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Synthesis, Characterization, Electrochemical and Antioxidant Studies of Novel Quinoline Schiff Base Derivatives

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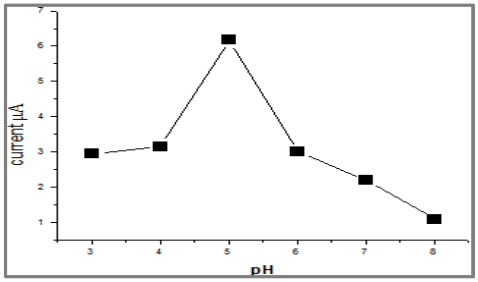
ABSTRACT

Free radicals particularly reactive oxygen species(ROS) and reactive nitrogen species (RNS) have a greater impact on humans both within the body and from the environment. The quinoline skeleton is present in numerous natural products, especially in alkaloids. Many quinolines display interesting pharmacological activities and found applications as pharmaceuticals, e.g., antimalarial drugs, such as quinine or chloroquin. The objective of the present study was to investigate the antioxidant activity of Schiff base ligand, electrochemical study and compared with at of the classical antioxidants, Vitamin C, for scavenging of 2,2-diphenyl-1-picrylhydrazyl (DPPH), and Hydroxyl radical (•OH) radical scavenging activities in vitro quinoline ring is commonly obtained by orthocondensation of benzene ring with pyridine A number of biological activities have been associated with quinoline-containing compounds. The present work reports the synthesis, spectral characterization and antioxidant and electrochemical studies of synthesized series of Schiff bases molecules. Molecules were screened for antioxidant analysis with DPPH scavenger methods. Present work indicates that the titled compounds were found to possess good antioxidant. Electrochemical behavior of 2-[(E)-{(2E)-[(2-chloroquinolin-3-yl) methylidene] hydrazinylidene} methyl] phenol of (analyte 4a to 4d) at SnO_2NPMGCE was studied and the redox potential for (analyte 4a -4c) was quite evident when compared to analyte (4d).This paper elucidates how electrochemically active compounds posses biologically significant activities that may further pave way for enhanced pharmaceutical and pharmacological applications.

Graphical Abstract



Plot of cathodic peak current vs pH 3.0-8.0 of 0.5 mM analyte (4a) at SnO_2 NPMGCE at scan rate 100 mVs^{-1}

Keywords: Cyclic voltammetry, Glassy carbon electrode, Antioxidant activity, Quinoline derivatives.

INTRODUCTION

Free radicals particularly reactive oxygen species(ROS) and reactive nitrogen species (RNS) have a greater impact on humans both within the body and from the environment. In living system, during endogenous stimulation of macrophages and leucocytes, aerobic respiration and other metabolic processes ≥ 5% of oxygen reduced univalently to get free radicals endogenously. While the tobacco smokes, pollutants, ionizing radiations, organic solvents and pesticides are the major exogenous sources of free radicals production [**1-3**]. It is now universally accepted that free radicals have a great impact on humans in the etiology of various diseases like cancer, liver injury, cardiovascular diseases [**4**], diabetes, neurodegenerative and rheumatism diseases [**5**] atherosclerosis [**6**] autoimmune disorders and aging [**7**]. Although, the body possesses defense mechanisms as enzymes and antioxidant nutrients, which arrest the damaging properties of ROS [**8, 9**], continuous exposure to contaminants and chemicals may increase the amount of free radicals in the body beyond its ability to control and cause irreversible oxidative damages [**10**]. Therefore, antioxidants with free radical scavenging potential may be relevant in the therapeutic and preventions of diseases where free radicals are implicated [**11**]. In addition to natural antioxidants such as Vitamin E, Vitamin C, flavonoids and carotenoids act as antioxidant [**12**].

The quinoline skeleton is present in numerous natural products, especially in alkaloids. Many quinolines display interesting pharmacological activities and have found applications as pharmaceuticals, e.g., antimalarial drugs, such as quinine or chloroquin [**13**]. Quinoline ring is commonly obtained by *ortho*condensation of benzene ring with pyridine. A number of biological activities have been associated with quinoline-containing compounds [**14-19**].

Schiff-base compounds have been used as fine chemicals and medical substrates [**20**]. Azomethine group (-C = N-) containing compounds, typically known as Schiff's bases, have been synthesized via condensation of primary amines with active carbonyls [**21**]. It is well established that the biological activity of hydrazone compounds is associated with the presence of the active (-CO-NHN =C-) pharmacophore and these compounds form a significant category of compounds in medicinal and pharmaceutical chemistry with several biological applications [**22-39**].

