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"SYNTHESIS OF BIOACTIVE IMIDAZOLES: A COMPREHENSIVE REVIEW"

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Abstract:
Imidazole, a five-membered heterocyclic ring containing two nitrogen atoms, has been a cornerstone in medicinal chemistry due to its broad spectrum of biological activities. This review highlights the current developments in the synthesis, biological applications, and therapeutic potentials of imidazole-based compounds. Advances in synthetic methodologies and the design of novel imidazole derivatives have led to significant progress in various therapeutic areas, including antimicrobial, anticancer, anti-inflammatory, antiviral, and cardiovascular diseases. This comprehensive review aims to provide an updated overview of the structural diversity, synthetic strategies, and pharmacological activities of imidazole derivatives, shedding light on future research directions and potential clinical applications.

Keywords: Imidazole, heterocyclic, antibacterial, anti-inflammatory, antifungal and antitumor.

Introduction:

Heterocyclic compounds are also used in medicine and agriculture. Based on a review of the scientific papers published in the past two years, there has been on overall trend towards modern drug research that involves changing bioactive matrix structures and designing compound structures molecularly. Imidazole cores are an important synthetic strategy for drug discovery. Imidazole products have shown antibacterial, anti-inflammatory, analgesic, antituberculosis and anticancer properties. One of the most important applications of imidazole derivatives is their use as a material for the treatment of denture stomatitis. The high therapeutic efficacy of imidazole-based drug has led pharmaceutical experts to synthesize many new drugs against cancer. Imidazole-containing drugs have expanded their reach in clinical medicine. The medicinal properties of imidazole include anticancer, anticoagulant, anti-inflammatory, antibacterial, antifungal, antiviral, antituberculosis, antidiabetic and antimalarial [i-vii].

Imidazole and its derivatives are useful in the treatment of a number of diseases and are said to be physiologically and pharmacologically active. Imidazole is an organic compound with the formula $(CH)_2N(NH)CH$ (Fig. 1). It is a colorless solid that turns into a slightly basic solution when dissolved in water. In chemistry, it is an aromatic heterocycle, classified as a

diazole and as an alkaloid. Imidazoles are a common component of a large number of natural products and pharmacologically active molecules.

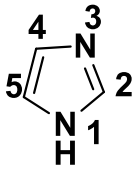
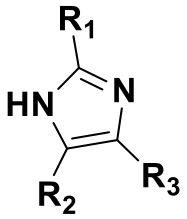
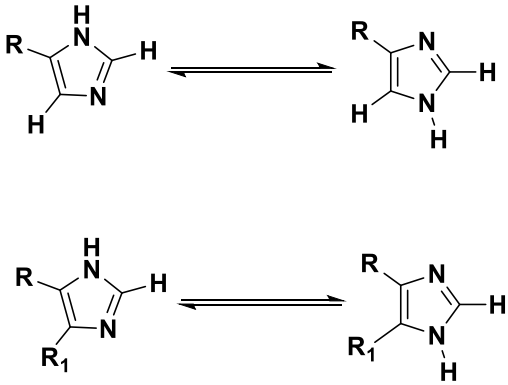


Fig. 1

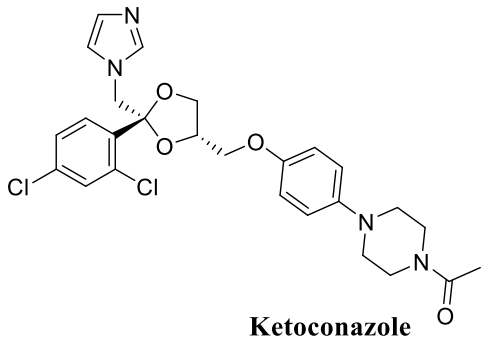
In 1858, Heinrich Debus created imidazole for the first time, but as early as the 1840s, other imidazole derivatives were found[viii-xi]. Glyoxal and formaldehyde are combined with ammonia to create imidazole[xii-xiii]. This synthesis, while producing relatively low yields, is still used for creating C-substituted imidazoles [xiv].

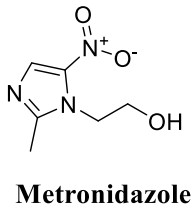


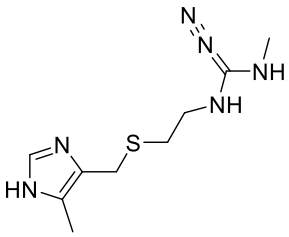
It is possible to predict that imidazoles will exist in their isomeric forms when they have a free imino hydrogen and a substituent in the 4- or 5-position, or two different substituents in these locations. The location of the imino hydrogen, which can be bonded to either of the two nitrogen atoms, differs between these isomers.

