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Review Article

Electrochemical Behavior of Biologically Important Indole Derivatives

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Voltammetric techniques are most suitable to investigate the redox properties of a new drug. Use of electrochemistry is an important approach in drug discovery and research as well as quality control, drug stability, and determination of physiological activity. The indole nucleus is an essential element of a number of natural and synthetic products with significant biological activity. Indole derivatives are the well-known electroactive compounds that are readily oxidized at carbon-based electrodes, and thus analytical procedures, such as electrochemical detection and voltammetry, have been developed for the determination of biologically important indoles. This paper explains some of the relevant and recent achievements in the electrochemistry processes and parameters mainly related to biologically important indole derivatives in view of drug discovery and analysis.

1. Indoles in Medicinal Chemistry

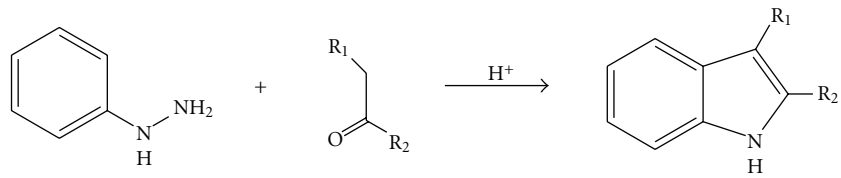
Indole is an aromatic heterocyclic compound that has a bicyclic structure. It is an accepted constituent of fragrances and the precursor to many pharmaceuticals. One of the oldest and most reliable methods for synthesizing substituted indoles is the Fischer indole synthesis (Scheme 1) developed in 1883 [1].

Indoles are present in many important biological compounds. Tryptophan is a significant indole derivative while serotonin and melatonin are biochemically active indole molecules. There are also many indole alkaloid derivatives found in nature. The plant hormone Auxin contains indol-3-acetic acid. Furthermore, there are many important indole derivatives used in treatment. The anti-inflammatory drug indomethacin, the betablocker pindolol, and the naturally occurring hallucinogen dimethyltryptamine are some of the important indole derivatives.

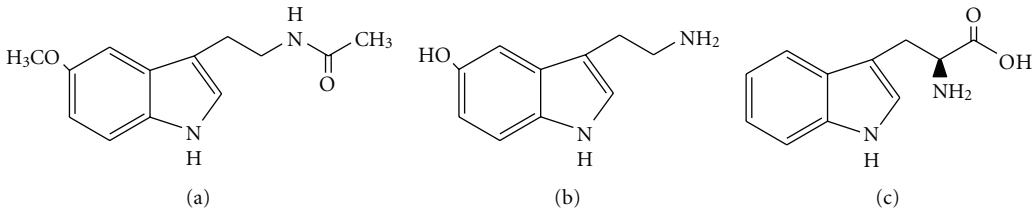
Indole derivatives represent many important classes of therapeutical agents in medicinal chemistry such as anticancer [2], antioxidant [3], antirheumatoidal [4], and anti-HIV [5, 6]. Studies showed that some of the 2-phenylindole (2PI) sulfamates are inhibitors of steroid sulfatase with antiproliferative activity in breast cancer cells [7, 8]. Some of the sulfur containing 2PI derivatives show *in vivo* antineoplastic and antiestrogenic activity [9, 10]. Furthermore, some indole derivatives, such as melatonin and serotonin, influence many important biochemical processes. They act as antioxidant and play an important role in the immune system [11–14].

Melatonin (MLT; Scheme 2(a)), is an indole ring containing hormone produced in the brain by the pineal gland, from the amino acid tryptophan. It has a significant role in the protection of nuclear and mitochondrial DNA. In recent years, many physiological properties of MLT have been described resulting in much attention in the development of synthetic compounds possessing the indole ring. MLT was initially found to function as a mediator of circannual reproductive rhythms and circadian cycles [15]. Furthermore, it has oncostatic effects [16], immune system stimulation [17], and anti-inflammatory functions [18]. MLT was identified as a powerful free radical scavenger and indirect antioxidant [19, 20].

Serotonin (Scheme 2(b)) or 5-Hydroxytryptamine (5-HT) is a monoamine neurotransmitter. Biochemically derived from tryptophan (Scheme 2(c)), serotonin is primarily found in the gastrointestinal tract, platelets, and in the central nervous system of humans and animals. It is a



Scheme 1: Fischer indole synthesis.



Scheme 2: Chemical formula of melatonin (a), serotonin (b), and tryptophan (c).

well-known contributor to feelings of well-being; therefore, it is also known as a happiness hormone.

