A REVIEW OF ELECTROCHEMICAL SYNTHESIS OF DIFFERENT INDOLE DERIVATIVES AND THEIR MEDICINAL IMPORTANCE

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Abstract

This study describes some of the most recent and significant advances in electrochemistry procedures and parameters pertaining to biologically significant indole derivatives in the context of drug discovery and research. Due to their ubiquity in natural goods, medicines, agrochemicals, and organic materials, the synthesis and functionalization of indoles have been one of the primary focuses of organic synthesis research. [1] The chemists' quest of the optimum synthesis and functionalization of indole derivatives has never ceased to seek to supply different indole-containing structures for drug discovery and material science in a greener, more sustainable manner, notwithstanding these historic breakthroughs. This article describes some of the indole derivatives produced using an electrochemical technique. [2]

Paper Identification

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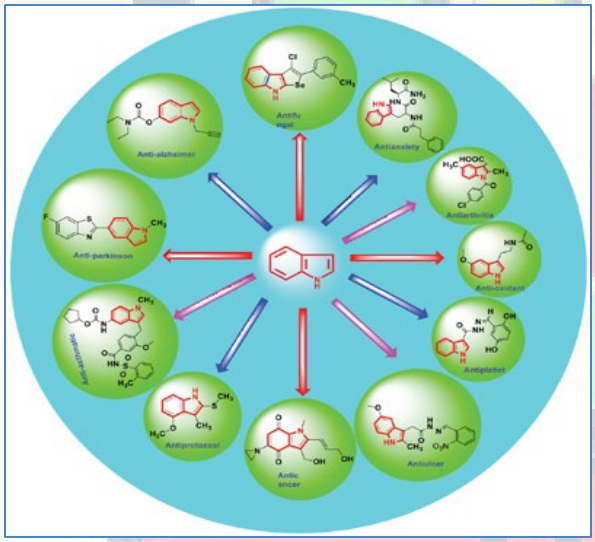
Introduction

Heterocyclic compounds play a significant role in various biological processes of the human body and many of them are in clinical use due to their diverse, chemical and biological properties. Among these, indole is one of the most promising pharmacologically active molecules. Due to its chemical reactivity, indole has been willingly modified to obtain a variety of new lead molecules, which has been successfully utilized to obtained novel drug candidates for the treatment of different pharmacological diseases.[3] Indole-based compounds describe the medicinal and pharmacological importance of the indole in uplifting human life. In this review, we compiled various reports on indole derivatives and their biological significance, including antifungal, antiprotozoal, antiplatelet, anti-Alzheimer's, anti-Parkinson's, antioxidant and anticancer potential. studies of the different derivatives have been included. We have also discussed novel synthetic strategies developed during this period for the synthesis of different indole derivatives.[4]

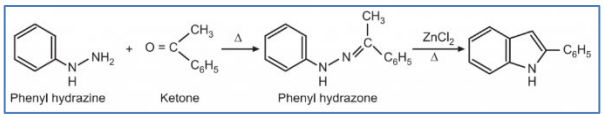
Use of electrochemistry is an important approach in drug discovery and research as well as quality control,

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.[5]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.[6] The chemists' pursuit of the ideal synthesis and functionalization of indole derivatives has lasted over years as their scaffolds have been widely found in natural products, pharmaceuticals, agrochemicals and organic materials.[7]

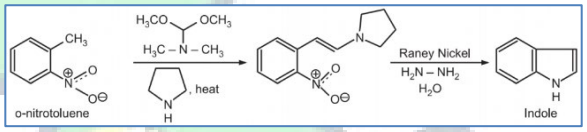


The synthesis and functionalization of indoles have been one of the central objects of research in organic synthesis due to their wild prevalence in natural products, pharmaceuticals, agrochemicals and organic materials. In this contest, a variety of well-established methods are now available including many classical named reactions such as the Fisher indole synthesis, the Gassman indole synthesis, the Bischler indole synthesis, the Batcho-Leimgruber synthesis, the Larock indole synthesis and so on.

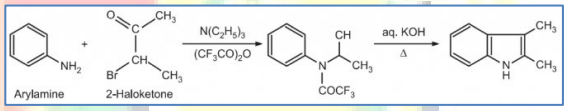
Fischer-Indole synthesis: This method was developed in 1883 by Emil Fischer. It is used to synthesize 2- and/or 3-substituted indoles. It consists of heating an arylhydrazine with an aldehyde or ketone, followed by acid-catalyzed rearrangement of resulting arylhydrazone with a loss of ammonia give an indole.



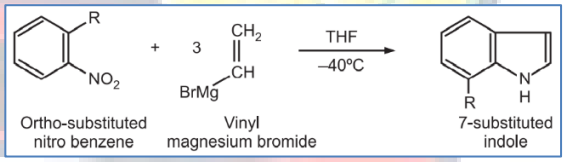
Leimgruber-Batcho indole synthesis: In this reaction, o-nitrotoluence reacts with pyrrolidine in the presence of N, N-dimethyl formamide dimethyl acetal (DMFDMA) to give an enamine. This enamine undergoes reductive cyclization to give an indole.