Summarized that Schiff bases have been used as chelating ligands in coordination chemistry, in anti-oxidative activity, anti-bacterial activity, catalysis, medicine as anti-inflammatory, antibiotics, and in industry for anti-corrosion properties.

Electrochemical methods are well recognized practices for several analytical studies mainly for the analysis of drugs and pharmaceuticals owing to their extraordinary electro sensitivity, adaptability, low detection limits and low-priced instrumentations. These electrochemical methodologies are greatly accomplished for analyzing the concentration of electro active analyte at very minute level and also to obtain valuable evidence regarding their oxidation potential, diffusion coefficients, electron transfer rates and electron transfer number and many other physical and chemical properties can be attained. Besides, these techniques play an important role in the study of pharmacologically active compounds and metabolites produced/synthesized by different metabolic pathways involving redox reactions [**40, 41**].Cyclic Voltametric studies of synthesized molecules in the present study were explored to assess their pharmaceutical potential. However, there are no studies on the electrochemical (CV) and biological activities of these derivatives so far.

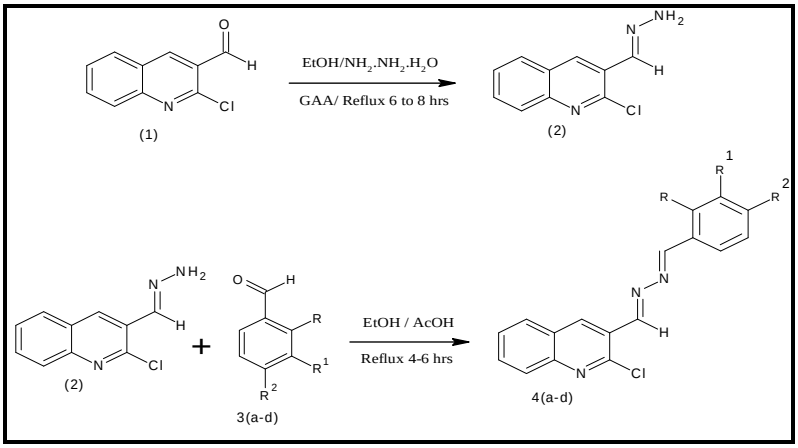
The objective of the present study was to investigate the antioxidant activity of Schiff base ligand, electrochemical study and compared with that of the classical antioxidants, Vitamin C, for scavenging of 2,2-diphenyl-1-picrylhydrazyl(DPPH) and Hydroxyl radical (•OH) radical scavenging activities *in vitro*.

MATERIALS AND METHODS

Materials: Chemicals used in the synthesis of compounds were purchased from Spectrochem Pvt. Ltd. Bangalore, India. The solvents were of reagent grade, purified and dried. Melting points of the synthesized compounds were determined.^{1}H and ^{13}C NMR spectra were recorded on Bruker 400 and 100 MHz instruments using DMSO-d6/$CDCl_3$ as a solvent and TMS as an internal standard; chemical shifts are expressed as δ values (ppm). The *J* values are expressed in Hertz (Hz). Mass spectra (MS) were recorded in GCMATE II LC–Mass spectrometer with electron impact ionization (EI) method.

General procedure for synthesis of (*E*)-1-((2-chloroquinolin-3-yl)methylene)hydrazine (2): 2-chloro quinoline-3-carbaldehyde **1** was taken sufficient quantity in a 100 ml round bottom flask, to this ethanol (50 mL) was added and refluxed around 4-6 hrs followed by the addition of hydrazine hydrate (excess) slowly. After completion of the reaction, the solid formed was filtered and recrystallized from ethyl alcohol.

General procedure for synthesis of 2-[(*E*)-{(2*E*)-[(2-chloroquinolin-3-yl) methylidene]hydrazinylidene} methyl] phenol derivatives 4(a-d): (*E*)-1-((2-chloroquinolin-3-yl)methylene) hydrazine **2** was taken in ethanol (10 mL) and substituted salicylaldehydes **3a-d**(equivalent) was added, and continued with reflux for about 2-3 hrs. The obtained mass was filtered and dried. Purification of the synthesized compounds was carried by recrystalization with suitable solvents.



R= -OH, -H, -OH. **R1**= -h, -OH, -H, -H. **R2**= -H, -H, -OH, -OH.