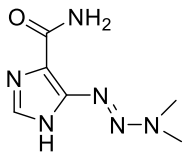


Scientific research has become interested in the imidazole nucleus throughout time because of its unique chemical and biological characteristics [xv]. For example, this nucleus is present in the structures of several natural products in the form of the essential amino-acid histidine or in alkaloids exhibiting anti-tumoral, anti-cancer (dacarbazine), antihistaminic (cimetidine), anti-parasitic (metronidazole), and antihypertensive (losartan) and anti-bacterial activities [xvi]. The imidazole nucleus is found in a wide variety of medications, such as ketoconazole, which is used to treat bacterial, fungal, and gastric ulcers, respectively Fig. 2 [xvii]. Its significance has made them a desirable target for synthetic and medicinal chemists. For the purpose of constructing and embellishing the imidazole ring with various functional groups, numerous synthetic techniques have been developed.









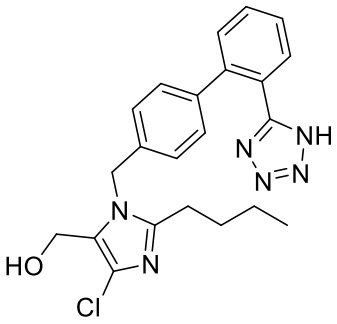
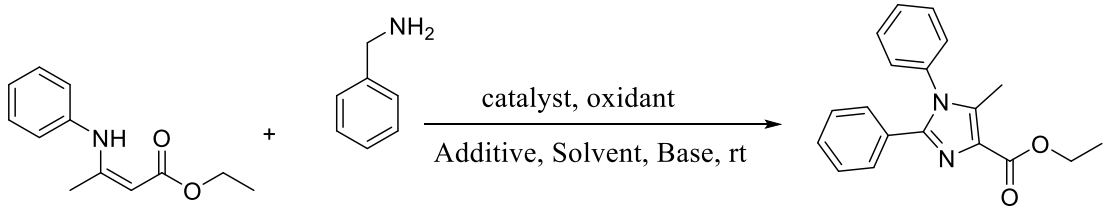


Fig: 2. Examples of significant imidazole containing pharmaceuticals

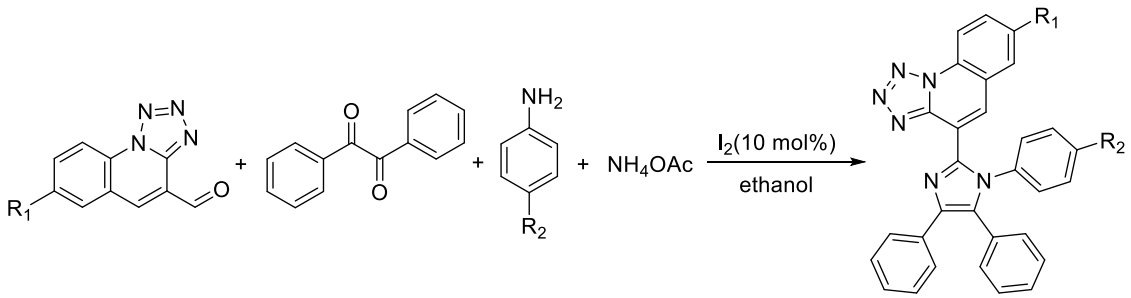
Synthesis of Imidazoles

Pandya et al. [xviii] reported a clear and easy method for creating highly substituted imidazole derivatives in good to high yields by reacting with aromatic aniline by copper-mediated oxidative C–H functionalization. The reaction's gentle reaction conditions and widely accessible starting materials are its main advantages.



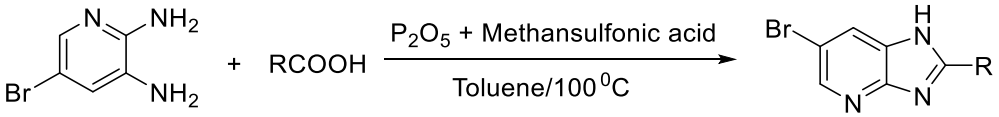
Scheme 1. Synthesis of ethyl 5-methyl-1,2-diphenyl-1H-imidazole-4-carboxylate

Mungra et al. [xix] also reported on a new series of tetrazolo[1,5-a]quinoline-based tetrasubstituted imidazole derivatives that were created by a one-pot multi-component reaction (MCR) approach involving tetrazolo[1,5-a]quinoline-4-carbaldehyde, benzil, aromatic amine, and ammonium acetate in the presence of iodine.