Bichler synthesis: An arylamine is treated with a 2-halo ketone to give α-arylaminoketone which on heating with a strong acid or zinc chloride undergoes cyclization to give an indole.



Bartoli synthesis: In this method, o-substituted nitrobenzene is treated with three moles equivalents of vinyl magnesium bromide to give 7-substituted indoles.



Despite these landmark advances, the chemists' pursuit of ideal synthesis and functionalization of indole derivatives has never stopped aiming to provide diverse indole-containing structures for drug discovery and material science in a greener, more sustainable manner.[8] Organic electrosynthesis, featuring the use of electrons as traceless reagents in lieu of chemical oxidants or reductants, is a green, sustainable synthetic platform for novel redox reactions. The capability of regulating reactions via the applied potential manipulation is particularly intriguing to organic

synthetic chemists. In addition, synthetic electrochemistry could also be adopted in the challenging chemical bond-forming reactions by tuning functional group polarity via selective addition or removal of electrons (umpolung) electrochemically which otherwise are difficult to achieve from conventional synthetic point of views.[9] 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. Some of the indole derivatives synthesized by electrochemical method are described here.

Electrochemically Synthesized Indole Derivatives

A metal-free electrochemical intramolecular C (sp2) −H amination using iodine as a mediator was developed. This method enables a switchable synthesis of indoline and indole derivatives, respectively, from easily available 2-vinyl anilines.[9] This electrochemical intramolecular C (sp2) −H amination reaction can avoid the use of a metal catalyst and a stoichiometric oxidant. The reaction can be carried out smoothly under mild conditions, which provides a rapid and efficient method for preparing functionalized indolines and indoles.[10]

We herein reported a versatile and environmentally friendly electrochemical oxidative C-H phosphonylation protocol. This ptotocol features broad substrates scope, not only C (sp2) -H phosphonylation, but also C(sp3)-H phosphonylation is tolerated well under the exogenous-oxidants-free and metal catalysts-free electrochemical oxidation conditions.Under an exogenous-oxidants-free and metal catalysts-free electrochemical oxidation conditions, a series of complex and significant phosphorus containing compounds were constructed with moderate to high yields accompanying with the hydrogen evolution. Notably, during the reaction, neither exogenous oxidant nor metal catalyst is required. With respect to the substrate scope, not only C (sp2)-H phosphonylation, but also C (sp3)-H phosphonylation is tolerated well under the electrochemical conditions.[11]

The dearomatization of arenes represents a powerful synthetic methodology to provide three-dimensional chemicals of high added value. Here we report a general and practical protocol for regioselective dearomative annulation of indole and benzofuran derivatives in an electrochemical way. Under undivided electrolytic conditions, a series of highly functionalized five to eight-membered heterocycle-2,3-fused indolines and dihydrobenzofurans, which are typically unattainable under thermal conditions, can be successfully accessed in high yield with excellent regio- and stereo-selectivity. This transformation can also tolerate a wide range of functional groups and achieve good efficiency in large-scale synthesis under oxidant-free conditions.[12]

A modest electrochemical dehydrogenative reaction with halogenated reagents was proposed under strongly basic conditions through N–R bond formation for synthesis of N-substituted indoles from 6-Nitro-1H-indole. The N protected indoles have been set under modest and scalable electrolytic conditions. Reactions was performed in a simple divided cell under constant current without using oxidizing reagents or transition-metal catalysts. According proposed method, a series of N-substituted indole derivatives was formed from 6-Nitro-1H-indole in 55-75% overall yield. 2.5 V potential was applied on the working electrode, and a graphite electrode was used as the anode and a reticulated vitreous carbon as the cathode while NBu4PF6 was used as the supporting electrolyte, the desired indole series can be gained by one-pot within 20-30 minutes over one step. For optimal results, stirring can be introduced to increase mass transfer. In this setup, the maximum N-functionalized indole derivatives concentration was reached within the first 20-25 minutes.[13]