Scheme 1. Scheme for General procedure for synthesis of 2-[(E)-{(2E)-[(2-chloroquinolin-3-yl) methylidene]hydrazinyli 20 dene} methyl] phenol derivatives 4(a-d)

Spectral characterization of 2-[(*E*)-{(2*E*)-[(2-chloroquinolin-3-yl) methylidene]hydrazinylidene} methyl] phenol4(a): Yield: 78 %. M. Pt. 154-156°C;^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm):13.54 (s, 1H), 8.88 (s, 1H), 8.40 (s, 1H), 8.07-8.09 (d, 2H, *J*=8 Hz), 7.95-7.97 (d, 2H, *J*=8 Hz), 7.71-7.73 (t, 2H, *J*=8 Hz), 7.41-7.43 (t, 2H, *J*=8 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm):152.0, 148.1, 134.5, 130.8, 130.7, 130.0, 128.1, 124.3, 123.7, 116.2; Calcd. 309.7gm/ml. EI-MS (*m/z*): 306.0 (M-2, M-3).

Spectral characterization of 3-[(*E*)-{(2*E*)-[(2-chloroquinolin-3-yl) methylidene]hydrazinylidene} methyl] phenol 4(b): Yield: 81 %. M. Pt. 206-208°C; ^{1}H NMR (DMSO-d_6,400 MHz, δ ppm): 13.53 (s, 1H), 8.89 (s, 1H), 8.40 (s, 1H), 8.08-8.10 (d, 2H, *J*=8 Hz), 7.95-7.97 (d, 2H, *J*=8 Hz), 7.72-7.74 (d, 2H, *J*=8 Hz), 7.42-7.44 (t, 2H, *J*=8 Hz); ^{13}C NMR (DMSO-d_6,100 MHz, δ ppm): 152.0, 148.1, 134.5, 130.89, 130.8, 130.0, 128.1, 124.3, 123.7, 116.2; Calcd. 309.7gm/ml. EI-MS (*m/z*): 306.0 (M-2, M-3).

Spectral characterization of 4-[(*E*)-{(2*E*)-[(2-chloroquinolin-3-yl)methylidene] hydrazinylidene} methyl] phenol 4(c): Yield: 78 %. M. Pt. 148-150°C; ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 13.59 (s, 1H), 8.81 (s, 1H), 8.37 (s, 1H), 7.94-7.96 (d, 2H, *J*=8 Hz), 7.69 (s, 2H), 7.39 (s, 2H); ^{13}C NMR (DMSO-d_6,100 MHz, δ ppm): 152.0, 148.1, 134.5, 133.6, 130.8, 130.7, 129.9, 128.1, 124.3, 123.7, 116.2, 109.2, 102.7; Calcd. 309.7gm/ml. EI-MS (*m/z*): 306.0 (M-2, M-3).

Spectral characterization of 4-[(*E*)-{(2*E*)-[(2-chloroquinolin-3-yl) methylidene] hydrazinylidene} methyl] benzene-1, 3-diol 4(d): Yield: 83 %. M. Pt. 151-153°C; ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 13.80 (s, 1H), 8.89 (s, 1H), 8.40 (s, 1H), 8.08-8.10 (d, 2H, *J*=8 Hz), 7.95-7.97 (d, 1H, *J*=8 Hz), 7.71-7.74 (t, 2H, *J*=12 Hz), 7.42-7.43 (t, 2H, *J*=12 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 152.0, 148.1, 134.5, 130.9, 130.8, 130.0, 128.1, 124.3, 123.7, 116.2; Calcd. 325.7gm/ml. EI-MS (*m/z*): 324.0 (M-1).

