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CONCEPTUAL STUDY ON IMIDAZOLE DERIVATIVES AND THEIR BIOLOGICAL ACTIVITIES

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ABSTRACT
The main intension of this research is to design, synthesis and development of biologically active imidazole derivatives. Imidazole is an aromatic heterocyclic organic compound, plays a major role in medicinal chemistry. **Medicinal chemistry,** for its life-saving feature, being one of the major divisions in chemistry. Small molecule drug design and development getting its attraction due to the need of novel and effective medications against existing and upcoming diseases. Organic synthesis of medicinally important drugs needs more efficient route of synthesis and novel methodologies in order to design a side-effect less therapeutic agents. In such a case, heterocyclic compounds are attracting researchers to do the same.
Keywords: imidazole derivatives, medicinal chemistry, biological activity etc.

1. OVERVIEW OF IMIDAZOLES

If a cyclic compound that has atoms of at least one dissimilar element as members of its ring(s) is named as a heterocyclic compound. The branch of chemistry that deals with the study of synthesis, properties and uses of such compounds is termed as Heterocyclic Chemistry. Heterocyclic compounds are prevalent in several areas of science, research, development and technology. Numerous therapeutically important small molecules with chemical entities and drugs are heterocyclic compounds.

Heterocyclic compounds can be obtained either synthetically or naturally. For instance, purines are a major source of genetic materials, and they are the most extensively occurring nitrogen-containing heterocycles in nature (Fig. 1). With their wide applications, a continued synthesis of heterocyclic compounds got its attention by worldwide researchers.

In this research study, some benzimidazole based heterocyclic compounds were aimed to be synthesized in the interest of developing few drugs as antibiotics and chemotherapeutics.

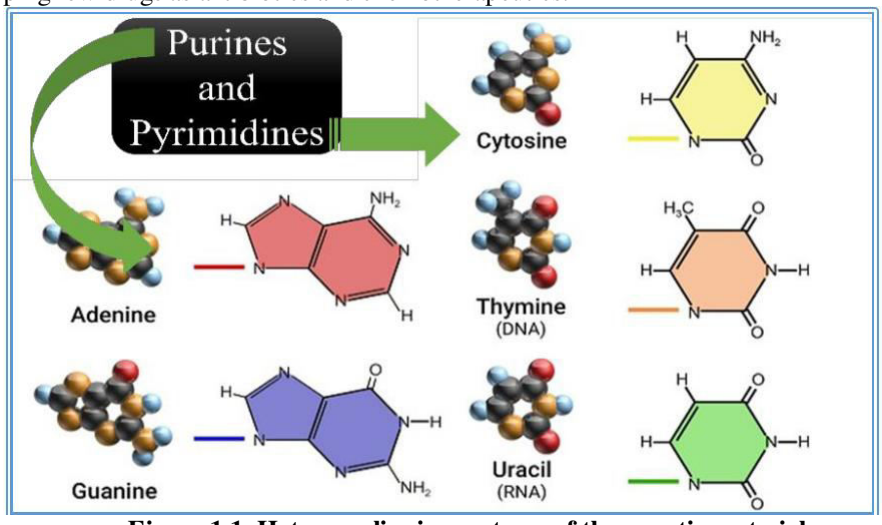

Figure 1.1. Heterocyclic ring systems of the genetic material

The target chemical entity of the present research is imidazole. Imidazoles are classified as alkaloid with five membered heterocyclic systems (Fig. 2). In general, imidazole is a five membered aromatic heterocyclic chemical with non-adjacent nitrogen atoms. Imidazole, known by the IUPAC name 1H-Imidazole and also known by other names such as 1, 3-diazole, glyoxaline (archaic), and 1,3-diazacyclopenta-2,4-diene.

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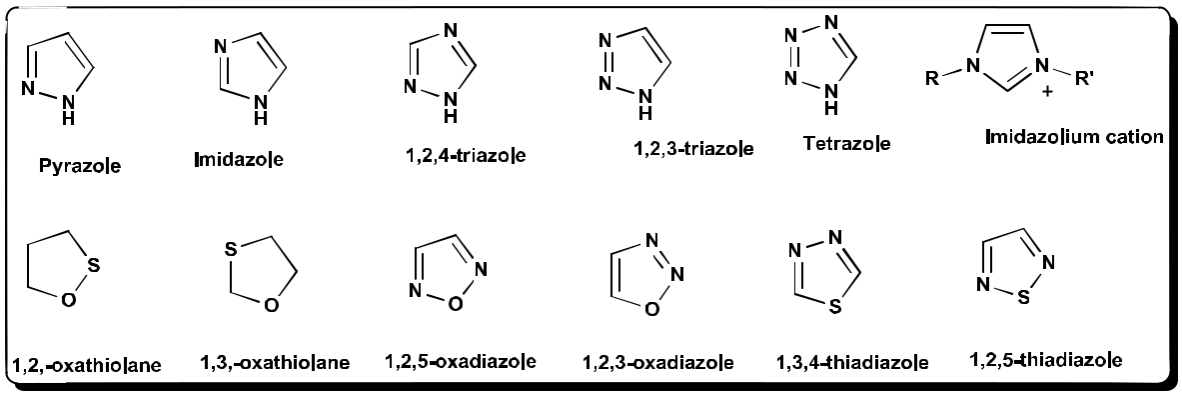