Due to have many varieties of pharmacologic properties coumarin derivatives gain importance. several coumarin-fused heterocycles show many biological activities like medicine decoagulant ant inflammatory and so forth and chromene moiety conjointly appears as a vital structural element in each biologically active and natural compounds. Chromene fragments occur in alkaloids, flavonoids, tocopherols, and anthocyanins. Moreover, functionally substituted chromenes have vie increasing roles in artificial approaches to promising compounds within the field of healthful chemistry. To develop Associate in Nursing economical and setting friendly procedures exploitation electrogenerated bases (EGBs), a rapid, high yielding, environmentally benign, and easy synthetic protocol for the synthesis of chromeno[30,40:5,6]pyrano[2,3-d]pyrimidine-6,8,10(7H,9H,11H)-triones, as a new category of coumarin derivatives was developed , supported the electrocatalytic transformation of barbituric acid, aromatic aldehydes, Associate in Nursingd 4-hydroxycoumarin in an undivided cell at temperature below a relentless current density. Initially, the three-component reaction of barbituric acid, 3-nitrobenzaldehyde and 4-hydroxycoumarin was investigated as a model reaction in CH_3CN, in Associate in Nursing undivided cell containing an iron conductor because the cathode and a noble metal electrode as the anode at constant current within the presence of varied electrolytes at space temperature. the electrolysis was supported by KBr, NaBr, and NaF as the electrolyte, the yield wasn't satisfactory. In contrast, electrolysis within the presence of tetrabutylammonium hydroxide (TBAOH), tetrabutylammonium bromide (TBAB), and tetrabutylammonium chloride (TBAC) because the supporting electrolyte, gave the merchandise 4ain sensible yields. However, improved results were obtained once the reaction was dispensed in the presence of tetrabutylammonium halide (TBAF) as the electrolyte.[14]

Indole plays a significant role in the intestinal microecological balance and human physiological activities because of it is a main metabolite of tryptophan. As indole becomes important for its researches. So, there is need to establish a sensitive and cost-effective method for indole detection. Herein, a sensitive electrochemical method was constructed to determine the concentration of indole using screen-printed carbon electrode (SPCE) with the signal amplification strategy by gold/iron-oxide composite nanoparticles (Au/Fe_3O_4). Au/Fe_3O_4 nanoparticles were successfully synthesized under the irradiation by high-energy electron beams. 4-aminothiophenol (4-ATP) was connected to Au/Fe_3O_4 via Au-S bond. And then $NaNO_2$ reacted with 4-ATP to form the azo bond, which could form the final product of Au/Fe_3O_4 at ATP-azo-indole by the coupling reaction. Thus, the concentration of indole was detected by the electrochemical signal produced by Au/Fe_3O_4 at ATP-azo-indole indirectly. The detection sensitivity was greatly improved by the large specific surface area provided by Au/Fe_3O_4 after the modification. The linear range of indole was from 0.50 to 120.00 mg L_1 and the limit of detection (LOD) was as low as 0.10 mg L_1 (S/N ¼ 3). Furthermore, the developed method exhibited acceptable intra-day and inter-day precisions with the coefficient of variations (CV) less than 4.9% and 8.2%, respectively. And the recoveries were from 97.2% to 105.4%. An innovative, sensitive, cost-effective method was established for indole determination in human plasma matrix in this manuscript, which provides a promising way for indole detection in conventional laboratories.[15]

The 4-(dihydroxyphenylthio)-2H-chromen-2-one derivatives have been synthesized by direct electrochemical oxidation of catechols in the presence of 4-mercaptocoumarin as a nucleophile in water/acetonitrile (50/50) solution, in a one-pot

process, at carbon rod electrode, in an undivided cell and in constant current conditions, through an EC mechanism. The products are characterized by spectra data. Besides, the difference in electrochemical oxidation of catechol in the presence of 4-hydroxycoumarin and 4-mercaptocoumarin explained by computational structure, natural bond orbital (NBO) analysis and density functional theory.[16]

Electrochemical synthesis of Pyrimido 4,5-b] indoles was carried out directly by electrochemical catechol oxidation in the presence of 2,4-diamino-6-hydroxyrimidine in aquas water. The results suggest that ECEC mechanism in the additive Michael-type reaction involved the electrogenated moieties of o-benzoquinone with 2,4-diamino-6-hydroxyrimidine. These new compounds are synthesized in a high yield and purity in an aqueous solution without toxic reactions or catalysts and in high atomic economy environment. Usually, 0.25 mmol of cateches and 0.25 mmol of 2.4-diamino-6-hydroxyrimidine (2) have been electrolyzed as a buffer and electrolyte-supporting solution (pH 7.0.1 M), using a split-cell in an aqueous solution containing phosphate salts. The progress of electrolysis was monitored by cyclic voltammetry [17]

A new bisquinone synthesis with a simple, green approach based on electric oxidation of 4-methylcatechol in 1,3-indandione presence. The electrical-chemistic methodology test results, such as cyclic voltammetry and constant coulometry potentials, showed that electrical oxidation ECCE mechanisms are possible. For this device reaction, eight-electron cycles (ECCE) were shown to be controlled-potential coulometry data. In addition, electrochemicals were the "strong method" to synthesize modern organic compounds like quinones in this research. The anode is made of platinum or aluminum titanium or of mild copder or steel. As a cathode, graphite was used. Solvents were water or double water or sea water.[18]