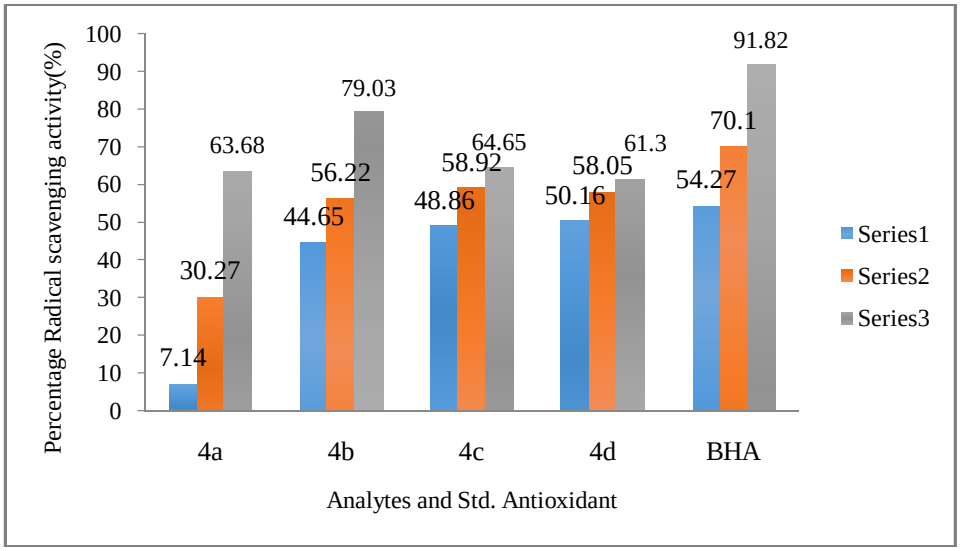
Biological evaluation

DPPH free radical scavenging assay: Different concentrations (10 µg, 25 µg and 50 µg) of samples in Dimethyl sulfoxide (DMSO), were taken in a series of test tubes. The volume was adjusted to 500 µL by adding Methanol. Five milliliters of a 0.1 Mm methanolic solution of 1, 1-diphenyl-2-picryl hydrazyl (DPPH, from Sigma–Aldrich, Bangalore) was added to these tubes and shaken vigorously. A control without the test compound, but with an equivalent amount of methanol was maintained. The tubes were allowed to stand at RT for 20 min. The absorbance of the samples was measured at 517 nm. Butylated Hydroxy Anisole (BHA) was used as reference standard. Free Radical scavenging activity was calculated using the following formula.

$$\% \text{ radical scavenging activity} = \frac{(\text{Control OD-Sample OD}) \times 100}{\text{Control OD}}$$

Table 1. Percentage free radical scavenging activity

Concentration	% Free radical scavenging				
	4a	4b	4c	4d	BHA
10µg	7.14	44.65	48.86	50.16	54.27
25µg	30.27	56.22	58.92	58.05	70.10
50µg	63.68	79.03	64.65	61.30	91.82



Graph 1. % of free radical scavenging assay (10 µg, 25 µg and 50 µg) with synthesized derivatives.

Inference: Among the test samples analyte 4b and 4c has shown better free radical scavenging assay followed by 4a and 4d in comparision to standard BHA. The lower concentration of 10 µg is not significant.

RESULTS AND DISCUSSION

Cyclic voltammetric studies

Electrochemical response of Potassium Ferrocyanide at SnO_2 nanoparticles modified Glassy Carbon Electrode (SnO_2NPMGCE): Potassium ferrocyanide was used as a standard to determine the efficiency of SnO_2 nanoparticles modifier. Figure 1 shows the electrochemical behavior of 0.1 mM potassium ferrocyanide ($K_4[Fe(CN)_6]$) in 0.1M HCl at bare glassy carbon electrode (BGCE) curve 'b' and at SnO_2NPMGCE curve 'a' respectively. The curve 'b' shows the cathodic peak current I_{pc} 5.1 µA of E_{pc}119 mV and anodic peak current I_{pa}5.18 µA of E_{pa} 241mV at BGCE. Whereas, curve 'a' shows the cathodic peak current I_{pc} 19.56 µA of E_{pc} 123 mV and anodic peak current I_{pa} 19.85 µA of E_{pa} 237 mV at the SnO_2NPMGCE has been observed. The enhancement of current peak showed excellent catalytic ability of SnO_2NPMGCE.

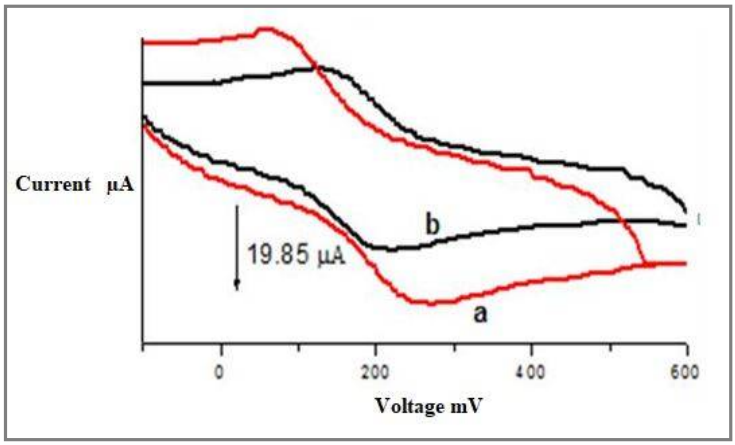


Figure 1. Cyclic voltammograms of 0.1mM analyte $K_4[Fe(CN)_6]$ in 0.1 M KCl solution at SnO_2 NPMGCE (a) and bare glassy carbon electrode (b).

