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RESEARCH ARTICLE

IMIDAZOLE, ITS DERIVATIVES & THEIR IMPORTANCE: A REVIEW

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A B S T R A C T

Heterocyclic compounds play an important role in various areas, of these Imidazole is one of the versatile compound used in pharmaceuticals. It is planner 5-memebered ring containing two nitrogen atoms. Molecular formula is C3H4N2 and having amphoteric in nature. It is used for preparing various types of drugs. Imidazole is a building unit of many drugs. Imidazole and its derivatives acts as antifungal, anti-microbial, analgesic, anti-inflammatory, anti-tubercular, anticancer, anticoagulants, anti-bacterial, anti-viral, anti-diabetic, anti-malerial activity etc.

INTRODUCTION

Medicinal chemistry is the discipline concerned with determing the influence of chemical structure on biological activity and in the practice of medicinal chemistry developed from an empirical one involving organic synthesis of new compound based largely on the modification of structure and then identifies their biological activity [1, 2]. Medicinal chemistry concerns with the discovery, development, interpretation and the identification of mechanism of action of biologically active compounds at the molecular level [3]. Various biologically active synthetic compounds have five-membered nitrogen-containing heterocyclic ring in their structures [4].

Heterocycles form by far the major of classical divisions of organic chemistry and are of immense use biologically and industrially. It is well known that the heterocycles are present in all kinds of organic compounds of interest in electronics, biology, optics, pharmacology, material sciences and so on. Heterocyclic nucleus imparts an important function in medicinal chemistry and serves as a key template for the development of various therapeutic agents [5]. Mostly researchers have maintained their interest in sulfur and nitrogen-containing heterocyclic compounds through decades of historical development of organic synthesis [6] Heterocyclic compounds comprise the major family of organic compounds. These are enormously essential with wide range of synthetic, pharmaceutical and industrial applications and are famous for their biological activities. There is an extensive spectrum of biological activities shown by many compounds containing five membered heterocyclic rings in their structure. The high therapeutic properties of these heterocycles have encouraged the medicinal chemists to synthesize a large number of novel chemotherapeutic agents. These heterocyclic compounds have broadened scope in remedying various dispositions in clinical medicines. Imidazoles and thiazoles have been reported to show pharmacological activities [7].

Heterocyclic compounds are also used in agriculture. Analysis of scientific papers in the last two decades revealed that there is a general trend in research for new drugs involving modification of existing biologically active matrices and molecular design of the structures of compounds. The imidazoles 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 clinical medicines. Medicinal properties of imidazoles include anticancer, anticoagulants, anti-inflammatory, antibacterial, antifungal, antiviral, antitubercular, antidiabetic and antimalarial [8- 14]. Imidazole and its derivatives are reported to be physiologically and pharmacologically active and find applications in the treatment of several diseases.

Heterocyclic compounds are rich sources of diverse physical, chemical, and biological Properties [15]. In medicinal chemistry they are commonly used as templates to design biologically active agents [16]. Imidazole-based heterocyclic molecules play important roles in various biochemical processes [17]. Therefore, the imidazolyl moiety is being used as a building block in developing new drugs [18], Moreover; imidazole derivatives have wide range applications in coordination chemistry [19], organometallic catalysis [20], and asymmetric catalysis [21].

Imidazole was first reported by Debus *et al.*, in 1858 from diketone an aldehyde and ammonia although various imidazole derivatives had been discovered earlier in the

1840s. Since then, this particular heterocyclic family has hugely expanded and imidazoles are found today in a myriad of applications. They play an important role in areas such as natural products, medicinal chemistry [22, 23], material sciences for nonlinear optical application [24], some imidazole derivatives are used as a catalyst in industrial uses [25, 26].