A tandem electrochemically induced reaction was developed for selective N1-alkylation and C3-halogenation of indoles. This electro-chemical difunction technique circumvents conventional, multi-stage procedures and effectively generates N-alkyl-3-halo-indol synthesis under environmentally friendly conditions. The reaction can occur in a simple undivided cell without using any oxidant, base or transition metal. The highly efficient atomic use, without nuclear waste, of alkyl halide as alkylating, halogenating building blocksis stressed. This difunctionalization reaction, driven by the galvanostatic electrolysis in an undivided cell, can be achieved in one-pot manner under more environmentally benign conditions. Being external base-free, oxidant-free and transition metal-free, the present strategy fully uses alkyl halide as both alkylating and halogenating reagent. Mechanistically we have demonstrated that C-H halogenation and N-H alkylation take place in a cascade sequence with the help of the recyclable metallic halide salt. The synthetic potential of this method is highlighted by its high atom economy and easy scalability, which may make a new path in term of synthetic chemistry and pharmaceutical industry.[19]

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. We developed a new application of the electrogenerated cyanomethyl anion that involves its use, as an electrogenerated base, in the synthesis of functionalized indoles from alkynylanilines. The approach proposed is very clean and safe and avoids the use of metal catalysts or classical organic acids and bases. The workup is very easy and simply requires filtration or flash chromatography of the evaporated reaction mixture without any extractive workup.

Thus, this electrochemical approach represents a valuable and competitive alternative to the reported procedures. A solution (12.0 mL) of CH_3CN/0.1 TEATFB was electrolyzed under galvanostatic control

(Pt cathode 1.5 cm2; J = 25 mAcm–2, Q = 2.5 Fmol–1 of 1) at 0 °C. No pre-electrolysis was required. At the end of electrolysis, 2-alkynylaniline 1 (0.4 mmol) was added to the cathode compartment, and the reaction was prolonged at the temperature and for the time reported in Table 2. The solvent was evaporated under reduced pressure. The crude mixture yielded pure indole after simple filtration through silica gel.[20]

A comparative study on electropolymerization of 2, 3, 5 and 6–carboxylic acid substituted derivatives of indole over glassy carbon electrode (GCE) is reported. Electropolymerization occurred in case of 2, 5 and 6–substituted indoles. Among these, the polymers resulting from 5 and 6– substituted derivatives are found soluble in aqueous medium and characterized by cyclic voltammetry, UV-vis spectroscopy and visual photographs. The processable polymers are cast over GCE using Nafion and used for selective sensing of Dopamine (DA) in presence of Ascorbic acid (AA). When such polymer matrix is coupled with redox mediators viz. tetracyanoquinodimethane (TCNQ), ferrocene (Fc) and dimethyl ferrocene (dmFc), differential amplified responses in each case on DA sensing are recorded. The sensitivity of DA analysis over these electrodes are found to be 18 μA + 6 nA/mM, 14 μA + 11 nA/mM and 16 μA + 9 nA/mM for TCNQ, Fc and dmFc respectively whereas the lowest detection limit is found to be 4μM in each case.[21]

An efficient method has been developed for the synthesis of 1,8-dioxo-octahydroxanthene derivatives in two-step. In the first step, the electrogenerated base (EGB) catalyzed multicomponent transformation of dimedone and aromatic aldehydes in an undivided cell in the presence of sodium bromide as an electrolyte into 2,2_-arylmethylene bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) at room temperature. In the second step, H_2SO_4 was employed as a dehydrating reagent for the cyclization process to give symmetrical heterocycles 1,8-dioxo-octahydroxanthene derivatives. Short reaction time, convenient work up, and using of inexpensive reagents, simple equipment, novel and eco-friendly procedure make this strategy more useful for the preparation of xanthene derivatives. A solution of aromatic aldehyde (1mmol), dimedone (0.280 g, 2 mmol) and sodium bromide (0.01 g, 0.1 mmol) in methanol (10 mL) was electrolyzed in an undivided cell equipped with a magnet stir-bar, platinum anode and an iron cathode at room temperature under constant current density 20 mA/cm^2 (I = 50 mA, electrodes square 2.5 cm^2) until the catalytic quantity of the electricity was passed. The progress of the reaction was monitored by thin layer chromatography using n-hexan/ ethyl acetate (2:1). After completion of reaction, the obtained precipitate was filtered, and the filter cake was washed with ethanol to yield pure products.[22]

Medicinally Important Derivative of Indole

Two series of different indole derivatives were prepared and evaluated for their radical-scavenging ability. Arylidene-1H-indole-2-carbohydrazones showed different extent antioxidant activity in DPPH, FRAP and ORAC assays. Good antioxidant activity is related to the number and position of hydroxyl groups on the arylidene moiety as well as to the presence of methoxy or 4-(diethylamino) group. On the contrary low antioxidant activity is showed by the isomeric 1H-indol-2-yl(methylene)-benzohydrazides. Furthermore, hydrazones showed photoprotective capacities with satisfactory in vitro SPF as compared to the commercial PBSA sunscreen filter. The indole showing the best antioxidant and photoprotective profile, were included in different formulation and their topical release was evaluated. Varying the formulation composition, it was possible to optimize skin adsorption and solubility of the active indole in the formulation. The antiproliferative effect of the hydrazones was tested on human erythroleukemia K562 and melanoma Colo-38 cells. Hydrazones

showed growth inhibition at sub micromolar concentrations on both cell lines. These results indicate indole hydrazones as potential multifunctional molecules especially in the treatment of neoplastic diseases being the good antioxidant properties correlated to their high antiproliferative activity.[23]