Electrochemical behavior of 2-[(*E*)-{(2*E*)-[(2-chloroquinolin-3-yl) methylidene]hydrazinylidene} methyl] phenol of(4a)analyte at SnO_2 NPMGCE: The electrochemical behavior of analyte **4a**was investigated in 0.2 M Acetate buffer solution of ABS-5 atSnO_2NPMGCE using cyclic voltammetric technique. Figure 2 shows cyclic voltammograms of 0.5mM analyte (4a) at bare GCE (curve 'b') and the curve 'a' represents the cyclic voltammograms of SnO_2NPMGCE. Above studies showed that only one reduction peak at 849 mV potential with peak current of 6.13 µA at SnO_2 NPMGCE, whereas no peak at ABS-5 without analyte at bare GCE in the potential range 450 to 1300 mV. No reduction peak was observed in the reverse scan, suggesting that the electrochemical reaction is a totally irreversible process and the reduction peak at the bare GCE is broad due to slow electron transfer, while the response was considerably improved at SnO_2NPMGCE and the peak potentials shifted to negative direction, the shape of the peak turns sharper and the peak current increased significantly.

Effect of pH: The electro reduction of analyte (4a) was studied at 0.5mM stock solution in 0.2 M acetate buffer solution over pH range from 3.0 to 8.0 at a scan rate of 100 mVs^{-1} at SnO_2 NPMGCE using cyclic voltammetric technique. The reduction peak current increases with increase of pH from 3.0 to 5.0 and reaches maximum and peak potential shifted negatively. While pH beyond 5, a great

decrease in the reduction peak current has been observed, then it decreased gradually with the further increase in pH of the solution as shown in figure 3.

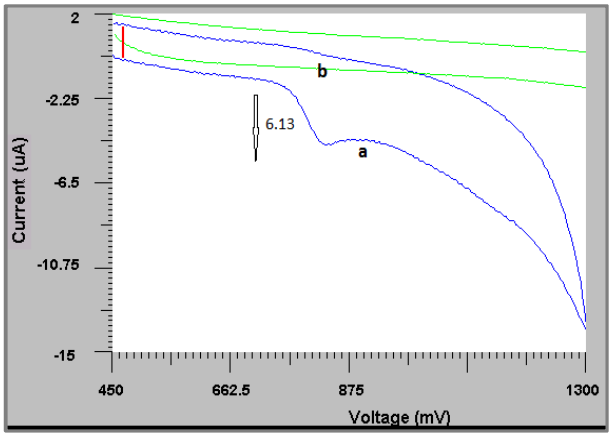


Figure 2. Cyclic voltammograms of 0.5 mM analyte (4a) at SnO_2 NPMGCE (a) and (b) bare glassy carbon electrode in acetate buffer at pH -5, scan rate 100 mVs^{-1}.

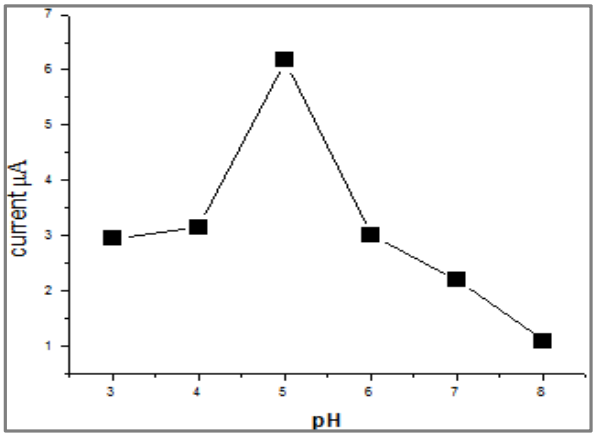


Figure 3. Plot of cathodic peak current vs pH 3.0-8.0 of 0.5 mM analyte (4a) at SnO_2 NPMGCE at scan rate 100 mVs^{-1}.

Effect of scan rate: Useful information involving electrochemical mechanism usually can be acquired from the relationship between peak current and scan rate. Therefore, the effect of scan rates on the electrochemical response of 0.5 mM analyte(4a) at SnO_2NPMGCE was studied at different scan rates. Redox peak current increase linearly with the scan rate in the range 25, 50, 75 and 100 mVs^{-1}. The cyclic voltammograms were shown in figure 4.

