IMIDAZOLE BASED FLUORESCENT CHEMOSENSORS

A DISSERTATION REPORT BY:

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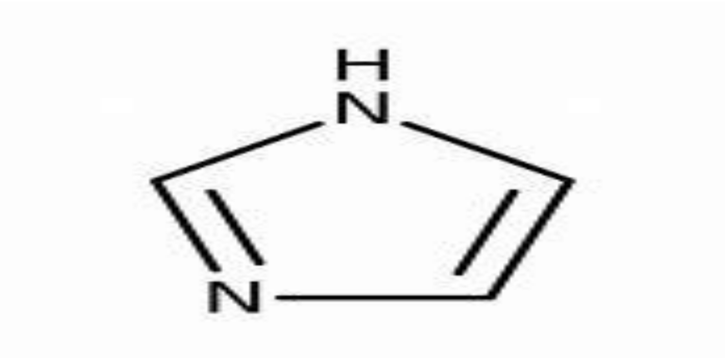
INTRODUCTION

Imidazole is a planer five-member heterocyclic ring with 3C and 2N atom and in ring N is present in 1st and 3rd positions. The imidazole ring is a constituent of several important products, including purine, histamine, histidine and nucleic acid. Being a polar and ionisable aromatic compound, it improves pharmacokinetic characteristics of lead molecules and thus used as a remedy to optimize solubility and bioavailability parameters of proposed poorly soluble lead molecules. Imidazole derivatives have occupied a unique place in the field of medicinal chemistry. The incorporation of the imidazole nucleus is an important synthetic strategy in drug discovery. The high therapeutic properties of the imidazole related drugs have encouraged the medicinal chemists to synthesize a large number of novel chemotherapeutic agents. Imidazole drugs have broadened scope in remedying various dispositions in clinical medicines. Numerous methods for the synthesis of imidazole and also their various structure reactions offer enormous scope in the field of medicinal chemistry. This articles aims to review the work reported, their chemistry and biological activities of imidazole during past years. Imidazoles are well known heterocyclic compounds which are common and have important feature of a variety of medicinal agents.

Imidazole is a 5-membered planar ring, which is soluble in water and other polar solvents. It exists in two equivalent tautomeric forms because the hydrogen atom can be located on either of the two nitrogen atoms. It is a highly polar compound, as evidenced by a calculated dipole of 3.61D, and is entirely soluble in water. The compound is classified as aromatic due to the presence of a sextet of π-electrons, consisting of a pair of electrons from the protonated nitrogen atom and one from each of the remaining four atoms of the ring. Imidazole is amphoteric, i.e. it can function as both an acid and as a base

Imidazole ring is an important five-membered aromatic heterocycle widely present in natural products and synthetic molecules.The unique structural feature of imidazole ring with desirable electron rich characteristic is beneficial for imidazole derivatives to readily bind with a variety of enzymes and receptors in biological systems through diverse weak interactions, thereby exhibiting broad bioactivities. The related research and developments of imidazole-based medicinal chemistry have become a rapidly developing and increasingly active topic. Particularly, numerous imidazole-based compounds as clinical drugs have been extensively used in the clinic to treat various types of diseases with high therapeutic potency, which have shown the enormous development value. This work systematically gives a comprehensive review in current developments of imidazole-based compounds in the whole range of medicinal chemistryasanticancer,antifungal,antibacterial,antitubercular,a nti-inflammatory,antineuropathic,antihypertensive, antihistaminic, antiparasitic, antiobesity, antiviral, and other medicinal agents, together with their potential applications in diagnostics and pathology. It is hoped that this review will be helpful for new thoughts in the quest for rational designs of more active and less toxic imidazole-based medicinal drugs, as well as more effective diagnostic agents and pathologic probe

STRUCTURE OF IMIDAZOLE



Biological significance of imidazole

Imidazole is incorporated into many important biological molecules. The most important is the amino acid histidine, which has an imidazole side chain. Histidine is present in many proteins and enzymes play a vital role in the structure and binding functions of hemoglobin. Histidine can be decarboxylated to histamine, which is also a common biological compound. It is a component of the toxin that causes urticaria, i.e. allergic.