Figure 1.2. Structure of 5 ringed heterocycles

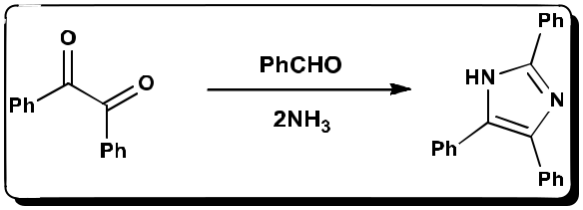
2. STRUCTURE AND PROPERTIES OF IMIDAZOLE

Imidazole is highly water soluble and other polar solvents soluble 5 membered planar ring chemical. The calculated dipole moment of 3.16D accounts for high water solubility as well as high polarity of compound. The presence of sextet of π-electrons in ring system accounts for aromatic compound with electrons pair on one of the nitrogen atom. N-substitution is a main process in drug discovery and development. Imidazole derivatives are an N-substituted heterocyclic compound. The need for the day is N-substituted derivatives with less or side-effect less drugs to cure a wide range of diseases that are affecting normal human health.

3. GENERAL SYNTHESIS OF IMIDAZOLES

In the early time of 1840's, there were a good numbers of new synthetic routes for the preparation of imidazole derivatives was developed and reported. In 1858 Heinrich Debus reported imidazoles first with relatively lower yield (Scheme 1). Other than the Debus method imidazole derivatives can prepared by different synthetic methods. Several of these synthetic routes can be adopted for the preparation of substituted imidazole by changing the functional groups on the key reactants. The below mentioned schemes are few examples for the route of synthesis of imidazole derivatives by using single component, two component, three component and multi-components reactions.

Scheme 1

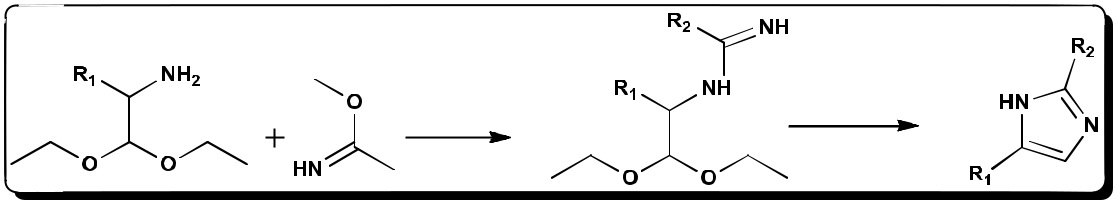


The microwave reaction of reactants benzaldehyde, aqueous ammonia and benzil in glacialacetic acid as solvent results in 2, 4, 5-triphenylimidazole (scheme 1).

a. One component

The reaction of α-aminoaldehyde and an imidate results in the formation of (1, 5) and (3, 4)bond formations. The below example revels to imidazole, when R1 and R2 are hydrogen(Scheme 2).

Scheme 2



b.Two component

The imidazole derivatives are resulted by treating 1,2-diaminoalkane with an aliphatic and aromatic alcohol, aldehyde or carboxylic acid with the assistance of dehydrogenating metal catalyst, such as platinum on alumina, palladium on carbon at high temperatures (Scheme 3).

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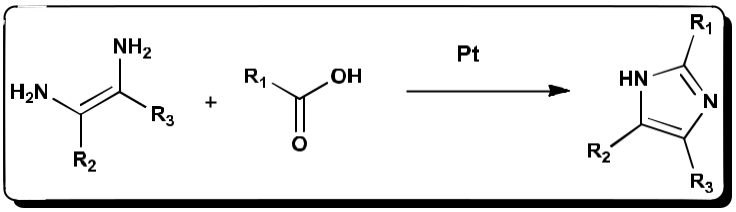
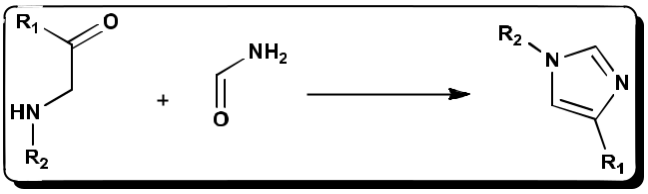
Scheme 3



1, 4-disubstituted imidazoles can be prepared by reacting α-aminoketones with N-substitutedand formamide results in (1,2) and (3,4) bonds formation at higher temperatures. Thissynthetic route accounts for high yielding and most economic method for the synthesis of 1,4- substituted products (Scheme 4).

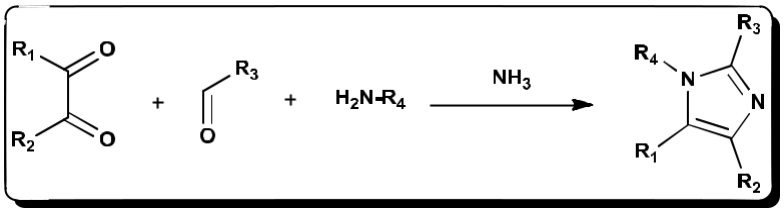
Scheme 4



c.Three component

The reactants such as alkyl or aromatic substituted glyoxal, aldehyde, amine and ammonia or a different ammonium salt produces appreciable yield of substituted imidiazoles with the inclusion of Debus method and also this is known as Debus-Radziszewski imidazole synthesis (Scheme 5).