Imidazole is an organic compound with the formula $C_3H_4N_2$. This aromatic heterocyclic is a "1, 3-diazole" and is classified as an alkaloid [27]. It was first named as gluoxaline (first synthesis with glyoxal and ammonia). Amphoteric nature is susceptible to electrophilic and nucleophilic attack. Highly stable to thermal, acid, base, oxidation and reduction conditions. It has extensive intramolecular hydrogen bonding. It exists in two equivalent tautomeric forms because the hydrogen atom can be located on either of the two nitrogen atoms. 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.

Imidiazole is amphoteric, because it functions as an acid as well as a base. As an acid, the pKa of imidazole is 14.5, making it less acidic than carboxylic acids, phenols and imides, but slightly more acidic than alcohols [28]. The use of imidazoles and their derivatives in chemical processes is becoming increasingly important. Derivatives of these strongly polar compounds are widely used in pharmacology. For instance, several ruthenium (III) complexes have been evaluated and used extensively in cancer therapy treatment [29, 30].

Insertion of the imidazole nucleus is an important synthetic strategy in drug discovery. These are currently used as tools in pharmacological studies. The important therapeutic properties of imidazole related drugs have encouraged the medicinal chemists to synthesize and test a large number of novel molecules [31]. Imidazoles have occupied a unique position in heterocyclic chemistry and its derivatives have attracted considerable interests in recent years for their versatile properties in chemistry and Pharmacology. Thus, imidazole compounds have been an interesting source for researchers for more than a century [32].

Irnidazole, an antimetabolite of histamine and nicotinic acid, has been found to be a safe and effective pesticide and is now undergoing field tests. Developed at U.C., Los Angeles, the new material has been patented and given the trade name "lrnutex." Imidazole, when synergized with boric acid, may be employed at low levels to proof fabric satisfactorily against insect attack. When synergized with 2-Aminopyridine, along with several newer synergists, and combined with base oil, imidazole is capable of controlling a number of insects and related arthropod species. Effectiveness is significantly increased by adding two surfactants to base oil. A hydrophilic surfactant increases the physiological activity of imidazole without improving the physical properties of the oil carrier, while perchloroethylene directly increases solubility. The particularly exciting quality about the material is its low mammalian toxicity [33].

Cancer is a class of diseases in which a cell, or a group of cells display uncontrolled growth, invasion and sometimes metastasis. These three malignant properties of cancers differentiate them from benign tumors, which are self-limited, and do not invade or metastasize. Most cancers form a tumor [34]. Cancer affects people at all ages with the risk for most types increasing with age. The traditional anticancer drugs are the basis for the new drug development for cancer in which imidazole is an important moiety. [35] The substitution on different positions gives a number of compounds of interest. Thus, imidazole compounds have been an interesting source for researchers for more than a century.

Structure activity relationships were reduced from biological results and will be used in further design of new active compound. Presently a number of drugs are used in the treatment of the cancer, but majority of them were produced controlled effect on the cancer cell. By application of these drugs the disease can be controlled. Imidazole and its derivatives are reported to be physiologically and pharmacologically active and find applications in the treatment of several diseases. In the drug discovery the imidazole is the most important synthetic strategy. Many imidazoles are reported as pharmacological agents like Azomycine, Clotrimazole, Miconazole, Ergothionine, Clonidine and Moxonidine. One of the most important applications of imidazole derivatives is their use as material for treatment of denture stomatities and in cancer [36, 37].

Imidazole drugs are a group of antifungal drugs which have broad-spectrum antifungal activities against wide range of fungi that cause many of mycotic infections. The members of this group are structurally related and have similar physicochemical properties and mechanisms of action. There are a number of imidazole drugs currently available, their efficacy may not be completely achieved in the treatment of human mycoses due to their poor water solubility and limited dissolution properties associated with slow drug absorption leading eventually to inadequate and variable bioavailability [38, 39].

Several efforts have been reported to enhance the water solubility and the dissolution properties of some imidazole drugs using cyclodextrin complexation [40, 41]. Pharmaceutical carriers, in particular, water-soluble carriers have been received an increasing attention in the pharmaceutical field because of their ability to enhance aqueous solubility, dissolution rate and bioavailbility of many poorly water soluble drugs [42].