APPLICATIONS

I} **Fluorescent imidazole-based chemosensors for the reversible detection of cyanide and mercury ions**

The coordination chemistry of anions and metals gained significant attention in recent times due to its relevance to ecology, health and other areas. Especially the development of fluorescent sensors and molecular receptors for the detection of chemical species for biological, environmental and security applications is a contemporary area of interest. Among the anions, cyanide is extremely toxic and deleterious to human health, causing vomiting, convulsions, loss of consciousness, and eventually leads to death. According to the World Health Organization, the maximum acceptable level of cyanide in drinking water is 1.9 μM. Due to the increased use of cyanide in many products and processes ranging from plastic, fibers, gold, dyes, chelating agents for water treatment, to pharmaceuticals it poses a significant threat to life likewise, among the dangers of various heavy metal ions, mercury ranks the highest due to its deleterious effects on human health and environmental impact.5 Even at very low concentrations the Hg2+ ion is extremely toxic to living creatures and can affect various organs of the body, including the nervous system due to the ease of membrane passage of Hg2+ and some of its derivatives.Therefore, it is desirable to develop sensitive, selective and practical methods to monitor the very low concentration of cyanide/mercury from contaminant sources and drinking water and in possible security scenarios., Although many chemical and physiochemical methods (chromatography, electrochemical analysis, etc.) have been developed for the detection of cyanide their practical applications have been limited due to difficulties in sample preparation, complicated measurements, and low sensitivity. Optical chemosensors for cyanide have attracted considerable attention in the last decades due to their simplicity and rapid measurements. Among various detection techniques, fluorescence detection is the most attractive as it offers several advantages including high sensitivity, the simplicity of operation and noninvasiveness. Accordingly, significant efforts have been expended on the development of fluorescent sensors for cyanide.As cyanide is a good nucleophile this characteristic can be used as a basis for the development of chemodosimetric probes in aqueous or semi aqueous solutions.10e Fluorescent dyes based on excited-state intra-molecular proton transfer (ESIPT) have emerged as a promising class of materials for many practical applications such as optical sensors, switches, laser dyes, and white light OLEDs. For example, Lochbrunner et al. explored the concept of ESIPT by using 2-(2-hydroxyphenyl)benzothiazole (HBS) and 2-(2hydroxyphenyl)- benzoxazole (HBO) moieties. Subsequently, many HBO and HBS derivatives were studied for their application in biological systems, as anion sensors, and in the fabrication of light-emitting devices.2-(2Hydroxyphenyl)-benzimidazole (HBI) derivatives have much higher quantum yields and show better sensitivity towards anions or cations in protic/polar solvents compared to HBO/HBS derivatives .Based on this advantage, benzimidazole derivatives have become attractive targets in opticals.sensing and material studies. In this context, we were interested to explore the potential of imidazolebased reversible chemosensors for the detection of cyanide and mercury ions.

II} Colorimetric detection of Fe3+ and Fe2+ and sequential fluorescent detection of Al3+ and pyrophosphate by an imidazole-based chemosensor in a near-perfect aqueous solution

A novel chemosensor was designed and synthesized for various analytes: Fe3+, Fe2+, Al3+ and pyrophosphate. The sensor showed a selective color change from yellow to orange toward both Fe3+ and Fe2+ in a near-perfect aqueous solution, which could be reusable simply through treatment with ethylene diaminetetraacetic acid. The detection limits (0.27 μM and 0.32 μM) for Fe3+ and Fe2+ were much lower than the environmental protection agency guideline (5.37 μM) in drinking water. The sensor could be used to quantify Fe3+ in real water samples. Moreover, this sensor acted as a 'turn-on' and 'turn-off' type fluorescent sensor toward Al3+ and pyrophosphate. The sensing mechanism of the sensor for Al3+ could be explained by chelation-enhanced fluorescence effect, which was supported by theoretical calculations. Through a metal-complex displacement method, the sensor-Al3+ complex selectively responded to pyrophosphate over various anions especially including phosphate-based anions. Interestingly, the sensor could be used to sequentially detect both Al3+ and pyrophosphate in the living cells. The development of chemical sensors for biologically and environmentally important metal ions and anions has received considerable attention because of their significant roles in industry, medicine, human health and the environment . The chemical Sensors have analytical merits, such as high selectivity, eidetic recognition, rapid response and real time monitoring . Among heavy metals, iron is one of the indispensable metal ions and plays an important function in a wide range of organic and biological processes such as oxygen-carrying, cellular metabolism, enzymatic reaction and various bio-syntheses . However, the deficiency or overload of iron in humans cause various diseases such as anemia, liver damages and hemochromatosis . For these reasons, detecting iron ions has steadily attracted a great deal of attention in various areas .