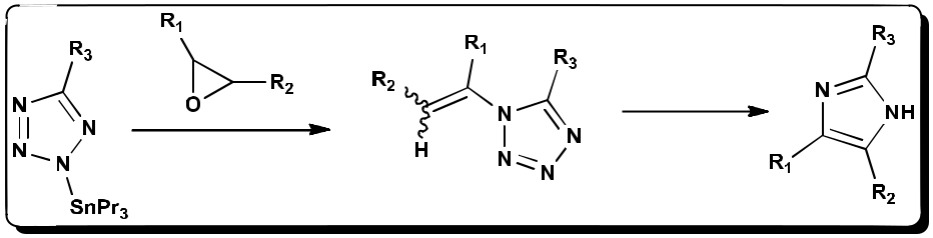
Scheme 5



d.Preparation of imidazole derivatives from other heterocyclic compounds

The photolysis of 1-vinyltetrazole produces remarkable yield of imidazoles when 1-vinyltetrazole is efficiently obtained from an organotin compound like 2-tributylstannyltetrazole. Imidazole as product resulted when R1, R2, R3 are hydrogen (Scheme 6).

Scheme 6



The vapor-phase reaction of formamide, ethylene diamine and hydrogen over platinum on alumina resulted in the formation of high pure imidazole at extremely higher temperature like 340 and 480 °C.

Van Leusen reaction

The Van Leusen reaction accounts for the formation of imidazole derivatives by using tosylmethyl isocyanide (TosMIC) and an aldimine as key starting materials. Later in situ preparation of aldimine accounts for the Van Leusen as Three-Component Reaction (vL-3CR).

4. RECENT REPORTS ON IMIDAZOLES AND LITERATURE SURVEY

A literature survey was made and reported data between 2010 to present day was taken in to account to analyze various tactics and methodologies used by global researchers.

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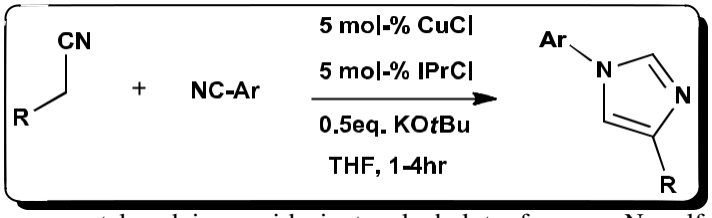
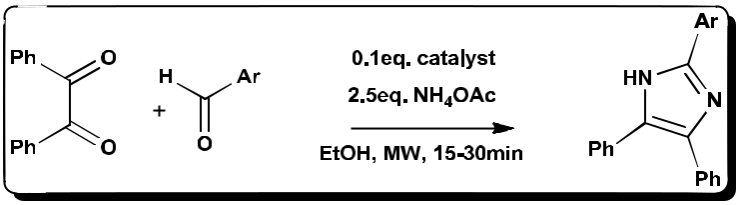
Scheme 7



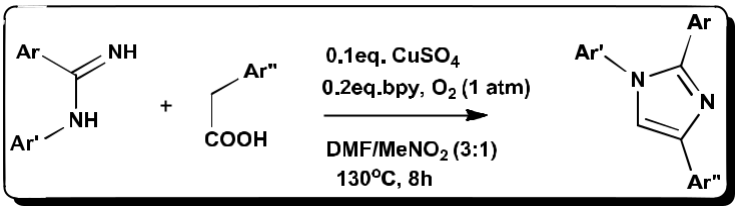
The insertion of NHC-copper-catalyzed isocyanide in to alcohol to form an N-arylformimidate intermediate followed by base-promoted cycloaddition with benzyl isocyanide derivatives due to inclusion of basic media produces a direct 1,4-diaryl-1H-imidazoles with significant yields (Scheme 7).

Scheme 8



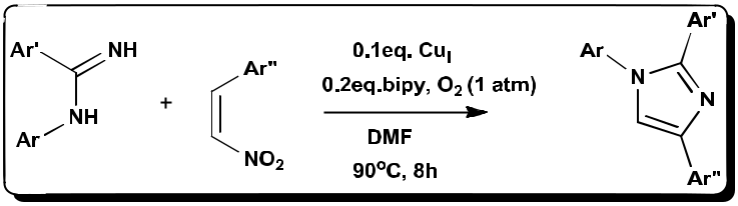
The single pot microwave prepartion of 2, 4, 5-trisubstituted imidazoles with remarkable yields can be achieved by reaction aldehydes, benzyl and ammonium acetate in presence of nickel catalyst (Ni-C) as a complex of Schiff's base. The reaction is very advantageous by easy recovery of catalyst by simple technique like filtration and can be reused (Scheme 8).