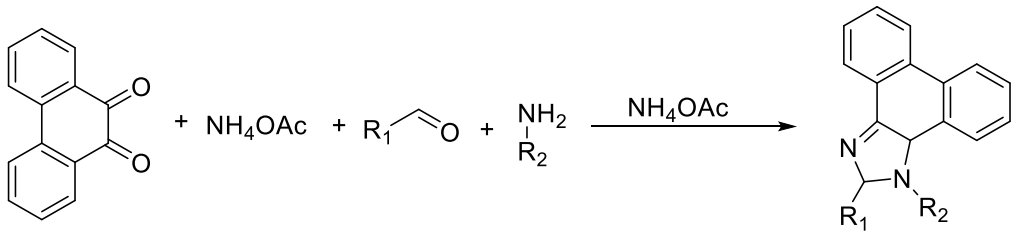
Scheme 2. Synthesis of new tetrazolo[1,5-a] quinoline based tetrasubstituted imidazole derivatives

Lavanya et al. [xx] reported the synthesis of 6-bromo-2 substitutedphenyl-1Himidazo[4,5-b]pyridine derivatives. To do this, 5-Bromopyridine-2,3-diamine was synthesized, and it then underwent easy condensation with a variety of aromatic carboxylic acid derivatives in the presence of Etan's reagent.



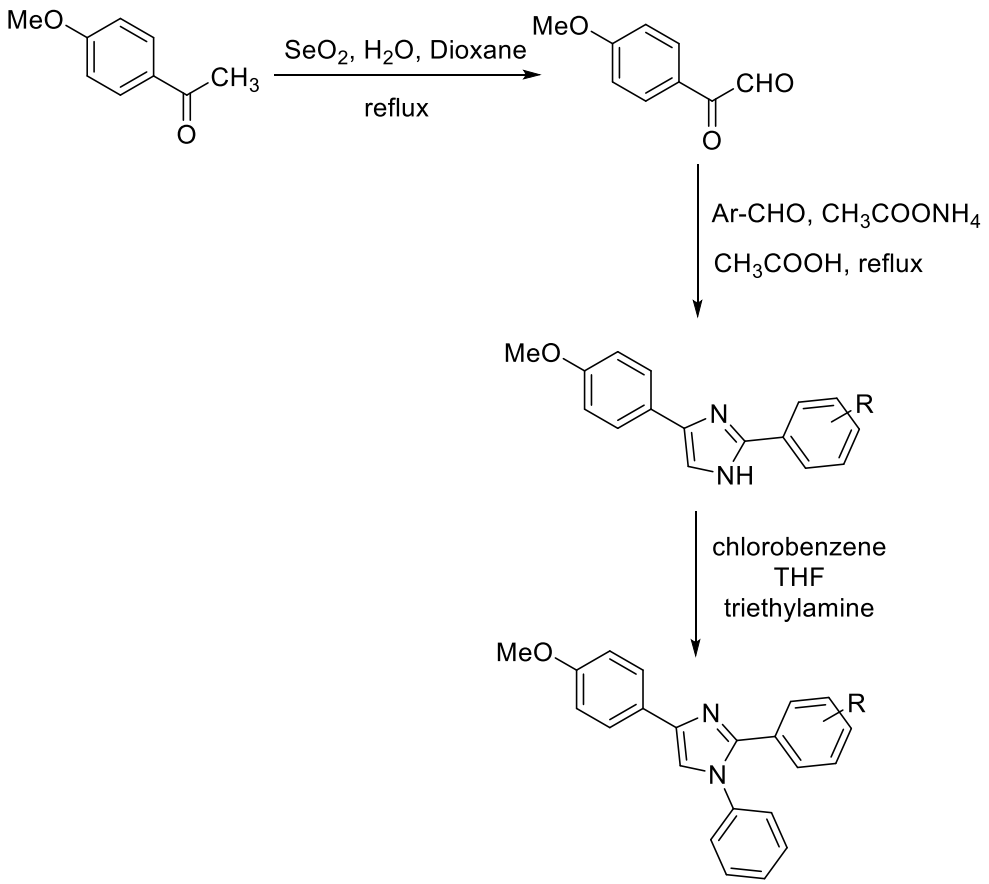
Scheme 3. Synthesis of 6-bromo-2-substitutedphenyl-1H-imidazo[4,5-b]pyridine derivatives

Jawaharmal et al.[xxi] reported tetrasubstituted imidazole by the refluxing of 9, 10-phenenthraquinone with aryl aldehyde , primary amines and ammonium acetate in the presence of glacial acetic acid.