Other than their pharmacological actions they also function as dyestuffs catalysts and polymerizing agents. Simple nitro derivatives of imidazole are effective as antibacterial agents. They also are useful in treating infections caused by protozoans, such as Trichomonus. Imidazole has benefitted several patients through various forms of treatment in diagnosing their diseases. The research on derivatives of imidazole was existing in the past and is continuously developing and varied new potentialities are emerging [43].

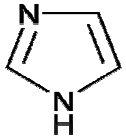

Figure1 STUCTURE OF IMIDAZOLE

General Methods of Preparation [44]

Imidazole is synthesized by various methods. Imidazole was first reported in 1958, although various imidazole derivatives had been discovered as early as the 1840s. Its synthesis, as shown below, used the glyoxal and formaldehyde in ammonia to imidazole. This synthesis, while producing relatively low yields, it still used for creating C-substituted imidazoles. In one microwave modification, the reactants are benzil, benzaldehyde and ammonia in glycial acetic acid, forming 2, 4,5-triphenylimidazole (lophine). Imidazole can be synthesized by numerous methods besides the Debus method. Many of these syntheses can also be applied to different substituted imidazole and imidazole derivatives by varying the functional groups in the reactants.

These methods are commonly categorized by which and how many bonds from to make the imidazole rings. For e.g., the debus method forms the (1, 2), (3, 4) and (1, 5) Bonds in imidazole, using each reactant as a fragment of the ring, and thus this methods would be a three-bond-forming synthesis. A small sampling of these methods is presented below.

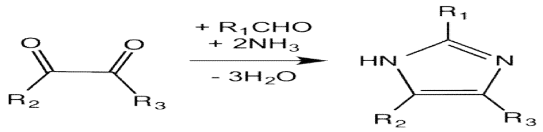

Figure 2

Formation of One Bond

The (1, 5) or (3, 4) bond can be formed by the reaction of an imidate and an alpha-aminoaldehyde or alpha-aminoacetal, resulting in the cyclization of an amidine to imidazole. The example below applies to imidazole when R=R_1= hydrogen.

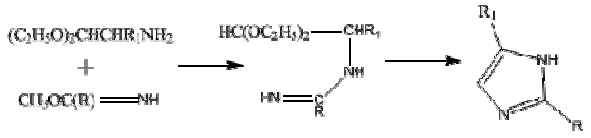

Figure 3

Formation of two Bonds

The (1, 2) and (2, 3) bonds can be formed by treating a 1, 2-diaminoalkane, at high temperatures, with an alcohol, aldehyde or carboxylic acid. Dehydrogenating catalyst, such as platinum on alumina, is required.

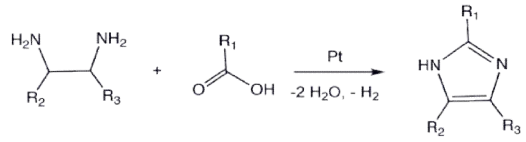

Figure 4

The (1, 2) and (3, 4) bonds can also be formed from N-substituted alpha-aminoketones and formamide with heat. The product will be a 1, 4-disubstituted imidazole, but here since, R=R_1= Hydrogen, imidazole itself is the product. The yield of these reactions is moderate, but it seems to be the most effective method of making the 1, 4 substitutions.

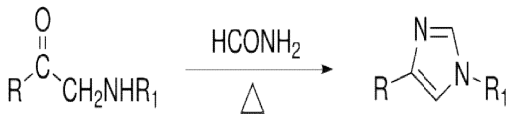

Figure 5

Formation of Four Bonds

This is a general method that is able to give good yields for substituted imidazoles. In essence, it is an adaptation of debus method called the Debus-Radeziszewski imidazole synthesis. The starting materials are substituted glyoxal, aldehyde, amine, and ammonia or an ammonium salt.