Scheme 9



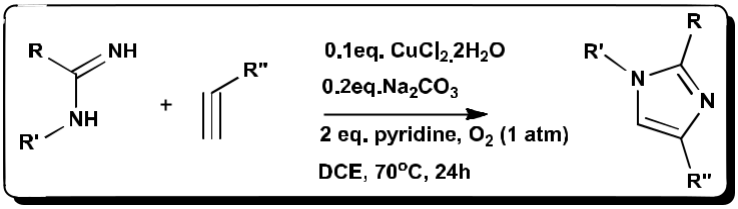
One-pot reaction of arylacetic acids, N-arylbenzamidines and nitroalkanes in presence of inexpensive copper catalyst leads to the simultaneous activation of hydrogen on Carbon and nitrogen resulted in the formation of multisubstituted imidazole derivatives (Scheme 9).

Scheme 10



Without the use of any expensive catalyst highly regioselctive and high yielding multisubstituted imidazole derivatives can be prepared by using oxygen as an oxidant with a simple copper-catalyzed [3+2] cycloaddition reaction (Scheme 10).

Scheme 11



Different 1,2,4-trisubstituted imidazole derivatives can be prepared efficiently by regioselective diamination of terminal alkynes with amidines in the presence of bases like sodium carbonate, pyridine, a catalytic of copper chloride dehydrate in oxygen pressure. (Scheme 11).

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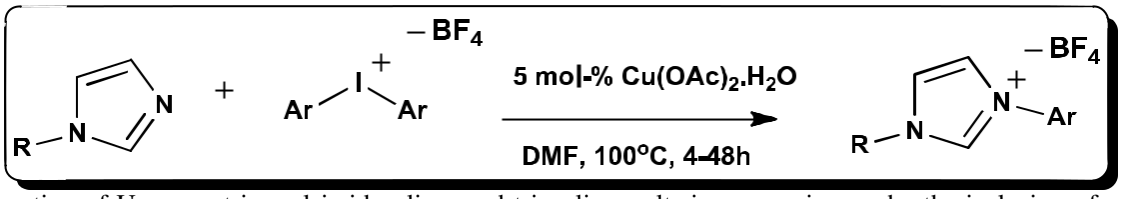
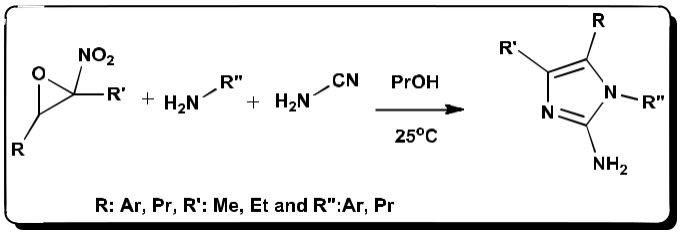
Scheme 12



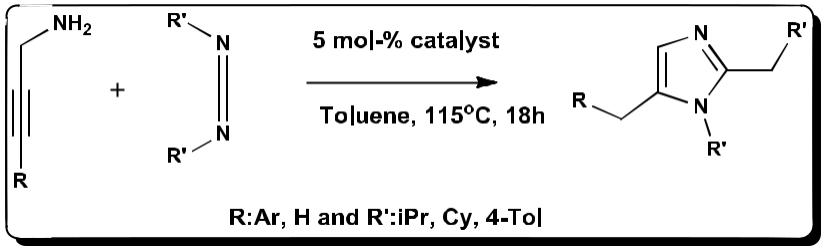
Construction of Unsymmetric aryl imidazolium and triazolium salts in economic way by the inclusion of copper catalyst in excellent yields with the use of N-substituted imidazoles and diaryliodonium salts. This reaction is well tolerable for a wide range of functional groups. (Scheme 12).

Scheme 13



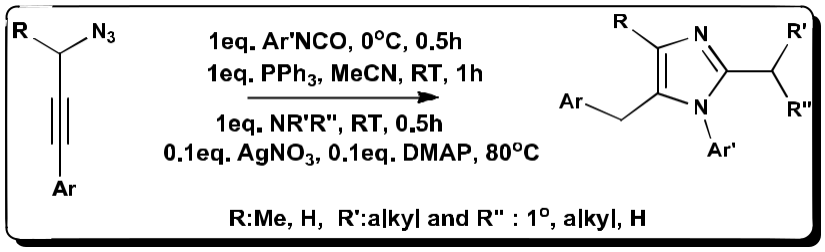
The simple reaction of three reactants with a series of alkyl and aromatic amines, such as α-nitroepoxides and cyanamide, helps to form functionalized 2-aminoimidazole derivatives under standard reaction conditions without the use of any additives. (Scheme 13).

Scheme 14



Alkyl and aromatic carbodiimide substitute aminopropargyl reactions in the presence of 5 mol percent titanacarborane monoamide [σ:η^1:η^5-(OCH2)(Me2NCH2)C2B9H9]Ti(NMe2) accounts for a new class of 2-aminoimidazoles substituted by [3+2] cancellations with impressive yields. (Scheme 14).

Scheme 15



A systematic Staudinger/aza-Wittig/Ag (I)-catalyzed cyclizationa and isomerization reaction of easily accessible propargylazide derivatives with triphenylphosphine, isocyanates, and amines provided fully substituted imidazoles in good overall yields (Scheme 15).