Neurotransmitter serotonin synthesize from tryptophan and can be converted to neurohormone melatonin via N-acetyltransferase and 5-hydroxyindole-O-methyltransferase activities. Niacin is synthesized from tryptophan as key biosynthetic intermediate.

Indole and its derivatives are well known electroactive compounds that are readily oxidized at carbon-based electrodes, for example, glassy carbon electrode [21]. Voltammetric techniques in general, and differential pulse voltammetry (DPV) in particular, are considered to be useful tools for the determination of indole derivatives [22, 23].

2. Introduction to Electrochemical Studies with Indole Derivatives

Electrochemistry deals with behavior of oxidation and reduction reactions connected by an external electric circuit to understand each process. Redox and electrochemical processes involve electron transfer to/from a molecule. This reaction can occur by the application of a voltage or by the release of chemical energy.

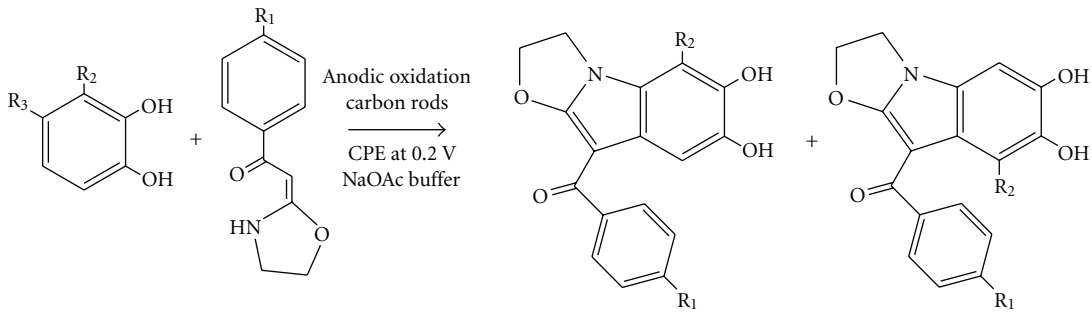
Electrochemical synthesis has shown to be a very useful procedure to obtain organic molecules. The main advantage of the electrochemical synthesis is the lack of oxidant and reducing agents, which makes the workup procedure easier [24–26]. The synthesis of the indole ring is of particular importance in organic, pharmaceutical, and medical chemistry. There is great effort to the improvement of existing methods for indole preparation in the pharmaceutical research. Electrochemistry offers an important alternative to the classical methodologies utilized in the synthesis of chemicals. Procedures in electroanalysis strongly depend on material aspects such as chemical and physical properties of electrode surfaces, the effects of applied potential, adsorption, and coatings applied to the electrode surface to enhance detection [27].

A good electrical conductivity of the electrodes is an important factor. Solid electrodes in general, especially carbon, are easy and practical as mercury for electroanalytical research. A detailed review was published by Uslu and Ozkan [27] including developments and applications of carbon-based electrodes for drug compounds in their dosage forms and in biological samples in the period from 1996 till 2006. Furthermore, compared to other voltammetric techniques, a squarewave voltammetry was presented in a minireview [28]. In the review, the several advantages such as high speed, increased analytical sensitivity, and relative insensitivity to the presence of dissolved oxygen were discussed.

Voltammetry is an electroanalytical method used in pharmaceutical, medicinal, analytical, and organic chemistry as well as various industrial processes. In this method, data about an analyte is obtained by measuring the current as the potential is varied. There are many types of voltammetry including linear sweep voltammetry, staircase voltammetry, squarewave voltammetry (SWV), cyclic voltammetry (CV), anodic stripping voltammetry, cathodic stripping voltammetry, adsorptive stripping voltammetry, alternating current voltammetry, rotated electrode voltammetry, normal pulse voltammetry and DPV.

CV is very suitable to investigate the redox properties of a new drug to give insights to metabolic fate. DPV and SWV voltammetry has been particularly useful for trace measurements of electroactive compounds in body fluids and tissues. SWV is a large amplitude differential technique in which a waveform composed of a symmetrical squarewave, superimposed on a base staircase potential, is applied to the working electrode [29].

2.1. Studies on the Substituted Synthetic Indole Derivatives. It is well known that voltammetric techniques are most suitable



Scheme 3: Some electrochemically synthesized fused indole derivatives.

to investigate the redox properties of a new drug in order to have more information about drugs metabolic fate [30].