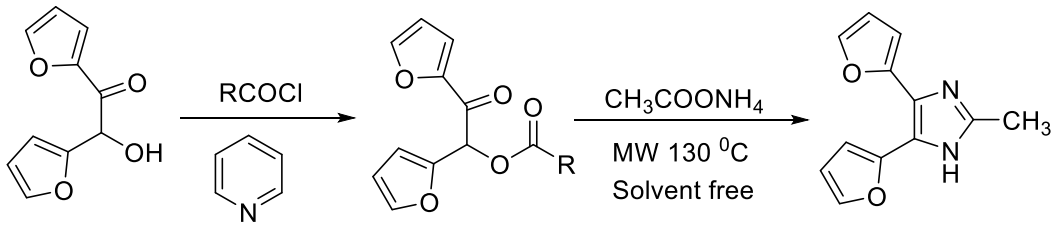
Scheme 4. Synthesis of tetrasubstituted imidazole

Husain et al. [xxii] a series of 1,2,4-trisubstituted-1 H-1 imidazoles were created by 2,4-disubstituted-1 H-1 imidazoles, and the title compounds were created via a multistep synthesis process starting with 4-methoxyphenyl glyoxal.



Scheme 5. Synthesis of 1,2,4- trisubstituted- 1 H- imidazoles

Li et al. [xxiii] have been synthesized trisubstituted imidazoles by the reaction of 1,2-di(furan-2-yl)-2-oxoethyl carboxylates in presence of RCOCl they form an intermediate then it is converted into the synthesized compound.



R= Alkyl, Aryl or substituted aryl

Scheme 6. Synthesis of trisubstituted imidazoles containing furan rings

Desai et al. [xxiv] reported the synthesis of N-(4-((2-chloroquinolin-3-yl) methylene)-5-oxo-2-phenyl-4,5-dihydro-1H-imidazol-1-yl)(aryl)amides by the reaction of 2-chloroquinoline- 3-carbaldehyde and N-amino arylcarboxamides in pyridine. They were reacting with 4-((2-Chloroquinolin-3-yl) methylene)-2-phenyloxazol-5(4H)-one was heated with again an N-amino arylcarboxamides in pyridine.