Electrochemical behavior of 3-[(*E*)-{(2*E*)-[(2-chloroquinolin-3-yl) methylidene]hydrazinylidene} methyl] phenol–analyte(4b)at Glassy Carbon Electrode (GCE): The electrochemical behavior of analyte (4b) was investigated in 0.2 M phosphate buffer solution of PBS-7 at GCE using cyclic voltammetric technique. Figure 5 shows cyclic voltammograms of 0.5mManalyte (4b)at GCE. Curve 'b' shows the cyclic voltammograms without analyte and the curve 'a' represents the cyclic voltammograms of GCE. Above studies showed that only one reduction peak was observed at 1052 mV potential with peak current of 14.18 µA at GCE, whereas no peak at PBS-7 without analyte at GCE in the potential range 450 to 1300 mV. No reduction peak was observed in the reverse scan,

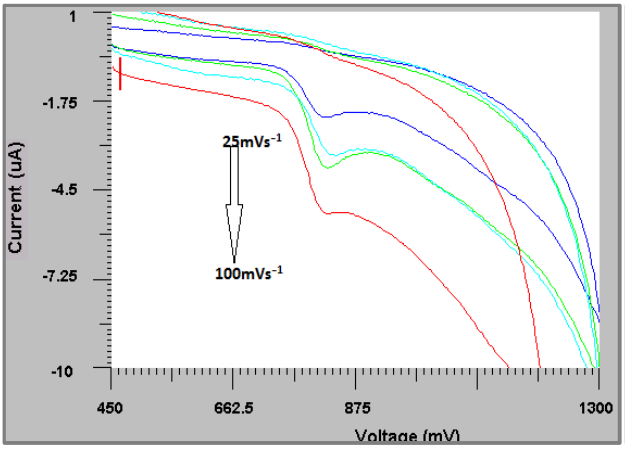


Figure 4. Cyclic voltammograms of 0.5 mM analyte (4a) at SnO_2 NPMGCE with different scan rates 25, 50, 75 and 100 mVs^{-1} in ABS-5.

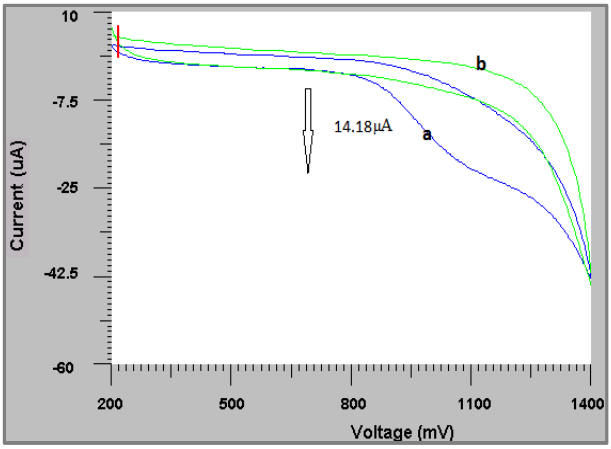


Figure 5. Cyclic voltammograms of 0.5 mM analyte(4b)at GCE (a) and (b) glassy carbon electrode without analyte (4b)in phosphate buffer at pH -7, scan rate 100 mVs^{-1}.

suggesting that the electrochemical reaction is a totally irreversible process and the reduction peak at the GCE is broad due to slow electron transfer and the peak potentials shifted to negative direction, the shape of the peak turns sharper and the peak current increased significantly.

Effect of pH: The electro reduction of analyte (4b)was studied at 0.5 mM stock solution in 0.2 M phosphate buffer solution over pH range from 3.0 to 9.0 at a scan rate of 100 mVs^{-1} at GCE using cyclic voltammetric technique. The reduction peak current increases with increase of pH from 3.0 to 7.0 and becomes maximum and peak potential shifted negatively. While pH beyond 7, a great decrease of the reduction peak current has been observed, then it decreased gradually with the further increase in pH of the solution is shown in figure 6.

Effect of scan rate: Useful information involving electrochemical mechanism usually can be acquired from the relationship between peak current and scan rate. Therefore, the effect of scan rates on the electrochemical response of 0.5 mM analyte (4b) at GCE was studied at different scan rates. Redox peak current increase linearly with the scan rate in the range 25, 50, 75, 100 and 125 mVs^{-1}. The cyclic voltammograms were shown in figure 7.