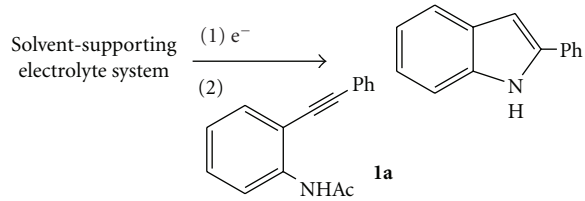
Applications of electrochemistry include the determination of electrode oxidation mechanisms. Knowing that there is a resemblance between electrochemical and biological reactions, it can be considered that the oxidation mechanisms taking place at the electrode and in the body may have similar principles.

A suitable electrochemical approach was described in a study for the synthesis of indole derivatives from catechols and R-oxoheterocyclic ketene N,O-acetals (Scheme 3) [31]. This is an environmentally friendly method to create fused indole derivatives containing active hydroxyls and carbonyl under mild reaction conditions.

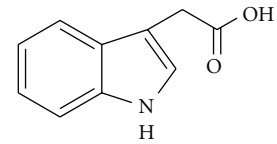
The electrochemical-mediated annulation of 2-alkynylanilines to the corresponding indole derivatives proceeds in good yields and under conditions that avoid the use of metal catalysts or classical organic acids and bases (Scheme 4) [32]. A novel preparation of the electrogenerated cyanomethyl anion as an electrogenerated base, in the synthesis of substituted indoles from alkynylanilines was developed. The workup process only requires filtration or flash chromatography of the evaporated reaction mixture. It was reported that this electrochemical approach represents an important alternative to the previous procedures.

The effect of indole and 5-chloroindole on the anodic dissolution of copper in acidic sodium chloride solutions was studied using voltammetry on a rotating disc electrode (RDE) [33]. Both compounds, used at 10^{-3} M concentration act as strong inhibitors on the copper dissolution, but indole exhibits better inhibiting properties. The influence of these organic additives on the electrodeposition of copper on platinum was also investigated using RDE and electrochemical quartz crystal microbalance (EQCM) techniques. The EQCM measurements show that a sparingly soluble layer of the inhibitor is responsible for the protective effects observed in chloride solutions.

A new voltammetric method was successfully used to detect indole-3-acetic acid (IAA; Scheme 5) in some plant leaves. Sodium dodecyl sulfate (SDS), an anionic surfactant, can strongly adsorb at the surface of a carbon paste electrode (CPE) *via* the hydrophobic interaction. In the presence of SDS, the cationic indole-3-acetic acid was highly accumulated at the CPE surface through the electrostatic



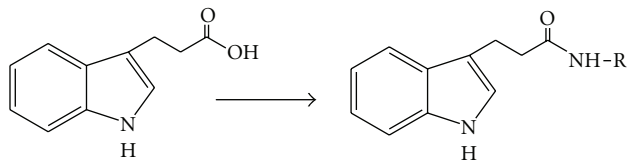
Scheme 4: Synthesis of 2-phenyl indole derivative by cyclization of **1a** induced by the electrogenerated cyanomethyl anion under different reaction conditions [32].



Scheme 5: Chemical formula of indole-3-acetic acid.

interaction between the negative-charged head group of SDS and cationic IAA, compared with that in the absence of SDS. The experimental parameters, such as pH, varieties of surfactants, concentration of SDS, and scan rate were optimized for IAA determination [34].

Metabolization usually progressed through the addition or the modification of a substituent; this will give rise to additional waves or to a shift of the main wave due to the metabolites. CV has been used in studying the redox mechanism that is related to antioxidant activity of synthesized indole-3-propionamide (Scheme 6) [21]. Based on this study, a simple, rapid, and sensitive voltammetric method was developed for the determination of the indole derivatives that are readily oxidized at the carbon-based electrodes. The oxidative behavior of the indole derivatives was studied as a function of pH at a glassy carbon electrode. The results showed that the compounds might have profound effects on our understanding of their *in vivo* redox processes and pharmaceutical activity. It was assumed that the oxidation step of indolic compounds is located on the nitrogen atom in the indole ring of the molecule, which is electroactive in both acidic and basic media, leading finally to hydroxylation of benzene ring.



Scheme 6: Chemical formula of indole-3-propionamides [21].

Electrochemical techniques offer important information about drug molecules and their mechanisms in the body, such as metabolism, which is one of the important actions in drug discovery. Two compounds, namely, 1-methylindole-3-carboxaldehyde isonicotinoyl hydrazone (Scheme 7(a)) and 5-chloro-1H-indole-3-carboxaldehyde isonicotinoyl hydrazone (Scheme 7(b)) were synthesized, characterized, and examined electrochemically using different voltammetric techniques in order to evaluate the possible biological behavior [35]. A linear response was obtained in the different media for the compounds with low detection limits of the synthesized compounds.