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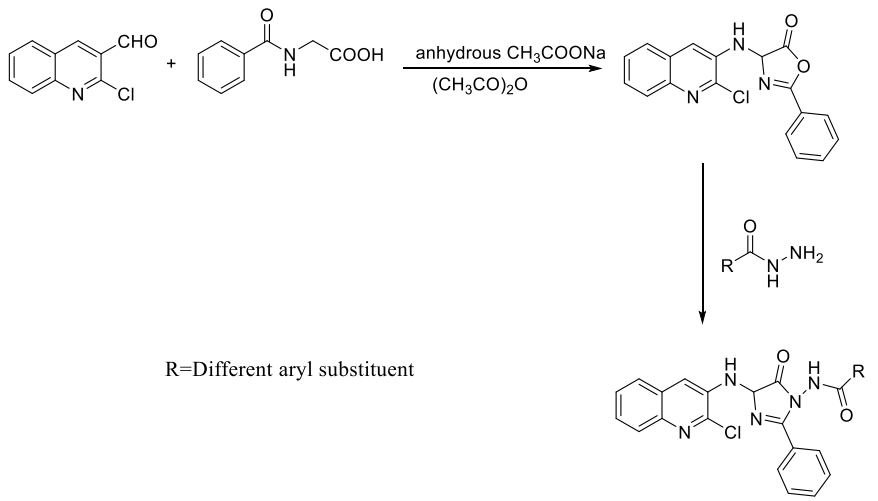
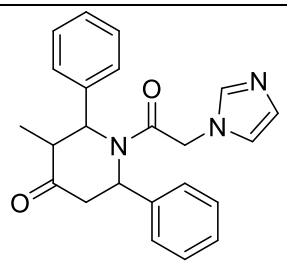
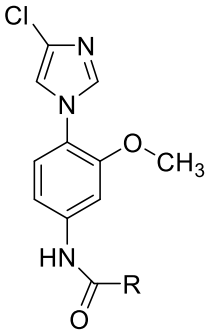
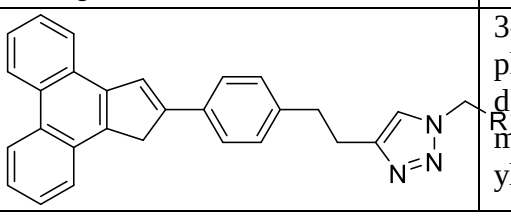
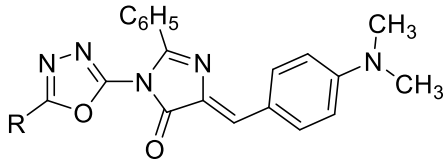
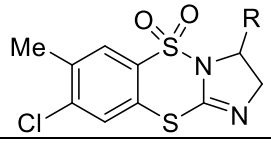
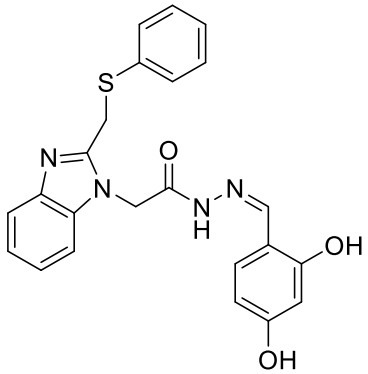
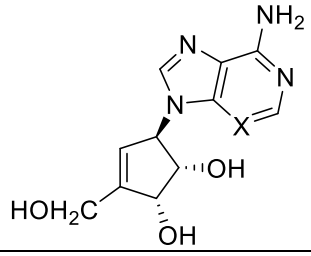


Scheme 7. Synthesis of N-(4-((2-chloroquinolin-3-yl)methylene)-5-oxo-2-phenyl-4,5-dihydro-1H-imidazol-1-yl)(aryl)amid

Pharmacological Profile of Imidazoles:

The most commonly used drugs in therapeutic settings are still imidazole and its derivatives, which have demonstrated broad-spectrum action against a variety of infections. Since the discovery of various drugs contain the imidazole nucleus, including ketoconazole, metronidazole and cimetidine, which are used to treat fungal infections, bacterial infections and gastric ulcers, respectively. On the basis of various literature surveys imidazole derivatives shows various pharmacological activities.

Sr. No.	Chemical Structure	Chemical Name	Activity	Ref.
1		1-[2-(1H-imidazol-1-yl)acetyl]-3-methyl-2,6-diphenylpiperidin-4-one	antibacterial and antifungal	xxv
2		2,4-Dichloro-N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)benzamide	antimicrobial and antitubercular	xxvi
3		3-(4-((4-(1H-phenanthro[9,10-d]imidazole-2-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)propan-1-amine	alzheimer's disease	xxvii

4		(5Z)-5-[4-(dimethylamino)benzylidene]- 3-(5- substituted - 1,3,4-oxadiazol - 2-yl)-2-phenyl-3,5-dihydro-4H-imidazol-4- one	anthelmintic	xxviii
5		2,3-dihydroimidazo[1,2-b][1,4,2]benzodithiazines	anti-HIV	xxix
6		N-(2,4-dihydroxybenzylidene)- 2-(2-(phenylthiomethyl)-1H-benzo[d]-imidazol-1-yl)acetohydrazide	antitumor	xxx
7		2 3-bromo-3-deazaneplanocin	antiviral	xxxi

Conclusion:

A heterocyclic molecule with five members is imidazole. Imidazole and its derivatives could be synthesized using a number of various conventional techniques. Based on the literature, it was discovered that imidazole could be synthesized in a solvent-free environment using the refluxing method and an effective catalyst, both with and without a catalyst, and with a good yield. Imidazole is a base in nature due to nitrogen atom. It under goes electrophilic substitution but nucleophilic substitution is rare one. From the extensive literature survey, it was found that it has antimicrobial, anticancer, analgesic, anti-inflammatory, anticonvulsant, antiviral, anthelmintic, antiulcer, antiallergic activity etc. Imidazole is a therapeutically active versatile moiety that has been used in the past to synthesize various compounds with a range of pharmacological activities. Based on the discussion above, it can be concluded that imidazole will continue to be used in the future to treat a variety of diseases and disorders.

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