A new series of thiazole nortopsentin analogues was conveniently synthesized with good yields. The antiproliferative activity of the new derivatives was tested against different human tumor cell lines of the NCI full panel. Four of them showed good antitumor activity with GI50 values from micro to nanomolar level. The mechanism of the antiproliferative effect of these derivatives, was pro-apoptotic, being associated with externalization of plasma membrane phosphatidylserine and DNA fragmentation. The most active and selective of the new thiazoles confined viable cells in G2/M phase and markedly inhibited in vitro CDK1 activity.[24]

Oxidative stress has been recognized as a contributing factor in ageing and various diseases including cancer and neuropathological disorders. Indole derivatives such as the neurohormone melatonin (MLT) constitute an important class of therapeutic agent in medicinal chemistry. MLT can scavenge different reactive oxygen species and can also stimulate the synthesis of antioxidant enzymes. As a part of our ongoing studies, a series of new indole-based hydrazide/hydrazone derivatives were synthesized as MLT analogues. Their antioxidant activity was investigated in human erythrocytes by evaluating their reducing effect against oxidation of a redox-sensitive fluorescent probe. Possible inherent cytotoxicity of the compounds was investigated in CHO-K1 cells by lactate dehydrogenase leakage test. Protection of neuronal PC12 cells against amyloid β-induced damage was examined by MTT assay and their ability in reduction of ROS generation induced by amyloid β was tested. MLT analogues having an o-halogenated aromatic moiety exhibited effective antioxidant properties without having any membrane-damaging effect. Moreover, derivatives having o-halogenated and dihalogenated aromatic side chain significantly protected neuronal cells at concentrations of 10 and 100 μM. In conclusion, MLT derivatives represent promising scaffolds for discovery of effective antioxidant and neuroprotective agents.[25]

Diabetic complications including nephropathy, neuropathy, and cataract are leading causes of end-stage renal diseases and neurological disorders. Aldose reductase (AR), the rate-limiting enzyme of the polyol pathway, catalyzes the reduction of glucose to sorbitol via NADPH. Excessive accumulation of intracellular sorbitol found in various tissues of diabetic animals and in cells cultured under high glucose conditions has been proposed to be an important factor for the pathogenesis of diabetic complications. Indole ring–containing AR inhibitors have received considerable attention as potential treatments for diabetic complications. we have reported preliminary in vitro biological evaluation of substituted 2PI and 2PIA derivatives as AR inhibitors. Compounds (2PI), and (2PIA) demonstrated some AR inhibition activity. Although the results are not significant, a correlation may be drawn between these compounds and their antioxidant activities (DPPH antiradical activity and superoxide radical scavenging activity). The results of the biological evaluation allowed us to obtain insight into the initial structural features critical for AR inhibition in this series. Thus, based on these findings, further modifications on the present series of compounds are needed.[26]

A new series of bis(indolyl) ketohydrazide-hydrazones was synthesized from the reaction of indolyl glyoxalyl hydrazides with appropriate aldehydes and evaluated there in vitro anticancer activity. Compound 21k exhibited the most potent anticancer activity against five tested cancer cell lines with IC50 values ranging 0.15-0.8 μM. The most potent compound 21k was selectively more cytotoxic to cancerous cells compared

to non-cancerous cells. SAR studies revealed that both side indole rings are critical for the excellent in vitro anticancer activity of ketohydrazide hydrazones. Mechanism of the action studies suggested that bis(indolyl) ketohydrazidehydrazones induced apoptosis via caspase 3/7 activation but was not toxic. Compound 21k arrested cell cycle in G2/M phase by binding to tubulin and inhibiting tubulin polymerization (IC50 = 0.6 μM). Moreover, molecular docking studies indicate that 21k tubulin binding is similar to colchicine/tubulin binds which supports inhibition of tubulin polymerization by 21k. [27]