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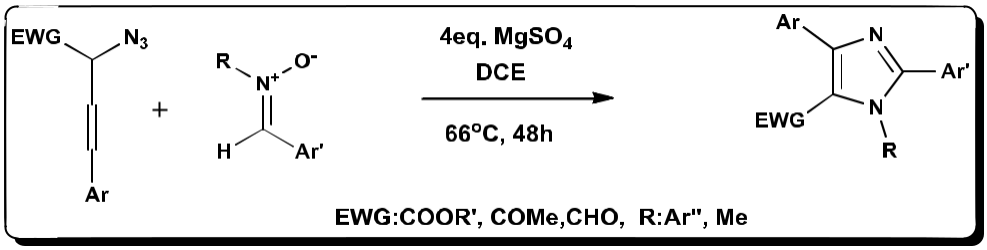
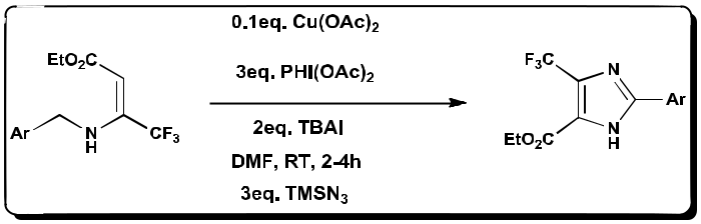
Scheme 16



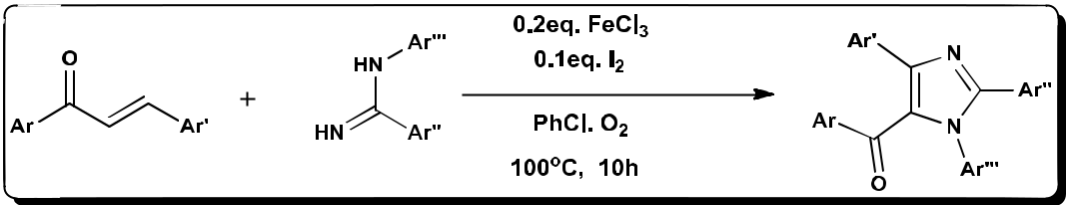
Practically convenient and most economical 1,2,4,5-tetrasubstituted imidazoles can be prepared by reacting readily available 2-azido acrylates and nitrones without the use of metal or any strong conditions (Scheme 16).

Scheme 17



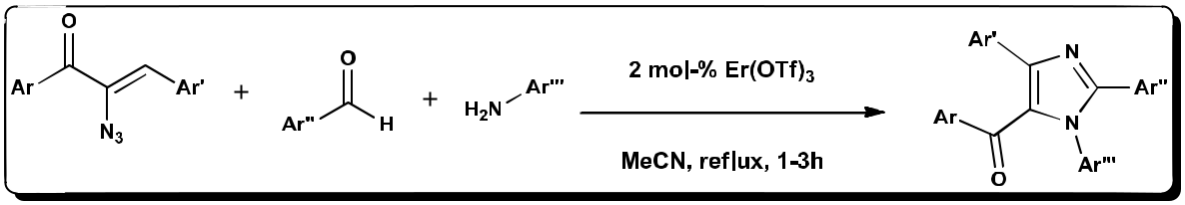
In the presence of (diacetoxyiodo) benzene and TMSN3 under catalysis of copper salt such as Cu (OAc)2 via domino azidation/intramolecular C(sp3)-H amination, N-Alkyl enamines can be effectively converted into substituted imidazoles. The above reaction conditions provide an effective method for 4-(trifluoromethyl) imidazole preparation. (Scheme 17).

Scheme 18



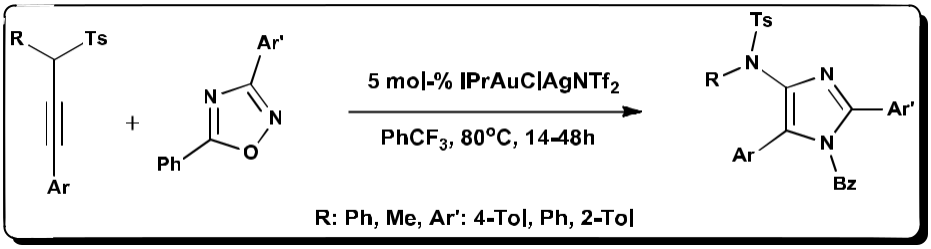
A practically convenient aerobic oxidative coupling of amidines and chalcones with efficient FeCl3/I2-catalytic conditions resulted in tetrasubstituted imidazoles in high yield and excellent regioselectivity. The reaction is very advantageous over functional group tolerance with normal reaction conditions (Scheme 18).

Scheme 19



The erbium triflate as a catalyst induced synthesis of highly substituted imidazole derivatives in excellent yield by three components like different α-azido chalcones, aryl aldehydes and aromatic anilines (Scheme 19).

Scheme 20



An atomic efficient fully substituted 4-aminoimidazoles can be synthesized by [3 + 2]cyclisation of 1, 2, 4-oxadiazoles with ynamides very selectively in presence of gold catalyst (Scheme 20).