Electrochemical behavior of some indolyl-thiohydantoin derivatives (Scheme 8) was studied in order to understand the electrochemical process that occurs on the glassy carbon electrode, both pH and scan rate [36]. For the quantitative determination, differential pulse voltammetric methods were applied. It was assumed that the oxidation steps occur for all the compounds on the nitrogen atom in the indole ring, which is electroactive in both acidic and basic media, leading finally to hydroxylation of the benzene ring. Studies of electrochemical oxidation of indole and some derivatives showed that the indole ring is most likely form dimers and trimers. This technique has been successfully applied to trace measurements of important pharmaceutical compounds.

The use of electrochemistry and combination of this method with other analytical techniques are becoming one of the important approaches in drug discovery. Many physiological processes depend on oxidoreduction reactions in the body. For that reason, it may be possible to find similarities between electrochemical and biochemical reactions. In a review by Suzen and Ozkan [37], the latest developments related to the use of electrochemical techniques in drug research will be surveyed in order to evaluate possible combinations of spectrometric methods with electrochemical techniques, were presented. The use of electrochemistry and combination with spectroscopic techniques are becoming one of the important approaches in drug discovery and research.

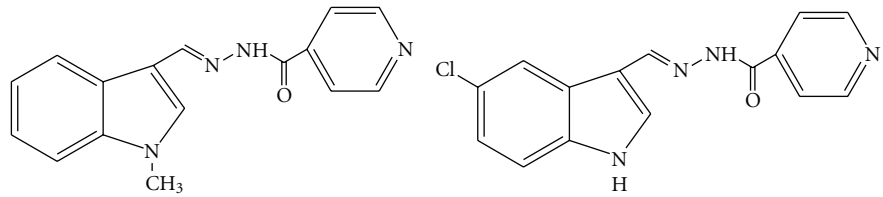
In a review published by Greci et al. [38], reactivity of radical cations of primary aromatic amines towards indoles and that of indoles towards primary aromatic amines were studied. It is known that radical cations can be generated from substrates with low oxidation potentials by electrochemical oxidation. For some researchers, many reactions interpreted by an electron transfer process actually occur through an ionic mechanism while others, described by an ionic mechanism, involve an electron transfer process [38]. Radical cations of primary aromatic amines were unable to attack nucleophiles such as 2-phenyl-1*H*-indole. The interaction between 2-phenyl-1*H*-indole, and primary aromatic amines may only occur through coupling of their neutral radicals. The 2-phenyl-1*H*-indolyl radical cation can dimerise as observed for tetrahydrocarbazoles, but dimerisation is faster when it reacts *via* the indolyl radical. As a result, 2-phenyl-1*H*-indole reacts with *p*-anisidine, 2-nitro-*p*-anisidine, and 2-nitro-*p*-methylaniline, under anodic oxidation, to give several products, depending on the potential used and on the presence or the absence of oxygen and a deprotonating agent. This study gives new information about the reactivity of radical cations generated by a controlled anodic potential and neutral radicals.

Some 2-phenyl indole (2PI; Scheme 9) derivatives were investigated electroanalytically by voltammetric determination as a function of pH at a glassy carbon and hanging mercury drop electrodes in different buffer media [29]. The studied molecules are extensively metabolized *in vivo*, mainly through oxidative processes in which we assume that the oxidation step of indolic compounds is located on the nitrogen atom in the indole ring of the molecule. Based on this study, simple, rapid, sensitive and validated voltammetric method was developed for the determination and investigation of electrochemical behaviour of the 2PI derivatives.

2.2. Studies-Related to Tryptophan Derivatives. The electrochemical behavior of an indole library of compounds that were found to be active free radical scavengers was investigated by Estevão et al. [39]. They used a voltammetric study and the oxidation potentials to make a correlation to the scavenging activity reported for the studied indoles. The study included several tryptophan and tryptamine derivatives. All the compounds showed an oxidation potential peak lower than that observed for indole, but higher than that described for the antioxidant melatonin. The electrochemical behavior showed a high correlation with the scavenging activity of peroxyl radical, for selected compounds. It was observed that for some reactive species the scavenging mechanism involves electron transfer while for other species some structural requirements, such as the steric hindrance between the substrate and the bulky oxidant, should be considered when analyzing the scavenging activity.

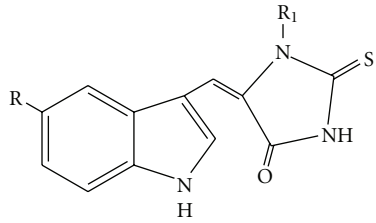
A method has been developed for the simultaneous determination of MLT and pyridoxine hydrochloride in pharmaceutical dosage forms by DPV, based on the oxidation of both drugs at a glassy carbon electrode [40]. Cyclic and linear scan voltammetry were used to examine the influence of pH, nature of the buffer, scan rate, and concentration. The proposed method was successfully applied to the commercial tablets containing this drug combination without any interference by the excipients.