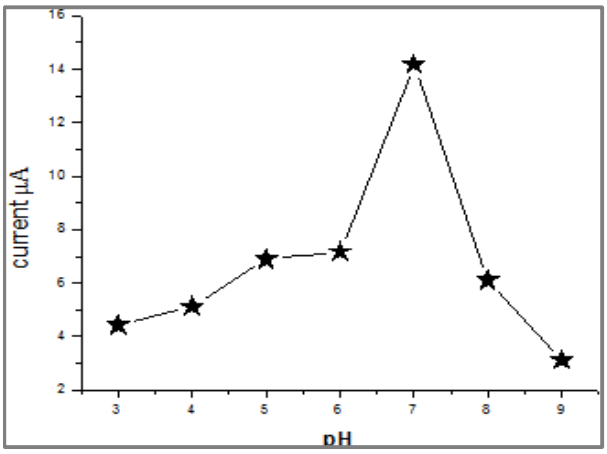


Figure 6. Plot of cathodic peak current vs. pH 3.0-9.0 of 0.5 mM analyte(4b)atGCE at scan rate 100 mVs^{-1}.

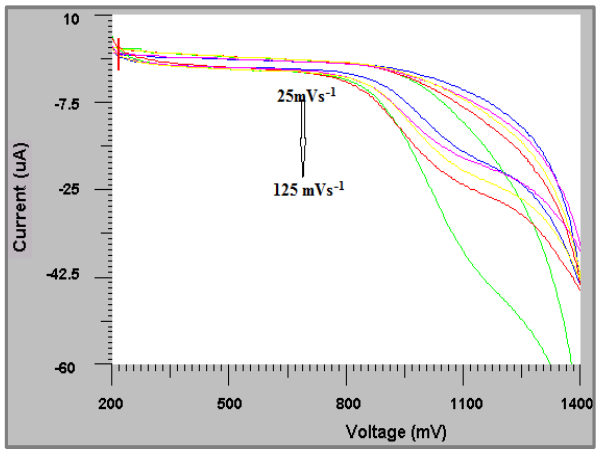
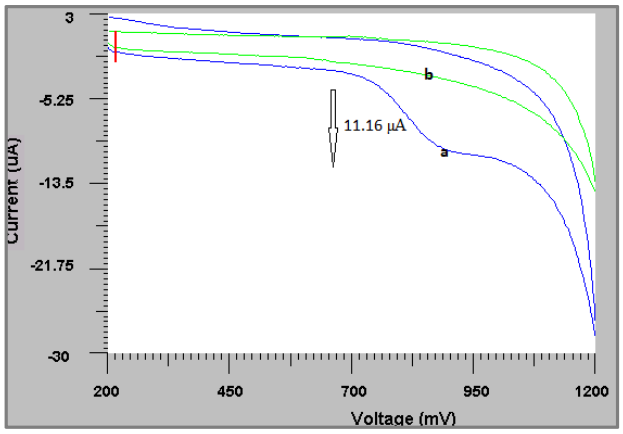


Figure 7. Cyclic voltammograms of 0.5 mM analyte(4b at GCE with different scan rates 25, 50, 75, 100 and 125 mVs^{-1} in pH-7 0.2M phosphate buffer solution.

Electrochemical behavior of 4-[(*E*)-{(2*E*)-[(2-chloroquinolin-3-yl)methylidene] hydrazinylidene} methyl] phenol -analyte (4c)at Glassy Carbon Electrode (GCE): The electrochemical behavior of analyte (4c) was investigated in 0.2 M phosphate buffer solution of PBS-8 at GCE using cyclic voltammetric technique. Figure 8 shows cyclic voltammograms of 0.5 mM analyte(4c) at GCE. Curve 'b' shows the cyclic voltammograms of without analyte and the curve 'a' represents the cyclic voltammograms of GCE. Above studies showed that only one reduction peak at 850 mV potential with peak current of 11.6 µA at GCE, whereas no peak at PBS-8 without analyte at GCE in the potential range 200 to 1200 mV. No reduction peak was observed in the reverse scan, suggesting that the electrochemical reaction is a totally irreversible process and the reduction peak at the GCE is broad due to slow electron transfer, and the peak potentials shifted to negative direction, the shape of the peak turns sharper and the peak current increased significantly.

Effect of pH: The electro reduction of analyte (4c) was studied at 0.5 mM stock solution in 0.2 M phosphate buffer solution over pH range from 3.0 to 10.0 at a scan rate of 50 mVs^{-1} at GCE using cyclic voltammetric technique. The reduction peak current increases with increase of pH from 3.0 to 8.0 and becomes maximum and peak potential shifted negatively. While pH beyond 8, a great

decrease of the reduction peak current has been observed, then it decreased gradually with the further increase in pH of the solution is shown in figure 9.