Aluminium, the third most prevalent metallic element in the earth, is extensively used in various fields, including food packaging, pharmaceuticals, water purification, and the manufacturing industry . Because of its wide use, aluminium ion can be easily accumulated in human body. The accumulation of the ion can lead to many hazardous diseases such as Parkinson’s disease and Alzheimer’s disease . Hence, the development of sensors for aluminium is highly desirable in environmental and biological system

Pyrophosphate (P2O74-, PPi), the product of adenosine triphosphate (ATP) hydrolysis under cellular conditions, has been received attention due to its important roles in many crucial reactions, such as energy transduction, metabolic processes and DNA/RNA polymerization . Also, the detection and quantification of PPi are of importance in cancer and various disease research areas. Therefore, there have been tremendous efforts to develop the sensors for PPi [27,28]. Recently, a metal-complex displacement method was recognized as one of the successful strategies in the design of detector for PPi, with a specific interaction between metal ions and PPi . Up to now, most of the metal complex displacement-type probes for PPi used Zn2+, Fe3+ and Cu2+ as a metal source , while only few examples were reported for Al3+ used as a metal source .

Imidazole derivatives have been utilized as a good sensor to detect the metal ions because they have excellent fluorogenic and chromogenic properties . Also, the julolidine moiety is well known as a good fluorophore and chromophore . In this regard, we designed and synthesized a new chemosensor 1 based on the imidazole and julolidine moieties, which was expected to detect various analytes through the change of unique photophysical properties.

III]Experimental and theoretical studies of imidazole based chemosensor for Palladium and their biological applications

An imidazole derivative bearing a thiophene group was developed as an ON-OFF fluorescent chemosensor for palladium ions. The UV–vis absorption and fluorescence spectral behavior of probe L1 towards various cations were investigated in HEPES buffer aqueous solution. The absorbance intensity of probe L1 considerably enhanced whereas the fluorescence emission intensity was quenched in the presence of Pd2+ ions, while the presence of other metal ions had no notable interference. The stoichiometry of the complex was determined using Job's plot and a plausible recognition mechanism of probe L1 and Pd2+ is proposed. Density Functional Theory (DFT) calculations were used to study the electronic properties and to optimize the structure on the selectivity of Pd2+ ions and are correlated with the experimental results. The intracellular Pd2+ ion detection in living cells was performed using probe L1 on brine shrimp nauplii (Artemia salina) up to 20µg/mL

Recently, development of selective and sensitive fluorescent diagnostics for important transition metal ions such as palladium is of huge curiosity due to the plentiful usage in various physical and profitable applications . For example, it is extensively used as a catalyst in synthesis because of its brilliant catalytic ability in pharmaceutically valuable products . Palladium plays a significant role in the manufacture of medical devices, dental, jewelry, catalytic convertor for automobiles, connecting plating for electronics and as essential catalysts in many organic reactions . Palladium can be found in biological materials and augmented by the food chain to cause an imminent fitness problems. After a thorough investigation, World Health Organization (WHO) has confirmed that the deadly doseofpalladium is 5–10ppm [8–10], and uptake may be controlled to ~ 1.5–15µg/day. Besides the need, palladium causes eye, skin, breathing tract irritation and the complex of Pd (II) are regarded highly toxic and carcinogenic. For example, it can coordinate with bimolecular DNA, proteins consisting of thiol or thiol – ether group containing amino acid, vitamin B6 etc. and are active energy driving centers in living cells .

Analytical instrumentation (plasma emission spectroscopy (e.g. ICP-MS and ICP-AES), atomic absorption spectrometry (AAS), solid phase micro extraction-high performance liquid chromatography and X-ray fluorescence) for the quantification of Pd (II) generally costs high price for the instrumentation and tedious complex procedures. Therefore, the development of palladium detecting probes, especially for imaging in living systems and to detect the trace level of the metal remaining in air, water, food product, beverages etc., are in high demand. Nevertheless, there are some reported analytical methods for the recognition of Pd2+ ion; however, fluorescent based detection has great attention due to its extreme sensitivity and selectivity and to some extent suitability to be active in biological samples. As a consequence, development of fluorescent chemosensors for palladium ion is highly needed.