Indole and its metabolites (e.g., tryptamine and serotonin) are of biochemical importance, and analytical procedures have been developed for their determination in mixtures, based on liquid chromatography with electrochemical detection [41] and voltammetry [42, 43].

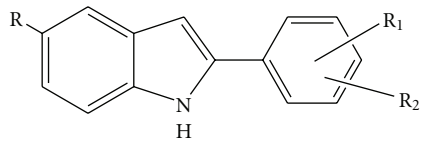


(a) (b)

Scheme 7: Chemical formula of 1-methylindole-3-carboxaldehyde isonicotinoyl hydrazone (a) and 5-chloro-1H-indole-3-carboxaldehyde isonicotinoyl hydrazone (b).



Scheme 8: Chemical formula of indolyl-thiohydantoin derivatives.



Scheme 9: Chemical formula of 2-phenyl indole derivatives.

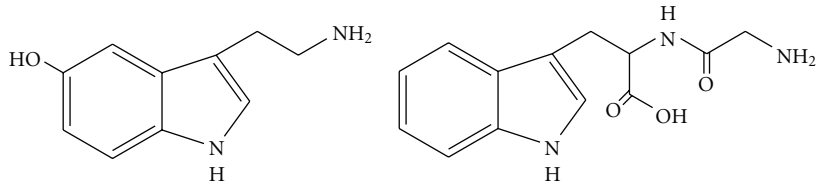
The electrochemical behavior of tryptophan and its derivatives, such as indole-3-acetic acid, 5-hydroxytryptamine (Scheme 10(a)), 5-hydroxy-indole-3-acetic acid, and glycyl-tryptophan (Scheme 10(b)) peptide at a glassy carbon electrode modified with hemin (natural metalloporphyrin) by electropolymerization have been investigated in detail [44]. The results showed that the hemin/GC electrode would catalyze the electrochemical oxidation of tryptophan and its derivatives, based on which a differential pulse voltammetric procedure. The results indicated that a two-electron and two-proton transfer was involved in the electrode reaction process.

Tryptophan is an essential amino acid for humans and a precursor for serotonin, melatonin, and niacin. It has been implicated as a possible cause of schizophrenia in people who cannot metabolize it properly. Therefore, simple, sensitive, and less expensive detection of tryptophan is of great interest. Concentration of amino acids in biological samples is low; therefore, it is necessary to use a highly sensitive method that provides determination of these analytes at subordinate concentrations. Electroanalytical technique is an attractive method due to simplicity, low expense, high sensitivity, and possibility of miniaturization. In a study [45], a modified carbon paste electrode was prepared by using TiO_2 nanoparticles and ferrocene carboxylic acid (FCCa) in carbon paste matrix. The electrocatalytic oxidation of glutathione (GSH) and tryptophan is individually and simultaneously investigated at the surface of FCCa-TiO_2 modified electrode using CV and DPV. High sensitivity and selectivity together with very low detection limit of the electrode response make it very suitable for simultaneous and individual determination of trace amounts of GSH and tryptophan in pharmaceutical and clinical preparations.