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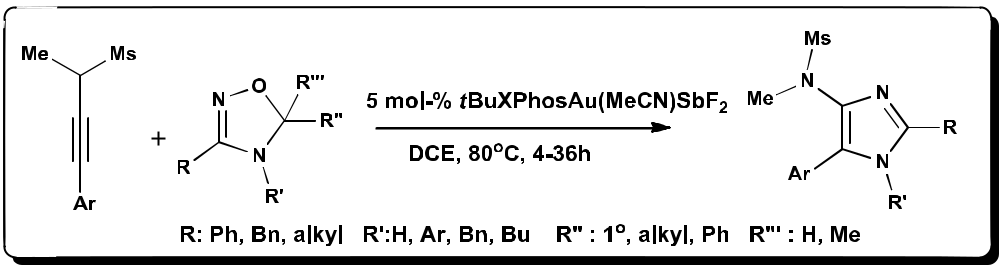
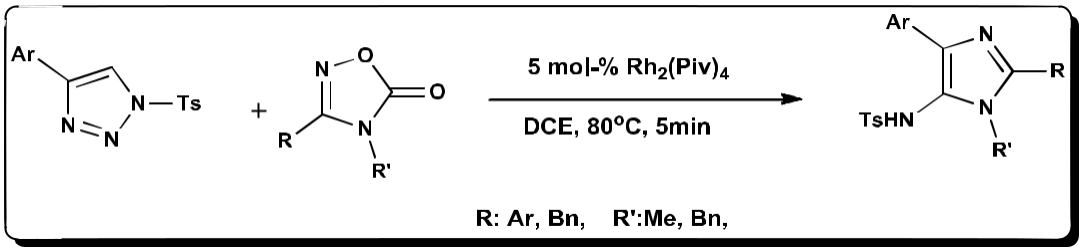
Scheme 21



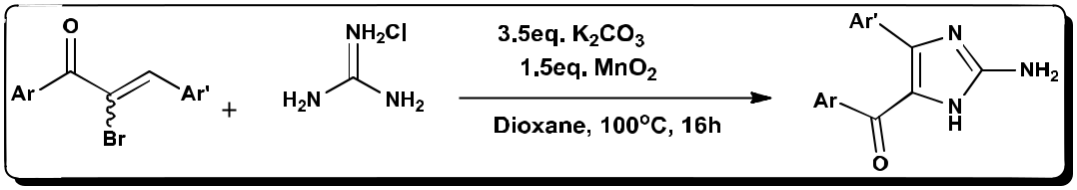
Usual [3+2] annulation of ynamides with 4,5-dihydro-1,2,4-oxadiazoles in presence of gold catalyst results a clean and regioselctive clearance to highly functionalized 4-aminoimidazoles through the formation of an α-imino gold carbene intermediate followed by cyclisation (Scheme 21).

Scheme 22



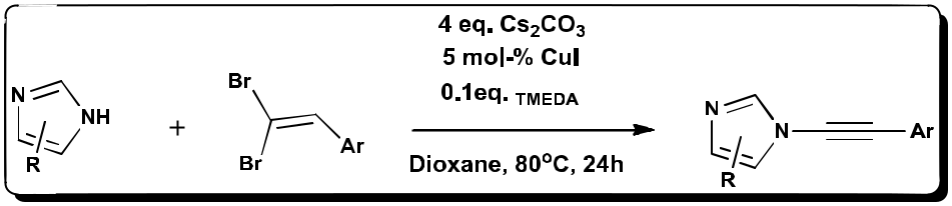
A Rh(II)-catalyzed transannulation of 1,2,4-oxadiazoles and 1,2,4-oxadiazol-5-ones with N-sulfonyl-1,2,3-triazoles provides fully substituted 5-sulfonamidoimidazoles. Both reactions are completely regioselective (Scheme 22).

Scheme 23



The NH-protection/derivatization strategy is prevented by a single step-economical access to polysubstituted aminoimidazoles through alkene vicinal C-N bond formation of 2-bromo-2-alkenones with guanidine. The reaction requires a tandem aza-Michael addition pathway, SN2, and a special redox-neutral process and provides an outstanding substratum selection. (Scheme 23).

Scheme 24



The cross coupling reaction of 1,1-dibromo-1-alkenes with substituted imidazole in copper catalyst resulted in the formation of N-alkynylheteroarenes with high yield and excellent functional group tolerance. The functional group tolerance achieved in presence of TMEDA as ligand in dioxane solvent media (Scheme 24).

5. APPLICATIONS OF IMIDAZOLES

5.1.Use as medicinal agents

Fig. 3 representing few medicinally important imidazoles reported by different researchers. There are reports on Anti-fungal (compound 1 in Fig.3) and Anti-bacterial activity (compound 2), Anti-depressant activity, Anti-inflammatory activity and analgesicactivity (compound 3 & 4), Anti tubercular activity (compound 7), anticancer (compounds 5&6), Anti-viral activity (compound 8) and Anti-leishmanial activity. Apart from all these medicinal

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values, many of imidazole based derivatives have been identified as candiovasculardysfuntion regulators and anti-neurodegenerative agents.