IV]Sequential detection of Cu2+ and cysteine using an imidazole-based chemosensor in aqueous solution

A highly substituted imidazole-based colorimetric and fluorogenic chemosensor, 2-methoxy-4-(4,5-diphenyl-1H-imidazol-2-yl)phenol (L), for the detection of Cu2+ ion and subsequent colorimetric detection of an amino acid, cysteine, was investigated. L exhibited a distinct color change from colorless to red in the presence of Cu2+ in an aqueous medium. The L-Cu2+ complex can also be used to detect cysteine by the naked eye over a series of amino acids. The receptor L behaves as a highly selective colorimetric and fluorescent sensor for Cu2+ ions at concentrations as low as 4.33 and 2.25 μM, respectively. These values are much less compared to the WHO recommended limit of 30 μM for Cu2+ in drinking water. From Job's plot and the ESI-MS spectrum, a 1:1 stoichiometric complex between L and Cu2+ ions can readily be reckoned. This binding was also substantiated by the EPR spectrum and magnetic susceptibility measurements. Additionally, the binding of L with Cu2+ ions was also manifested in the detection of B16F10 cells. This was substantiated through fluorescence microscopy. The spectrum of the L-Cu2+ entity was also attempted to reproduce theoretically. The probable structure of this was also propounded through Density Functional Theory.

Recognition of cations has been the focus of contemporary research. This is owing to obvious reasons. Cations exert myriad effects, beneficial as well as adverse, on biosystems. Among the good number of existing detection methods of cations, methods based on chemosensors have primarily been found to be smart in terms of simplicity, selectivity, sensitivity, response time, high level of specificity, and very low detection limit.Chemosensing methods are based on ion-induced alterations of fluorescence. Recognition of metal ions employing chemosensors has received contemporary attention because of their possible toxicity effects on environmental and biological systems.Copper, the last of the first row transition element, is the third most abundant essential metal in the human body followed by iron and zinc .Copper ions are involved in a plethora of primary physiological processes. Several factors regulate copper homeostasis. The roles of copper transport proteins and chaperones are noteworthy in this perspective. Unregulated copper[II] ions often pose adverse deleterious health effects on human kind. For ready reckoning, excess ingestion of Cu2+ can cause neurodegenerative diseases including Parkinsons,Alzheimers, Menkes, Wilsons, and prion diseases. In contrast, deficiency of copper is related to myelopathy. Copper is a potential metal-based pollutant as well. Hence, its prodigal use in chemistry, biosciences, medicine.

V] Fluorescence quenching study of new coumarin-derived fluorescent imidazole-based chemosensor

In this study, we report a new coumarin-based fluorescent sensor (CUM-P10)for sensitive detection of different inorganic quenchers(halide ions, aromatic amines or transition metal ions).The CUM-P10 copolymer was obtained through a post-synthesis modification reaction with coumrin flurophore of an imidazole based copolymer.CUM-P10 derivative exhibited strong fluorescence in the visible region (around 460nm) and its interection with different quenchers was studied in detail via fluorescence technique .In this context,the detection of different toxic pollutants has gained great importance and multitude of analysis technique (high performance liquid chromatography ,atomic absorption spectrometry, plasma emission spectroscopy,) were employed for this goal. Fluorescence spectroscopy represents probably ,one of the top standard technique for molecular sensing of toxic contaminants (including metal ions ,colorant ,explosive ,etc)since is correlated to numerous advantages including high sensitivity ,low cost ,simplicity of the operation procedure.

Several fluorescent chemosensors with diverse molecular structures and recognition mechanism were developed for the detection of hazardous substance .they are viewed as powerful tools facilitating quantitative and qualitative identification of undesired materials and their characteristic fluorescence quenching processes have been noted by many group .

Chemosensors with coumarin as signaling units have also been widely investigated in terms of their optical properties .beside notable biological activities ,these derivatives were considered efficient flurophores possessing high emission quntum yield ,improved photostability and excellent spectroscopic properties. These advantages allowed their use as efficient sensors for halide ions,transition metal ions,haloalkanes,fullerene,aromatic amine,sin labels,amino acid,Ph etc.

VI)A Simple Perceptive Diphenyl-Imidazole-Based Dipodal Schiff-Base Chemosensor for Zn2+ and PPi ions and Its Live-Cell Imaging Applications