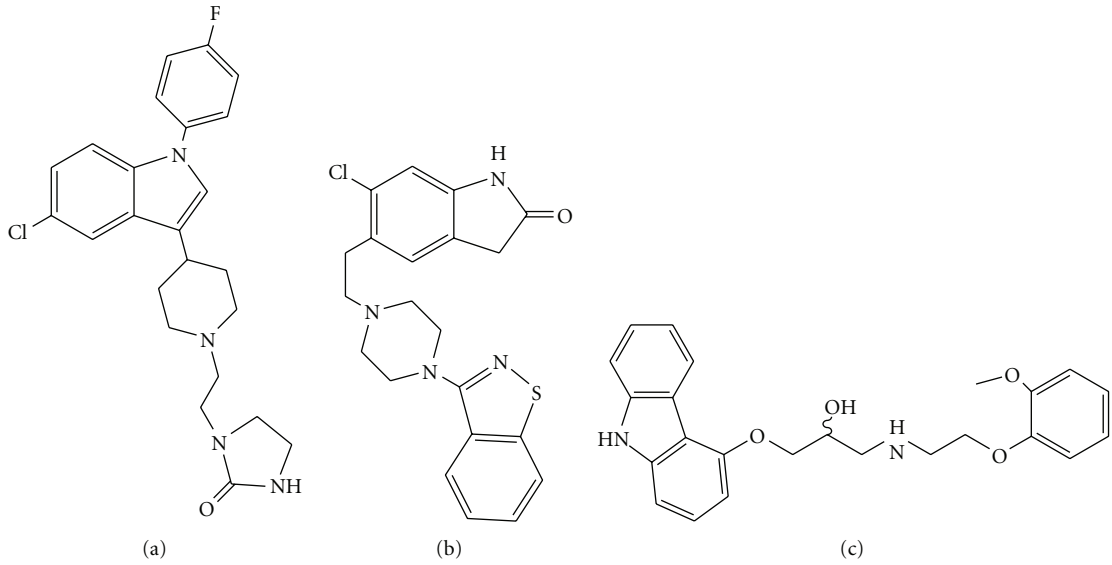
In a study, a modified electrode that was prepared by mixing 10 wt% of multiwalled carbonnanotube (MWCNT) and fine graphite powder with mineral oil (Nujol) and modified with cobalt salophen (CoSal) to applied for the selective determination of tryptophan in the presence of potentially interfering compounds such as cysteine and ascorbic acid [46]. A complete resolution between DPV peak of tryptophan from those of cysteine and ascorbic acid provides a very suitable and effective method for simultaneous determination of tryptophan, cysteine, and ascorbic acid in pharmaceutical and clinical preparations.

2.3. Studies on the Indole Ring Containing Drugs. The electrochemical oxidation of sertindole (Scheme 11(a)), the newer atypical antipsychotic was investigated using cyclic, linear sweep voltammetry at a glassy carbon and boron-doped diamond electrodes [47]. Sertindole levels were determined in serum and pharmaceutical formulations, by means of electrochemical methods. In CV, depending on pH values, sertindole showed one or two irreversible oxidation responses that were found related to the different electroactive part of the molecule. Using second and sharp oxidation peak, two voltammetric methods were described for the determination of sertindole by differential pulse and squarewave voltammetry at the glassy carbon and boron-doped diamond electrodes. To find out the relationship between the oxidative behavior and protonation constant, pK_a value of sertindole was determined. The proposed methods might be alternatives to the LC techniques in therapeutic drug monitoring or the experimental data might be used for the development LC-EC method.

Another psychotropic agent, Ziprasidone (Scheme 11), used for the treatment of schizophrenia was investigated electrochemically at boron-doped diamond and glassy carbon electrodes using cyclic, differential pulse, and squarewave voltammetry [48]. The dependence of the peak current and peak potentials on pH, concentration, nature of the buffer, and scan rate were examined. The proposed methods were



Scheme 10: Chemical formula of 5-Hydroxytryptamine (a) and Glycyl-tryptophan (b).



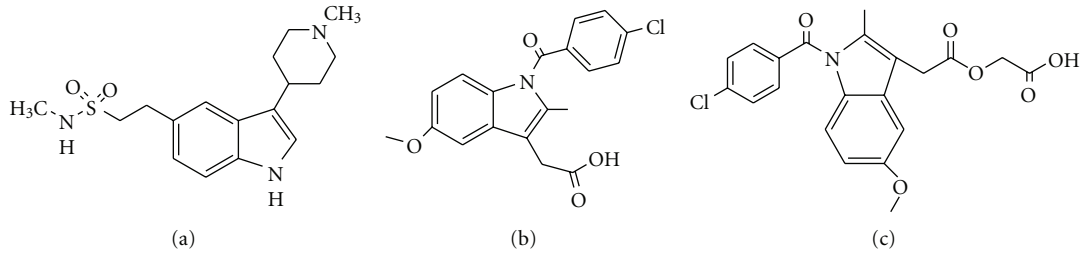
Scheme 11: Sertindole (a), ziprasidone (b), and carvedilol (c).

applied for the determination of ziprasidone from pharmaceutical dosage forms and human serum samples without any time-consuming extraction, separation, evaporation, or adsorption steps prior to drug assay except precipitation of the proteins using acetonitrile. The results were statistically compared with those obtained through an established LC-UV technique, no significant differences were been found between the voltammetric and LC methods.

Carvedilol (Scheme 11(c)) is a nonselective β-adrenergic blocking agent with α_1-blocking activity. It is used in the management of hypertension and angina pectoris and as an adjunct to standard therapy in symptomatic heart failure [49]. The electrochemical oxidation of carvedilol was investigated using cyclic, linear sweep voltammetry at a glassy carbon electrode [50]. These methods were successfully applied for the analysis of carvedilol pharmaceutical dosage forms and spiked human serum samples and were found to be rapid, requiring less than 7 min to run a sample. The electrochemical oxidation of carvedilol molecule has two irreversible electrode processes and both of them are pH dependent. No electroactive interferences from the tablet excipients and endogenous substances from biological material were found. These recovery results reveal that the proposed methods had adequate precision and accuracy, and, consequently, can be applied to the determination of carvedilol without any interference from tablet excipients.