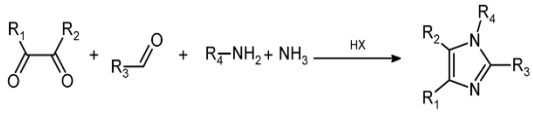

Figure 6

Table 1 Physico-Chemical Properties [45-56]

Property	Value	Reference/comment
Physical state	colourless to pale yellow crystalline flakes with a weak amine-like odor	BASF AG, 1997
Melting point	88.3 - 89.9 °C	BASF AG, 1989a; BASF AG, 1987a; BASF AG, 1991
Boiling point	267.8 °C, 268.1 °C at 1013.3 hPa	BASF AG, 1987b; BASF AG, 1987d
Relative density	1.111 g/cm3 at 95^{0}C	BASF AG, 1989b
Vapour pressure	0.00327 hPa at 25 ^{0}C	BASF AG, 1987c
Water solubility	663 g/l at 20^{0}C (pH 10.5 for 68 g/l at 20°C)	BASF AG, 1988a
Partition coefficient	n-octanol/water (log value) –0.02 at 25°C	BASF AG, 1988b
Henry's law constant	0.38 Pa*m^3/mol at 25°C (calculatedvia HENRYWIN v3.10)0.000034 Pa*m^3/mol	BASF AG, 2002a calculated using the above described values for water solubility and vapor pressure
Organic carbon/water Partition Coefficient, Koc	9.72	BASF AG, 2002a
Viscosity	2.696 mPa*s at 100 °C	Ullmann, 2000
Dissociation Constant	pKa = 14.9 pKa = 7.0	Ullmann, 2000

Applications of Imidazole

- Imidazole has become an important part of many pharmaceuticals. Synthetic Imidazoles are present in many fungicides and antifungal, antiprotozoal, and antihypertensive medications.
- Imidazole is part of the theophylline molecule, found in tea leaves and coffee beans, which stimulates the central nervous system. It is present in the anticancer medication mercaptopurine, which used in leukemia by interfering with DNA activities
- Imidazole also used in industry as a corrosion inhibitor on certain transition metals, such as copper.
- Many compounds of industrial and technological importance contain imidazole derivatives. The ther mostable polybenzimidazole imidazole fused to a benzene ring and acts as a fire retardant.
- Imidazole can also be found in various compounds which are used for photography and electronics [57].
- One of the applications of imidazole is in the purification of His tagged proteins in immobilized metal affinity chromatography (IMAC). Imidazole is used to elute tagged proteins bound to Ni ions attached to the surface of beads in the chromatography column. An excess of imidazole is passed through the column, displaces the His-tagged

from nickel coordination and free the His-tagged proteins.

- Imidazole can be used to prepare buffers in the pH range of 6.2-7.8 at room temperature. It is recommended as a component of a buffer for assay of horseradish peroxides. It is also used as a chelator for the binding of different divalent cations [58].

Biological Activities

Imidazoles are well known heterocyclic compounds which are common and have important feature of a variety of medicinal agents. On the basis of various literature surveys Imidazole derivatives shows various pharmacological activities.

- Anti fungal activity
- Anti-bacterial activity
- Anti-diabetic activity
- Anthelmintics activity
- Anti-inflammatory activity
- Anti-cancer activity

Imidazoles as Anti-Fungal Agents

Recently, there has been a renewed interest in anti-fungal drug research and development. The currently available therapy suffers from drug related toxicity, hazardous drug–drug interactions, less satisfactory pharmacokinetics, and development of resistance. Imidazole drugs such as miconazole, econazole, and ketoconazole have been used to treat fungal diseases because of their low toxicity and wide anti-microbial spectrum that includes yeasts, mycelia fungi, and Gram positive bacteria. This created interest in researchers to develop a new anti-fungal agent based on imidazole nucleus. Herein, summarized some of the reported work on imidazoles as anti-fungal agents. The lipophilic imidazoles such as clotrimazole, econazole and miconazole exhibited poor systemic availability following oral administration due to both poor absorption and extensive first pass metabolism so their use has been limited to topical treatment of superficial fungal infection. Ketoconazole (IV) a more polar imidazole introduced into therapy in the late 1970s, represented a break through in the treatment of antifungal disease. E.g. 1-vinyl imidazole