With some indoles and azaindoles being successfully developed as anticancer drugs, the design and synthesis of indole and azaindole derivatives with remarkable antitumor activity has received increasing attention and significant progress has been made. This paper reviews the recent progress in the study of tumorigenesis, mechanism of actions and structure activity relationships about anticancer indoles and azindoles derivatives. Combining structure activity relationships and molecular targets-related knowledge, this review will help researchers design more effective, safe and cost-effective anticancer indoles and azindoles agents. Based on the scaffold of indole and azaindole, design and synthesis of heterocyclic compounds including monoindoles, bisindoles, 4-azaindoles, 5-azaindoles, 7-azaindoles and azaindole complexes has generated many potent anticancer compounds and some of them have exhibited inhibitory activity on cancer cell lines or target at nanomolar concentration range with less side effects and toxicity. More important, the design of indole and azaindole molecules targeting growth factors/receptors/ enzymes/kinases have become the trend due to the NH group in the indoles and azaindoles often forms the key hydrogen bonds with corresponding receptor, and the SAR and detail mechanism of actions of active compounds also have been elucidated as far as possible. Although it is still in the primary stage, the design of indole and azaindole compounds for targets such as HDAC, COX, EGFR, VEGFR, PI3K, mTOR, CDKs, c-Met, GSK-3β, PIM, DYRK1A have been carried out. And more than ten intriguing anticancer lead compounds containing indole or azaindole skeleton were found and several of them were identified effectively inhibiting the growth of solid tumors and metastasis of cancer cells. The remarkable anticancer lead compounds obtained by designing of hybrids of indole or azaindole with other active moiety and azaindole heterocyclic scaffolds targeting on specific target are undoubtedly bright spots in past few years, these achievements provide valuable strategies and clues to the development of better antitumor activity agents.[28]

A series of thirty-eight novel 3-(4-((substituted-1H-1,2,3-triazol-4-yl) methyl) piperazin-1-yl/1,4-diazepan-1-yl) benzo[d]isoxazole and 1-(4-(benzo[d]isoxazol-3-yl) piperazin-1-yl/1,4-diazepan-1-yl)-2-(1H-indol-3-yl) substituted-1-one analogues were synthesized, characterized using various analytical techniques and evaluated for in vitro antitubercular activity against Mycobacterium tuberculosis H37Rv strain and two ‘wild’ strains Spec. 210 and Spec. 192. The titled compounds exhibited minimum inhibitory concentration (MIC) ranging from 6.16 - >200 μM. The tested compound showed moderate activity (MIC = 24.03 – 29.19 μM) and very good anti-tubercular activity (MIC = 6.16 μM). Furthermore, some compounds were found to be non-toxic against mouse macrophage cell lines when screened for toxicity. All the synthesized compounds were docked to pantothenate synthetase enzyme site to know deferent binding interactions with the receptor.[29]

A novel series of twenty 3-thiocyanato-1H-indoles, carrying diversification at positions N-1, C-2 and C-5 of the heterocyclic core, were synthesized; their antiproliferative activity against four human cancer cell lines (HL60, HEP-2, NCI-H292 and MCF-7) was evaluated, employing doxorubicin as positive control. Indole, N-methylindole and 2-(4-chlorophenyl)-N-

methylindole demonstrated to be essentially inactive, whereas several of their congener 3-thiocyanato-1H-indoles displayed good to excellent levels of potency (IC50 _ 6 mM), while being non-hemolytic. N-Phenyl-3-thiocyanato-1H-indole and 1-methyl-2-(4-chlorophenyl)-3-thiocyanato-1H-indole showed good to high potency against all the cell lines. On the other side, the N-(4-chlorophenyl)-, 2-(4-chlorophenyl)- and 2-phenyl- 3-thiocyanato-1H-indole derivatives were slightly less active against the test cell lines. Overall, these results suggest that the indole-3-thiocyanate motif can be suitably decorated to afford highly cytotoxic compounds and that the substituted indole can be employed as a useful scaffold toward more potent compounds.[30]

The enzyme isoprenylcysteine carboxyl methyltransferase (Icmt) plays an important role in the posttranslational modification of proteins that are involved in the regulation of cell growth. The indole acetamide cysmethynil is by far the most potent and widely investigated Icmt inhibitor, but it has modest antiproliferative activity and may have pharmacokinetic limitations due to its lipophilic character. We report here that cysmethynil can be structurally modified to give analogues that are as potent in inhibiting Icmt but with significantly greater antiproliferative activity. Key modifications were the replacement of the acetamide side chain by tertiary amino groups, the n-octyl side chain by isoprenyl and the 5-m-tolyl ring by fluorine. Moreover, these analogues have lower lipophilicities that could lead to improved pharmacokinetic profiles.[31]

All the newly synthesized compounds were evaluated for their anti-inflammatory activity against carrageenin-induced paw edema method in rats, using indomethacin as reference drug at a dose of 0.2 mmol/kg I.P. Percent of the edema inhibition was calculated after 4 hr of carrageenin treatment. The tested compounds showed good anti-inflammatory activity ranging between 72.3 – 89.3%.