The electrochemical behavior and the analytical application of the selective serotonin agonist naratriptan (N-methyl-3-(1-methyl-4-piperidyl)indole-5-ethanesulfonamide; Scheme 12(a)) was presented by Velasco-Aguirre and Álvarez-Lueje [51]. Naratriptan exhibits an anodic response in aqueous media over a broad pH range (pH 2–12), as determined by DPV and CV using glassy carbon electrodes. This response is irreversible in nature, diffusion controlled, and, probably, caused by the oxidation of the naratriptan indole moiety. Selectivity trials revealed that the oxidation signal of the drug was not disturbed by the presence of excipients or degradation products. It was concluded that the method offered is useful for the quantification of naratriptan in pharmaceutical drugs and that this method requires no separations or extractions. The method was found not to be time consuming and is inexpensive when compared with the Pharmacopoeial HPLC method.

Indomethacin, 1-(p-chlorbenzoil)5-metoxy-2-methyl-3-indolylacetic acid (Scheme 12(b)) is an important nonsteroidal anti-inflammatory drug, derived from indol, used in the treatment of some forms of inflammatory and degenerative diseases of articulations [52, 53]. A boron-doped diamond electrode was used to examine the possibility of



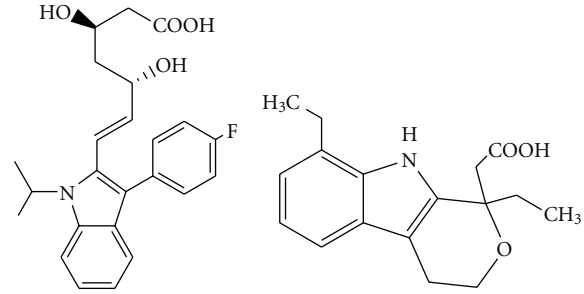
(a) (b) (c)

Scheme 12: Chemical formula of naratriptan (a), indomethacin (b), and acemethacin (c).

anodic detection and determination of indomethacin by CV. The oxidation of this drug exhibited an irreversible character. Very sensitive output signal to low concentrations has been associated with a relative high background current. Scan rate dependencies suggested a diffusion-controlled process complicated by certain surface effects [53]. In another study, procedures for the determination of indomethacin and acemetacin (Scheme 12(c)) by differential pulse adsorptive stripping voltammetry with a mercury electrode have been described and optimized [54]. In a different study, the reduction of acemetacin was established using linear-sweep voltammetry at Hg electrode [55]. Indomethacin and acemetacin in urine were determined with good results and without the need for prior separation. Determination of indomethacin was described by a fully validated squarewave adsorptive cathodic stripping voltammetric procedure [56]. The procedure was based on the reduction of the C=O double bond of the drug molecule after its preconcentration onto the mercury electrode surface. The proposed procedure was successfully applied for determination of the drug in tablets and human serum with good recoveries.

Fluvastatin sodium (Fluvastatin; Scheme 13(a)) is a water-soluble cholesterol-reducing agent which acts by inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A reductase. The oxidation of fluvastatin sodium on a glassy carbon electrode has been studied by use of a variety of voltammetric techniques [43]. Oxidation of fluvastatin sodium was found to be diffusion controlled and irreversible. The best results for the determination of fluvastatin sodium were obtained by using differential pulse and squarewave voltammetric techniques. The proposed methods were successfully applied to the determination of the drug in capsules and biological fluids. Determination of fluvastatin sodium in *Loscol capsule* and the electrochemical behavior of fluvastatin sodium on a glassy carbon electrode were investigated by CV, linear sweep voltammetry, and DPV by Yan [57]. Fluvastatin sodium gave a sensitive oxidation peak under the differential pulse voltammetric mode. The electrochemical analysis method described in the study enables simple and rapid determination of fluvastatin sodium in real samples.

Etodolac [1,8-Diethyl-1,3,4,9-tetrahydropyrano (3,4-b)-indole-1-acetic acid] (Scheme 13(b)) is a nonsteroidal anti-inflammatory drug used in postoperative pain and rheumatoid arthritis and inhibits the activity of prostaglandin synthetase. The drug appears to be uricosuric. The electrochemical oxidation of etodolac was investigated by cyclic, linear sweep, differential pulse, and squarewave voltammetry using glassy carbon electrode [22]. Based on this study, simple, rapid, selective, and sensitive two voltammetric methods were developed for the determination of the etodolac in tablet dosage form and human serum.