Imidazoles as Anti-Bacterial Agents

As pathogenic microorganisms continuously evolve mechanisms of resistance to currently used anti-microbial agents, the discovery of novel and potent bactericides is the best way to overcome bacterial resistance and develop effective therapies. E.g metronidazole and nitrosoimidazole.

Imidazoles as Anti-Diabetic Agents

A number of imidazoline-containing compounds have been reported to induce insulin release from isolated pancreatic islets and more importantly to improve glucose tolerance in both rats and mice. The putative imidazoline receptor site responsible, present on the pancreatic b-cells, has been termed the atypical imidazoline or I3 site since it shows pharmacological properties which distinguish it from the previously identified I1 and I2 sites found in other tissues [59].

Imidazoles as Anthelmintics

It was found that imidazole is less sensitive in extra intestinal parasites particularly intravascular and intestinal dwelling parasites than gastrointestinal parasites. The activity against developing stages is superior to that against arrested or adult stages in comparable habitats. The hatching and larval development are inhibited at doses which are sub- efficacious against adult *in vivo*. They required to achieve efficacy against nematodes are lower than those used for cestode and trematode control. For cestode or trematode control higher dose of drug or multiple treatments is needed. The member of class (2-alkyl benzimidazole) has been found to remove various species of nematodes and trematodes from different hosts.

Imidazoles as Anti-Inflammatory Agents

The search for the new and better drug in anti-inflammatory therapy is never ending process. The search for anti-inflammatory agent to relieve the swelling, redness, pain and fever associated with rheumatism dates back to antiquity. The synthetic studies include work on a variety of heterocyclic system, in isolation or fused with other system. Amino acids are reported to posses' anti-inflammatory activity [60, 61] and bearing this in mind Kumar *et al* [62] prepared various heterocyclic derivatives having both carboxylic and amino group.

The structure activity relationship studies indicated the conversion of the carboxylic group into a heterocyclic ring usually potentiated the inhibition of edema. Conversion into benzimidazole and 1, 2, 3, 4-tetrahydroquinoline ring resulted in compounds possessing better activity than that formed by the conversion of the carboxylic group into imidazole ring. Though imidazole and benzimidazole derivative are associated with a broad spectrum of biological activities they also have anti inflammatory activity, various N-substituted imidazoles [63] and substituted imidazolone [64]

Imidazoles as Anti-Cancer Agents

Past few years imidazole moiety is exclusively studied as an important structure as an anticancer or antineoplastic agent. Principally importance is given at the various substitutions at different positions in the moiety. The cyclin-dependent kinase (CDK) families are two groups of serine–threonine protein kinases with roles in the coordination of the eukaryotic cell cycle and transcriptional regulation. Because of their critical role in the regulation of the cell cycle and the observed expression/activity pattern in most human cancers, considerable effort has been focused on the development of small molecule CDK cell cycle inhibitors as potential therapeutic agents [65]. Incorporation of a basic group into CDK imidazole pyrimidine amide inhibitor series offered the best opportunity to achieve the CDK inhibitor properties. Imidazolesulfone AZD5438 (I) was investigated further as an orally bioavailable anti-cancer agent. Replacement of the sulfone with piperazine led to a new series of potent CDK inhibitors (II) with improved physical properties that were also suitable for oral dosing [66].

CONCLUSION

Imidazole and its derivatives play an important role in medicinal chemistry. Because of its synthetic application

researchers are attracted to synthesis of various types of drugs of Imidazole. Present review summarize that Imidazole and its derivative have more scope in future, for synthesis of novel drugs. Those are beneficial for society.

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