers scan, suggesting that the electrochemical reaction is a irreversible process at SnCuO NPs MGCE, the anodic peak current (Ipa) increased to 7.030 µA with a peak potential (Epa) of -0.165 V, represented by the dark curve in Fig. 2(b). The enhanced sensitivity and selectivity observed for SnCuO NPs MGCE can be attributed to its increased surface roughness and active surface area. Consequently, SnCuO NPs MGCE was chosen for further investigation. The proposed mechanism is given for fig 3.

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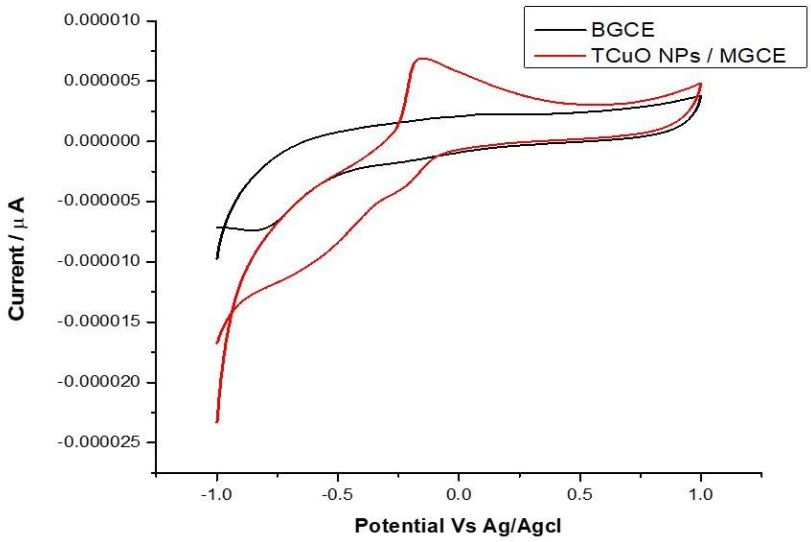

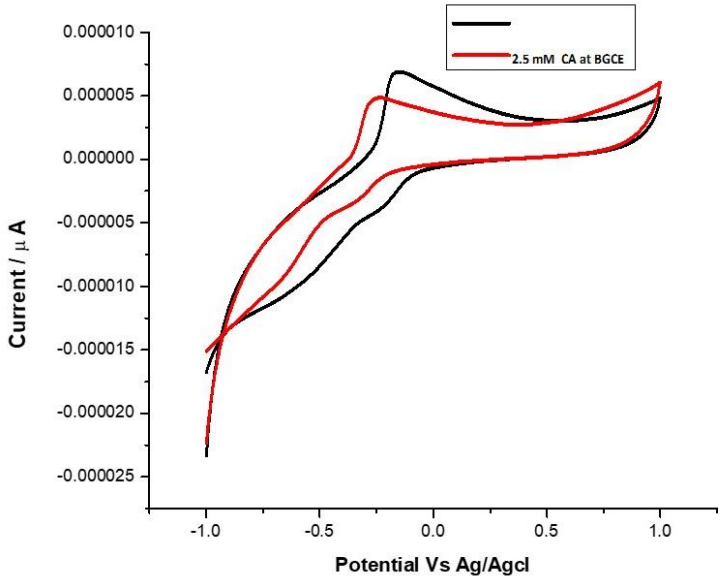

Fig. 2a, 2b. Cyclic Voltammograms of 2.5 mM FQCA in 0.2 M PBS (pH 7.5) with a sweep rate of 50 mVs-1

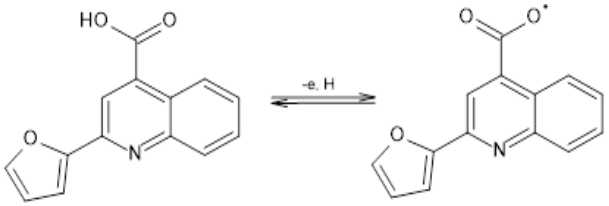

Fig 3. Tentative mechanism of FQCA molecules

3.3b Effect of scan rate at SnCuO NPs MGCE

The reaction kinetics were analysed by examining the influence of scan rate on the peak currents and peak potentials of FQCA using the cyclic voltammetry (CV) technique. Fig. 4 illustrates the voltammograms of 2.5 mM CA in 0.2 M PBS (pH 7.5) at different scan rates ranging from 50 to 250 mV s^{-1}. The results demonstrate a gradual increase in oxidation peak currents with rising sweep rates, accompanied by a slight positive shift in the oxidation peak potential.