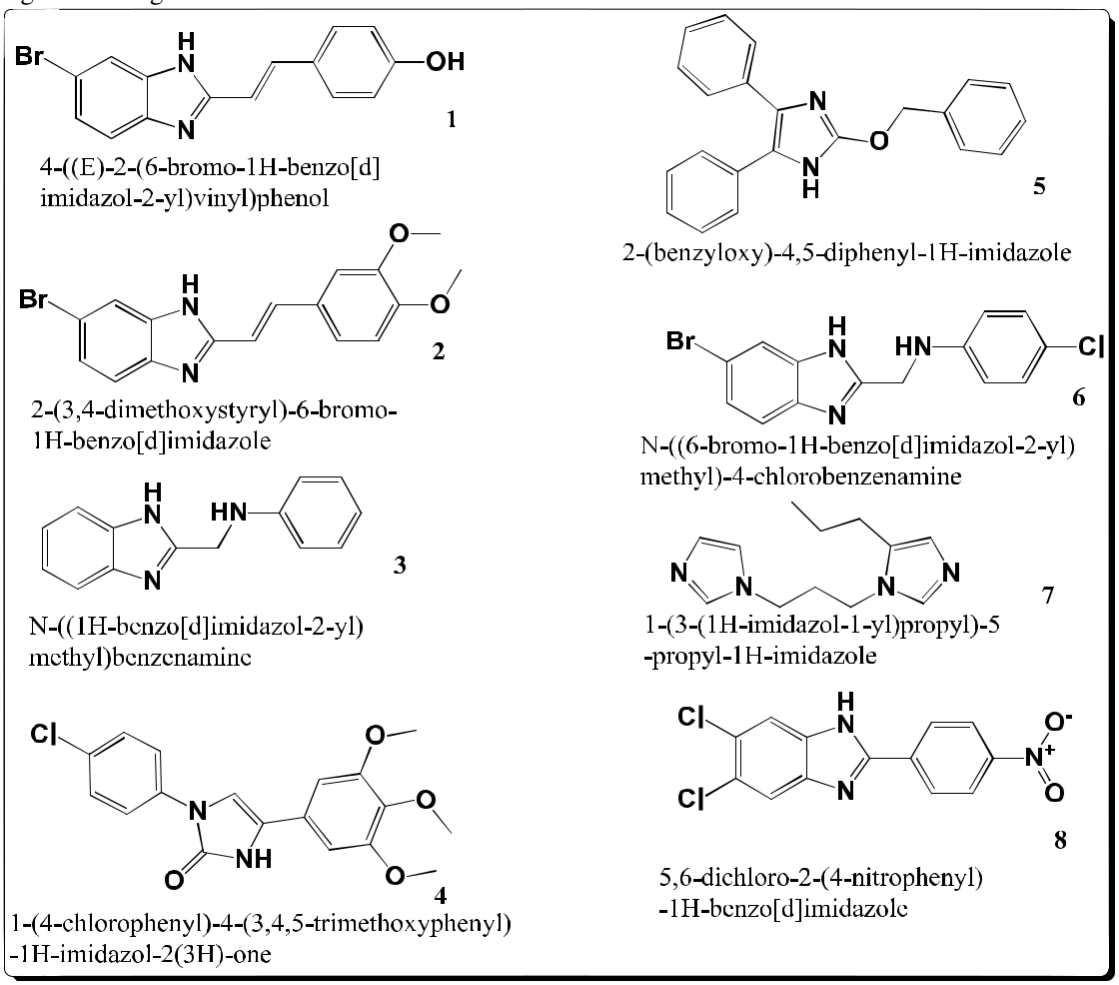

Figure 1.3. Different biologically and medicinally significant imidazoles. 1 and 2 antifungalagents; 3 anti-inflammatory and 4 anticancer agents; 7 anti-tuberculosis and 8 antiviral agent

5.2.Biological significance of imidazole

Many important biological molecules contain imidazole as main component. In which most important is imidazole side chain involved amino acid histidine. As we know many enzymesand proteins accounts for a very vital part in the structure and constituting functions of hemoglobin id due to the presence one of the important component called histidine. Histamine is again one of the important biological component produces from the result of decarboxylation of histidine. It is a constituent of the toxin that imparts urticaria, i.e. allergic. The purification of His tagged proteins in immobilized metal affinity chromatography (IMAC) involves the use of biological important imidazole derivatives. Assay evolution of horseradish peroxides involves the use of buffer which in turn contains imidazole.

Binding of different divalent cations achieved by using imidazole as chelating agent. The oral application of imidazole shows attractive effects on psoriasis and seborrheic dermatitis. In psoriasis the improvement begins after a period of forty five to ninety days. In seborrheic dermatitis the patients starts from less redness, itchiness and scaling within a period of twenty eight days to forty two days. This treatment advantage happens without the necessity for use of ointments or other different topical applications.

As we know that, the central nervous system stimulated by tea leaves and coffee beans due to the presence of theophylline molecule which contain Imidazole as main component. Imidazole is present as a main ring in mercaptopurine as anticancer medication like leukemia by interfering with DNA activities.