(a) (b)

Scheme 13: Chemical formula of fluvastatin (a) and etodolac (b).

2.4. Studies on the Other Indole Compounds. The indole nucleus is present in a wide range of natural products, and the synthesis of this important structure has been a steady topic of interest for many years. The electrochemical oxidation of catechol has been studied in the presence of indole using CV and controlled-potential coulometry methods [58]. The results revealed that the quinone derived from the oxidation of catechol participates in Michael addition reactions with indole and converts it to the trisindolyl-oquinone in a good yield via electrochemical oxidation. In another study, electrochemical behavior of some dihydroxybenzoic acid and catechol derivatives in the presence of indole as a nucleophile using cyclic strategy for the synthesis of some new indolyl derivatives of quinones and catechols was studied [59]. These products were obtained with good yields based on electrochemical oxidation under controlled-potential conditions in aqueous solutions, without toxic reagents and solvents at a carbon electrode, using an environmentally friendly method.

Electrochemical reduction of indole derivatives were studied by mechanism with many researchers [60]. Synthesis and discovery of new potent fluorinated active plant hormones was described [61]. The indirect electrochemical reduction, by means of an aromatic anion mediator,

of perfluoroalkyl halides in the presence of purine and indolyl anions was carried out. The corresponding C-perfluoroalkylated products were obtained in moderate to good yields. It was demonstrated that the electrochemical induction of the SRN_1 mechanism is a useful synthetic tool to obtain new F-alkylated purine and indole derivatives.

The oxidative dehydrocyclization of the 3-(indolizin-2′-yl)-2-oxoquinoxaline, performed either electrochemically or under the action of molecular iodine, affords new redox-active heterocyclophane [62]. The CV study of heterocyclophane showed the three-step oxidation of the indolizine fragments accompanied by the single-electron transfer in each step.

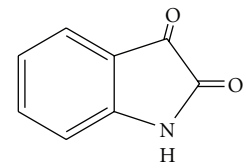
2.5. Studies on the Isatin Derivatives. The indole is known as a potent pharmacodynamic compound. One of the indole derivative, isatin (indole-2,3-dione; Scheme 14), present in mammalian tissues and body fluids, is a modulator of different biochemical processes in the body. This molecule was discovered as an inhibitor of monoamine oxidase (MAO), and subsequently identified as a selective inhibitor of MAO_B. Further investigations have shown that isatin acts as an antagonist of both atrial natriuretic peptide-stimulated and nitric oxide-stimulated guanylate cyclase activity [63]. Concentration of isatin in urine is a diagnostic marker in the clinical studies of Parkinson's disease in humans [64].

In a study with isatin, a molecule with a broad range of applications in synthetic, biological, and clinical activity undergoes oxidation and reduction at a glassy carbon electrode. The oxidation of isatin was found to be pH dependent and the reduction of isatin was irreversible. Using CV, two consecutive electron transfer reactions were identified [63].

The electrochemical behaviors of isatin, monoamine neurotransmitters, and their metabolites at chemically modified electrode were investigated by CV [65]. It was found that the PdHCF chemically modified electrode displayed high sensitivity and stability for determination of monoamine neurotransmitters and could effectively catalyze the oxidation of isatin and increase the sensitivity for determination of monoamine neurotransmitters.

The electrochemical behavior of eosin, isatin, and alloxan on the hanging mercury drop electrode was investigated using the CV and the electrochemical impedance techniques (EIS) [66]. The CV assay showed that the electroreduction of isatin was completely irreversible and a diffusion-controlled process is observed only in aprotic media. EIS data of these compounds is mostly characterized by a semicircle similar to that expected for a purely capacitive response.

Some electrochemical studies were carried out with a series of Schiff bases of 3-[5-phenylpyrazol-3-ylimino]indol-2-ones. The results have been compared with corresponding isatin in dimethylformamide in 0.1 M LiCl using CV at hanging mercury drop electrode [67]. All synthesized Schiff bases exhibit a single irreversible two-electron reduction wave in contrast with the two discrete one-electron transfer reduction waves observed for isatin in this medium. A mechanism for the electroreduction process has been proposed. Kinetic parameters have also been calculated.



Scheme 14: Chemical formula of isatin.

3. Conclusion

Indole derivatives are certainly very important 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 vivo* and *in vitro* experiments of drug candidates.

This paper reviews the current status and the recent studies of how electrochemical techniques are being used to maintain research studies of biologically important indole derivatives. The review is meant to present a general overview of the various research activities in this expanding field.

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