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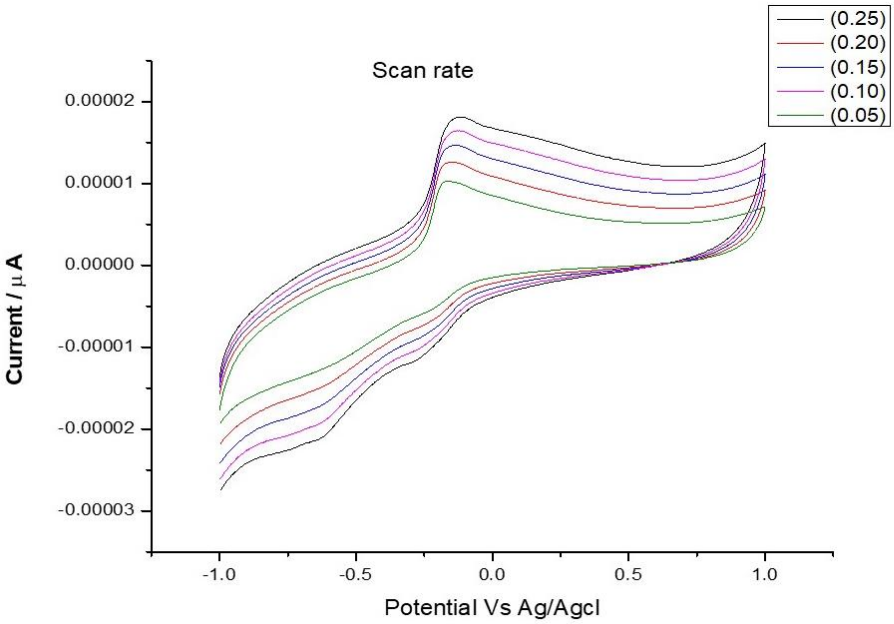

Fig. 4. Cyclic Voltammograms of 2.5 mM FQCA in 0.2 M PBS of pH 7.5 with sweep rates (50–250) mVs - 1 at SnCuO NPs MGCE.

Table - 02: Depicting MIC of compound FQCA in comparison with the standard

SL. NO.	SAMPLES	*100 µg/ml*	*50 µg/ml*	*25 µg/ml*	*12.5 µg/ml*	*6.25 µg/ml*	*3.12 µg/ml*	*1.6 µg/ml*	*0.8 µg/ml*
1	FCA-2	S	S	S	S	S	R	R	R
2.	PYRAZINAMIDE	S	S	S	S	S	S	R	R
3.	CIPROFLOXACIN	S	S	S	S	S	S	R	R
4.	STREPTOMYCIN	S	S	S	S	S	S	S	R

S = sensitive, R= resistance

3.4 THE INVITRO ANTI-TB ACTIVITY

Procedure

MICROPLATE ALAMAR BLUE ASSAY: The antimycobacterial activity of various substances against was evaluated Mycobacterium tuberculosis using the microplate Alamar Blue assay (MABA). This method gives strong comparison with both proportional techniques and BACTEC radiometric methods, while being non-toxic and utilizing a thermally stable reagent. To minimize medium evaporation during incubation, 200 µL of sterile deionized water was added to the wells of a sterile 96-well plate. Subsequently, 100 µL of Middlebrook 7H9 broth was introduced into each well, and the test compounds were serially diluted directly on the plate. The final drug concentrations ranged from 100 to 0.2 µg/mL.

The plates were incubated at bacterial growth temperature at 37°C for five days, sealed with parafilm to prevent contamination. After incubation, 25 µL of a freshly prepared 1:1 mixture of Alamar Blue reagent and 10% Tween 80 was added to the wells, followed by an additional 24-hour incubation period.

The results were assessed based on visual colour changes, from pink coloration indicates bacterial growth, while blue coloration indicates inhibition of bacterial growth. The minimum inhibitory concentration (MIC) was defined as the lowest drug concentration that prevented the colour transition from blue to pink.

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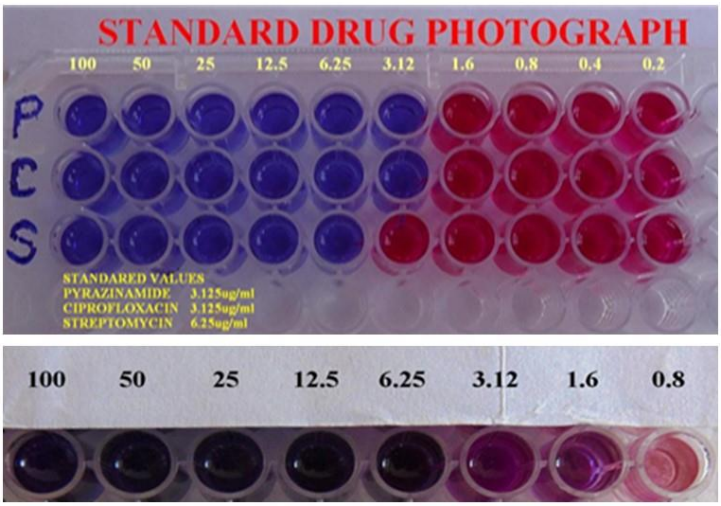

Fig 5: Anti-TB activity of standard and synthesized FQCA compound

4. Conclusion

The quinoline derivative, 2-(furan-2-yl) quinoline-4-carboxylic acid (FQCA), has been synthesized and characterized using ^{1}H-NMR and ^{13}C-NMR spectroscopy. The compounds were then evaluated for anti-tuberculosis (anti-TB) activity using the Microplate Alamar Blue method. The results showed that the synthesized compounds exhibited activity comparable to standard drugs like pyrazinamide, ciprofloxacin, and streptomycin. The study also found that FQCA's redox properties were elucidated through cyclic voltammetry, revealing a diffusion-controlled electrode mechanism with distinct oxidation and reduction peaks. The enhanced sensitivity observed with modified electrodes, such as SnCuO NPs MGCE, underscores its applicability in electrochemical sensing technologies. The study highlights the intersection between medicinal chemistry and electrochemistry, showcasing FQCA's dual role as a bioactive molecule and an electroactive species. The findings are expected to lead to future advancements in optimizing quinoline derivatives for therapeutic interventions and electrochemical devices.

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