The synthesized target compounds were evaluated for their cytotoxic activity in vitro against Human breast carcinoma cell line (MCF7) using doxorubicin as a reference compound. The results of single dose experiment (100µg/ml) of synthesized compounds performed on Human breast carcinoma cell line (MCF7). From the results found that some compounds exhibited the percent of inhibition 65% at the dose 100 µg/ml. While, the rest of compounds showed less activity (the percent of inhibition were ranged between 0 - 20.5 %). Also, the derivatives at meta- position had higher activity than derivatives at para-position.[32]

Numerous studies indicate that indole and its derivatives affect host physiology via a number of different molecular mechanisms and may contribute to intestinal and systemic homeostasis by regulating the crosstalk between the microbiota and host innate immune system. Several indole derivatives have been described as ligands of the aryl hydrocarbon receptor (AhR), a cytosolic ligand-activated transcription factor widely expressed by immune cells that regulates intestinal immune homeostasis. AhR is involved in antimicrobial defence via induction of interleukin-22 expression. Interleukin-22 further regulates microbial composition and enhances antimicrobial defence via the induction of antimicrobial proteins such as regenerating islet-derived protein three gamma (REG3G). Secondly, AhR acts anti-inflammatory via the regulation of the development of intraepithelial lymphocytes and innate lymphoid cells, which are important in defending against infiltrating pathogens and facilitating gut homeostasis. These activities of AhR help ensure that commensal bacteria outcompete pathogenic bacteria in the gut microbiota and prevent dysbiosis to occur. Importantly, differences exist in the affinity for AhR ligands between humans and rodents, and even within laboratory mouse strains. Recent studies suggest that human AhR has a higher affinity for a number of tryptophan-derived ligands. Whereas most predictions for human studies are done based on

results from rodents, the difference in AhR ligand affinity is important to consider in translational studies.Indole has been described in both in vitro as well as in vivo studies as a beneficial molecule for the gut by increasing epithelial tight junctions.[33]

Indole and its derivatives have been shown to interfere with the quorum sensing (QS) systems of a wide range of bacterial pathogens. While indole has been previously shown to inhibit QS in Serratia marcescens, the effects of various indole derivatives on QS, biofilm formation, and virulence of S. marcescens remain unexplored. Hence, in the present study, we investigated the effects of 51 indole derivatives on S. marcescens biofilm formation, QS, and virulence factor production. The results obtained revealed that several indole derivatives (3-indoleacetonitrile, 5-fluoroindole, 6-fluoroindole, 7-fluoroindole, 7-methylindole, 7-nitroindole, 5-iodoindole, 5-fluoro-2-methylindole, 2-methylindole-3-carboxaldehyde, and 5-methylindole) dose-dependently interfered with quorum sensing (QS) and suppressed prodigiosin production, biofilm formation, swimming motility, and swarming motility. Further assays showed 6-fluoroindole and 7-methylindole suppressed fimbria-mediated yeast agglutination, extracellular polymeric substance production, and secretions of virulence factors (e.g., proteases and lipases). QS assays on Chromobacterium violaceum CV026 confirmed that indole derivatives interfered with QS. The current results demonstrate the antibiofilm and antivirulence properties of indole derivatives and their potentials in applicationstargeting S. marcescens virulence.[34]

Enteropathogenic Escherichia coli (EPEC), enterohemorrhagic E. coli (EHEC) and enteroaggregative E. coli (EAEC) are intestinal pathogens that cause food and water-borne disease in humans. Using biochemical methods and NMR-based comparative metabolomics in conjunction with the nematode Caenorhabditis elegans, we developed a bioassay to identify secreted small molecules produced by these pathogens. We identified indole, indole-3-carboxaldehyde (ICA), and indole-3- acetic acid (IAA), as factors that only in combination are sufficient to kill C. elegans. Importantly, although lethal to C. elegans, these molecules downregulate several bacterial processes important for pathogenesis in mammals. These include motility, biofilm formation and production of Shiga toxins. Some pathogenic E. coli strains are known to contain a Locus of Enterocyte Effacement (LEE), which encodes virulence factors that cause ‘‘attaching and effacing’’ (A/E) lesions in mammals, including formation of actin pedestals. We found that these indole derivatives also downregulate production of LEE virulence factors and inhibit pedestal formation on mammalian cells. Finally, upon oral administration, ICA inhibited virulence and promoted survival in a lethal mouse infection model. In summary, the C. elegans model in conjunction with metabolomics has facilitated identification of a family of indole derivatives that broadly regulate physiology in E. coli, and virulence in pathogenic strains. These molecules may enable development of new therapeutics that interfere with bacterial small-molecule signalling.[35]

YafQ is an endoribonuclease toxin that degrades target gene transcripts such as that of tnaA, a gene encoding tryptophanase to synthesize indole from tryptophan. DinJ is the cognate antitoxin of YafQ, and the YafQ-DinJ system was reported to regulate persister formation by controlling indole production in Escherichia coli. In this study, we investigated the role of YafQ-DinJ, indole production, and persister population in bacterial heat tolerance. yafQ (ΔyafQ), dinJ (ΔdinJ), and tnaA (ΔtnaA) single-gene knockout mutants showed approximately 10-fold higher heat tolerance than wild-type (WT) E. coli BW25113. Persister fractions of all mutants were slightly larger than that of the WT. Interestingly, these persister cells showed an approximately 100-fold higher heat tolerance than normal cells, but there was no difference

among the persister cells of all mutants and the WT in terms of heat tolerance. Indole and its derivatives promoted a drastic reduction of bacterial heat tolerance by just 10 min of pretreatment, which is not sufficient to affect persister formation before heat treatment. Surprisingly, indole and its derivatives also reduced the heat tolerance of persister cells. Among the tested derivatives, 5-iodoindole exhibited the strongest effect on both normal and persister cells.[36]