In current years, researchers focused on recognition of metal ions by using fluorescent chemosensor. Because fluorescent chemosensor is very inexpensive method to identify the metal ions when compared to other sophisticated utensils like AAS, ICP-MS etc.,Now a day’s transition metal ions play a vital role in the environment and human health. Among the metal ions present in the human body, zinc is found to be second most abundant transition metal ion after iron and it involves in several biological evolution such as, enzyme regulation, neurotransmission and apoptosis etc.However the presence of a lower amount of zinc ions in human may cause diseases like alzheimer, osteoporosis cerebral ischemia and epilepsy, and also extreme presence of zinc ions in the environment tends to reduce the activity of microbes present in soil. Hence, selective and sensitive sensors for the detection of zinc ion is become very much needed. The spectroscopic or magnetic properties based zinc sensors have faced some complications in detection of zinc due to their stable electronic configuration of zinc i.e 3d10 4 s0. Therefore, fluorescent sensors have

been taken up by the researchers as better alternative for monitoring Zn2+ ions particularly in biological processes. Like zinc ion, phosphate anion is another important biological molecule which has been used as energy storage device and as signal transducers. Apart from phosphate, pyrophosphate ion (PPi) also plays a key role in various biological processes such as DNA replication and DNA sequencing. Therefore, the development of sensors for recognition of phosphate anion is also of great importance. The transition metal complexes have been reported as good candidates for the recognition of anions because structural and geometrical flexibility of metal centers in such complexes can provide excellent way for anion binding. In this connection, zinc complexes have been found to be the most successful ones owing to the strong binding affinity between zinc ion and PPi ion. However, the reported zinc complexes have some limitations in binding affinity and fluorescence responses for detection of pyrophosphate. In order to overcome the limitations, attention has been given in recent years to find new fluorescent chemosensors for sequence detection of Zn2+ and pyrophosphate ions. in the solid state due to its high fluorescence While designing, the new fluorescent chemosensors need a strong luminescent fluorophores for the fast fluorescence response. In this direction, recent years, attention has been diverted to a new fluorophore, namely 4-methyl-2,6-diformylphenol (DFP) which gives a dual fluorescence emission both in solution or nature.

CONCLUSION

On the basis of various literature survey imidazole derivatives show various activity against antimicrobial, anti-inflammatory, analgesic, antitubercular, anticancer etc. The possible improvements in the activity can be further achieved by slight modifications in the substituents on the basic imidazole nucleus. Having structural similarity with histidine imidazole compound can bind with protein molecules with ease compared to the some other heterocyclic moieties. Thus imidazole offers better pharmacodynamic characteristics. Furthermore, some imidazole drugs, at high concentrations, could exert direct inhibitory effects on membranes, without interference with sterols and sterol esters. Various recent new drugs developments in imidazole derivatives show better effect and less toxicity.

The field of fluorescent chemosensors has developed significantly over the 150 years since Goppelsro ̈der reported the first fluorescent chemosensor for Al3+. In particular, we have witnessed the explosive development of the field of fluorescent.

chemosensors over the past 50 years. The authors of this review believe that this phenomenal growth can in part be attributed to the pioneering research of Professor Anthony W. Czarnik's (DOB: 21-11-1957), and Professor A. Prasanna de Silva (DOB: 29-4-1952) who have inspired countless researchers through their seminal contributions to the field of chemosensors and molecular logic.We prepared this tutorial review in order to pay homage to their pivotal contributions to this field and to wish them both very happy birthdays in 2017. The review is also important since it demonstrates how a field can develop and flourish over a short 50-year period to become a recognized and established branch of chemistry. This review highlights representative examples of fluorescent chemosensors for various analytes including cations, anions, small neutral molecules and biomacro molecules from around 40 groups. Readers, requiring additional information are directed to the following recent reviews. On reading this tutorial review, it may seem to young researchers that all the great problems in chemosensors research have already been solved. Nothing could be further from the truth, since we will always need ''new'' chemosensors for yet unknown analytes. This could be in the form of new biomarkers or trace pollutants in our air and water supplies. Also, biological and environmental analysis has increasingly stringent requirements imposed by regulatory bodies, so while a current chemosensor may work it may fall short of the required selectivity or sensitivity required for use in a specific practical application. So whether the problem requires bespoke new receptors or an improvement of existing systems, we will continue to need an increasing number of chemosensors to meet these challenges. In summary, we expect that chemosensor research will continue to expand and develop. As well as new and improved chemosensors, we anticipate that new applications or approaches to use existing fluorophores as chemosensors will emerge. For example,Gunnlaugs son and Scanlan have repurposed anaphthalimide fluorophore in the formofa‘‘pre-probe’’.These pre-probe chemosensors consists of atargeting group(carbohydrate)which is selectively cleaved (enzymatically) within target cancer cells to release the fluorophore allowing selective visualization. We envision that many of the other ‘‘old’’ chemosensors can similarly be repurposed for use in as yet unknown

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