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5.3.Imidazole derivatives as drugs in different therapeutic areas

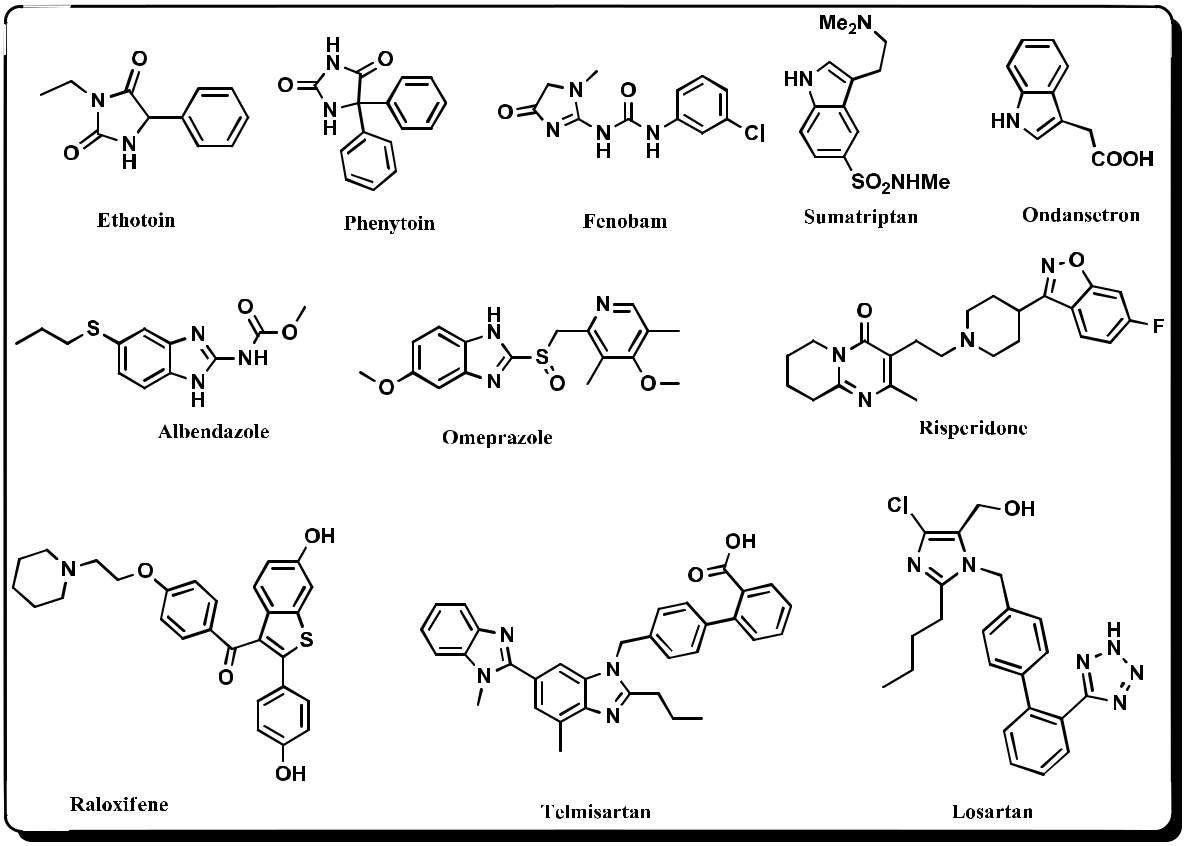

Figure 1.4. Commercially available imidazole derivatives in different therapeutic areas.

Ethotoinand **Phenytoin** are a class of hydantoins and known as anticonvulsant orantiepileptic drugs. These are used to prevent and control seizures by reducing abnormal electrical activity in the brain. **Fenobam** as a novel anxiolytic, a potent and selective negative allosteric modulator. Migraine headaches and cluster headaches treated by using Samaritan. **Ondansetron** used for the suppression of the nausea and vomiting as a result of cancer chemotherapy and radiotherapy. Albendazole a oral administrative drug used for the treatment of variety of parasitic worm infestations. Omeprazole useful drug for gastrophageal reflux disease, Zollinger-Ellison syndrome and peptic ulcer disease. Peoples who are at high risk due to upper gastrointestinal bleeding can be prevented by using omeprazole. **Risperidone** is an oral or injectable antipsychotic active ingradient used for the treatment of bipolar disorder, irritability associated with autism and schizophrenia. **Raloxifene** is an oral drug used to control and prevent high risk of breast cancer andosteoporosis in postmenopausal women. **Telmisartan** and **Losartan** are antihypertensive drugs.

5.4.Industrial applications of imidazole

Many compounds of industrial and technological importance contain imidazole derivatives. A fire retardant can be prepared by fusing the thermo stable polybenzimidazole imidazole with benzene ring. Imidazole derivatives widen their applications even in non-medicinal photography and electronics.

6. CONCLUSION

A wide range of literature survey was made in order to understand the various tactics involved in the route of synthesis of present study target compounds. Thus, in this research, our mission is towards design, discovery, synthesis and molecular substantiations of medicinally important and functionally effective N-substituted imidazole based heterocyclic compounds to develop the as novel drugs against cancers, inflammation and microbial pathogens was initiated and accomplished through these literature survey and understanding different types of methods was used and the same were given a path to develop novel techniques to achieve the N-substituted heterocyclic compounds.

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