The key objective of the present study to contribute to the growing drug design area (such as treatment innovation and improvement) by examining protein-drug interactions. We aimed to present a summary of the protective effects of MMINA against cisplatin allied hepatotoxicity, neurotoxicity, cardiotoxicity, and nephrotoxicity, during cisplatin therapy. MMINA can compensate cisplatin-induced neurotoxicity, hepatotoxicity, neurotoxicity, cardiotoxicity, and nephrotoxicity frequently through anti-inflammatory and antioxidant and mechanisms. In this context, the protective effects of MMINA essentially root in a variation of STAT3, TNF-α, COX2, IL1, and NF-κB transcription factors which are significant regulators of inflammation and oxidative stress. Our comprehensive experimental and in silico studies provide novel insights into the protective activities of novel indole derivative MMINA and its potential uses in combination anticancer therapy. These promising possessions require proof-of-concept clinical trials to be conducted and additional efforts to test the protective effects of MMINA and its structural analogs.[37]

Natural prenylated indoles have been proposed as potential anticancer agents. To exploit this discovery for developing new peptide therapeutics, we report the first studies whereby incorporation of prenylated indoles into primary sequences has been achieved. We developed a route to synthesise Nα -Fmoc-protected tryptophan derivatives in which the prenyl group is linked to the N-indole core, using PdIJII)-mediated C–H functionalisation of 2-methyl-2-butene. Based on the Substance P antagonist G (SPG), a well-known Small Cell Lung Cancer (SCLC) anticancer agent, we designed a new penta-peptide sequence to include a prenyl moiety on one of the tryptophan residues. The N-tert-prenylated tryptophan analogue was assembled into the pentameric peptide using standard solid phase peptide synthesis or liquid phase synthesis by fragment coupling. In vitro screening showed that the N-tert-prenylation of the indole ring on the tryptophan residue located near the C-terminal of the penta-peptide enhanced the cytotoxicity against H69 (IC50 = 2.84 ± 0.14 μM) and DMS79 (IC50 = 4.37 ± 0.44 μM) SCLC cell lines when compared with the unmodified penta-peptide (H69, IC50 = 30.74 ± 0.30 μM and DMS79, IC50 = 23.00 ± 2.07 μM) or the parent SPG sequence (IC50 > 30 μM, both cell lines). SCLC almost invariably relapses with therapy-resistant disease. The DMS79 cell line was established from a patient following treatment with a number of chemotherapeutics (cytoxan, vincristine and methotrexate) and radiation therapy. Treating DMS79 tumour-bearing nude mice provided a human xenograft model of drug resistance to test the efficacy of the prenylated peptide. A low dose (1.5 mg kg−1) of the prenylated peptide was found to reduce tumour growth by ∼30% ($P < 0.05$) at day 7, relative to the control group receiving vehicle only. We conclude that the availability of the FmocTrpIJN-tert-prenyl)-OH amino acid facilitates the synthesis of prenylated-tryptophan-containing peptides to explore their therapeutic potential.[38]

This review article illustrates the growing use of azaindole derivatives as kinase inhibitors and their contribution to drug discovery and innovation. The different protein kinases which have served as targets and the known molecules which have emerged from medicinal chemistry and Fragment-Based Drug Discovery (FBDD) programs are presented. The various synthetic routes used to access these

compounds and the chemical pathways leading to their synthesis are also discussed. An analysis of their mode of binding based on X-ray crystallography data gives structural insights for the design of more potent and selective inhibitors.

The synthesis and the use of azaindoles in the design of new kinase inhibitors, clearly shows that this scaffold continues to be of major importance for the preparation of biologically active compounds. The creation of an azaindole "platform", functionalized by a variety of reactions (lithiation, protection, oxidation, palladium catalyzed coupling etc.) is the key to molecular diversity. These compounds display a strong biocompatibility, and are easily tolerated in living organisms. The azaindole is an excellent bioisostere for the indole ring system and this fact is confirmed by the growing number of literatures references each year which use this concept to create active molecules. In parallel to the drug design process which brings together medicinal chemists, computational chemists, biologists and pharmacologists, an important number of fundamental organic syntheses are also being developed. New reactions and methodology based on the creativity of organic chemists are being explored with (hetero)-aromatic or heterocyclic non-aromatic systems (pseudo-sugars and peptides). These strategies make full use of the different possibilities offered by the growing field of organocatalysis, the use of rare metals or enzymes to remove restrictions and create new structures or functionalization. One day, some of them will undoubtedly be applied to the azaindole ring system, and thus the necessary continuum that exists between fundamental chemistry and medicinal chemistry will be reinforced. [39]

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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