Figuyre 8. cyclic voltammograms of 0.5 mM analyte (4c) at GCE (a) and (b) glassy carbon electrode without analyte (4c)in phosphate buffer at pH -8, scan rate 50 mVs^{-1}.

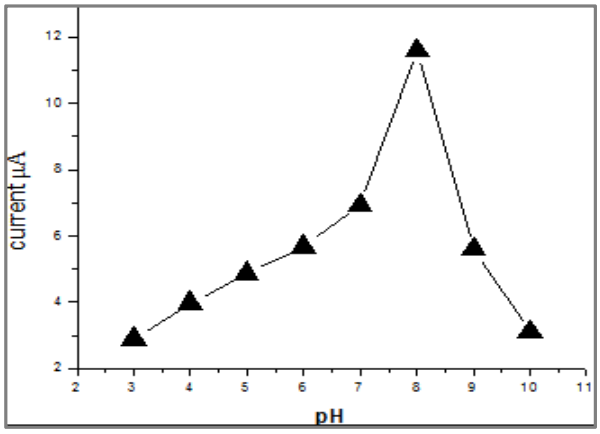


Figure 9. Plot of cathodic peak current vs. pH 3.0-10.0 of 0.5 mM analyte (4c)atGCE at scan rate 50 mVs^{-1}.

Effect of scan rate: Useful information involving electrochemical mechanism usually can be acquired from the relationship between peak current and scan rate. Therefore, the effect of scan rates on the electrochemical response of 0.5 mManalyte(4c) at GCE was studied at different scan rates. Redox peak current increase linearly with the scan rate in the range 25, 50, 75, 100 and 125 mVs^{-1}. The cyclic voltammograms were shown in figure 10.

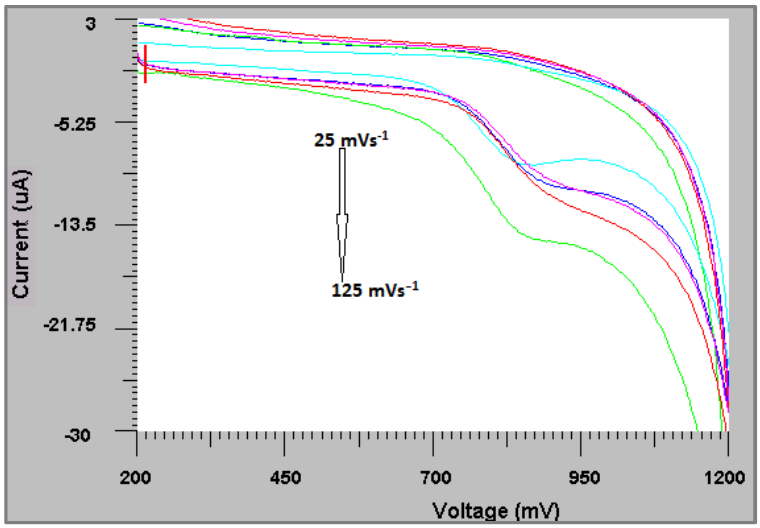


Figure 10. Cyclic voltammograms of 0.5 mM analyte(4c)atGCE with different scan rates 25, 50, 75, 100 and 125 mVs^{-1} in pH-8 0.2M phosphate buffer solution.

Electrochemical study indicates that, the entitled molecules 4(a-c) have exhibited well to moderate oxidation and reduction potentials because of the presence of hydroxyl group present on phenyl ring. Electrochemical analysis of Analyte (4d) did not reveal the prominent electrochemical activeness which may be attributed to low oxidation to reduction potent ion.

APPLICATION

Nitrogen heterocycles are one of the very essential heterocycles in the drug-discovery studies. They are a very important class of compounds that play a major role in cell physiology and are potential intermediates for many biological reactions. There has been an increasing interest in the use of electrochemical cells to generate oxidation and reduction profiles, drug stability experiments, quantitative analyses, and in vitro experiments of drug candidates. Further they play the role of antioxidant enhance the immune system. Schiff bases have also been used as chelating ligands in coordination chemistry, anti-bacterial activity, catalysis, medicine as anti-inflammatory, antibiotics, and in industry for anti-corrosion properties as well suggesting their diversity in biochemical applications.

CONCLUSION

The present work reports the synthesis, spectral characterization and antioxidant and electrochemical studies of synthesized series of Schiff bases molecules. Molecules were screened for antioxidant analysis with DPPH scavenger methods. The work indicates that the titled compounds were found to possess good antioxidant and entitled titled compounds were electrochemically significant.

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Conflict of interest: There is no any conflict of interest.

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