ISSN: 2278-2648

International Journal of Research in Pharmacology & Pharmacotherapeutics (IJRPP)

IJRPP |Vol.15 | Issue 1 | Jan - Mar -2026

www.ijrpp.com

DOI : https://doi.org/10.61096/ijrpp.v15.iss1.2026.529-545

Review

A Comprehensive Study on Imidazoles

Palupanuri.Naveena[1]*, K. Manasa[2], G. Surekha[3], K. Pranith[4], P. Sai Krupani[5], P. Ram Mohan[6]

Department of pharmaceutical chemistry, Malla Reddy pharmacy college, secunderabad, Telangana, India.

*Corresponding Author: Palupanuri.Naveena
Email: gummulanaveena@gmail.com

Published on:
30.03.2026

Published by:
Futuristic Publications

Abstract

Introduction: Imidazole and its derivatives have attracted considerable attention in recent years due to their broad spectrum of biological activities. This heterocyclic moiety is of significant interest to medicinal chemists for exploring its diverse pharmacological potential. The present article reviews the chemistry of imidazole and highlights its pharmacological activities, including antihelmintic, anticancer, antifungal, and anti-inflammatory effects, based on studies of various synthesized derivatives.

Materials and Methods: A comprehensive literature survey was conducted using research articles and published reports that describe the chemistry of imidazole and the pharmacological evaluation of its structurally modified derivatives.

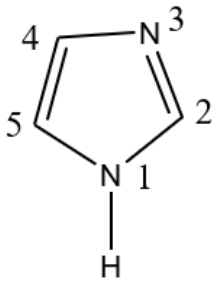
Results: Available data indicate that imidazole, a heteroatomic planar five-membered ring system, exhibits versatile chemistry with diverse physicochemical properties. These properties can be effectively modulated through structural modifications, leading to derivatives with varied pharmacological activities. The present review summarizes the effects of different substituents and moieties incorporated into the imidazole nucleus and their influence on biological activity.

Conclusion: The review discusses various synthetic approaches to imidazole and its derivatives, emphasizing their chemical characteristics. Based on these chemical insights, different substituted and fused imidazole compounds are analyzed for their potential pharmacological applications.

Keywords: Anthelmintic, Anticancer, Antifungal, Anti-inflammatory, Imidazole.

1. INTRODUCTION

Imidazole (1,3-diaza-2,4-cyclopentadiene) is a planar, five-membered heterocyclic ring system containing three carbon atoms and two nitrogen atoms located at the 1 and 3 positions. The simplest member of this family is imidazole itself, with the molecular formula $C_3H_4N_2$. Its systematic name is 1,3-diazole. One of the ring nitrogen atoms bears a hydrogen atom and resembles a pyrrole-type nitrogen.Imidazole is soluble in water and other polar solvents and exists in two equivalent tautomeric forms, as the hydrogen atom can shift between the two nitrogen atoms. It is classified as an aromatic compound due to the presence of a six-π-electron system, comprising a lone pair from the protonated nitrogen atom and one π-electron from each of the remaining four ring atoms.Imidazole exhibits amphoteric behavior, meaning it can act as both an acid and a base. The acidic proton is located on the N-1 atom. As a base, the pKa of its conjugate acid is approximately 7, indicating that imidazole is about sixty times more basic than pyridine. The basic character arises from the nitrogen atom at the N-3 position.



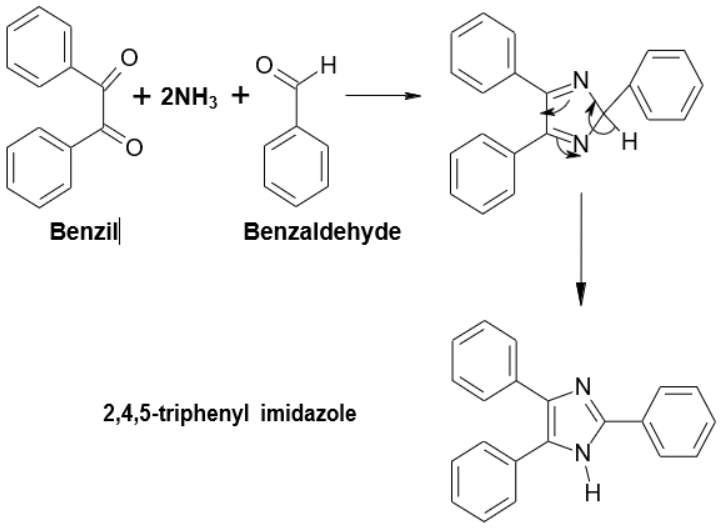
Imidazole is a key structural component of numerous biologically important molecules. One of the most significant examples is the amino acid histidine, which contains an imidazole side chain. Histidine is widely distributed in proteins and enzymes and plays a crucial role in the structural integrity and oxygen-binding function of hemoglobin. Decarboxylation of histidine produces histamine, another biologically important compound involved in various physiological processes.Imidazole also has important applications in biotechnology, particularly in the purification of His-tagged proteins using immobilized metal affinity chromatography (IMAC). In addition, imidazole forms the core structure of many pharmaceutical agents. Synthetic imidazole derivatives are commonly found in fungicides, antifungal, antiprotozoal, and antihypertensive drugs. The imidazole ring is also present in theophylline, a naturally occurring compound found in tea leaves and coffee beans, which acts as a central nervous system stimulant.Beyond pharmaceutical applications, imidazole and its derivatives are widely used in industrial fields. Imidazole has been extensively employed as a corrosion inhibitor for certain transition metals, particularly copper, where corrosion prevention is critical in aqueous systems to maintain electrical conductivity. Several compounds of industrial and technological importance incorporate imidazole derivatives. For example, the thermostable polymer polybenzimidazole (PBI), which consists of imidazole rings fused to benzene and linked to additional benzene units, is used as a fire-retardant material. Imidazole derivatives are also utilized in photographic and electronic applications.This review primarily highlights the pharmaceutical significance of the imidazole moiety.

2. CHEMICAL ASPECTS OF IMIDAZOLE

Imidazoles were prepared in 1858 from glyoxal and ammonia. Several approaches are available for synthesis of imidazoles as, Radiszewski synthesis, dehydrogenation of imidazolines, from alpha halo ketones, Wallach synthesis, from aminonitrile and aldehyde and Marckwald synthesis. Details of the synthetic procedures are given below:

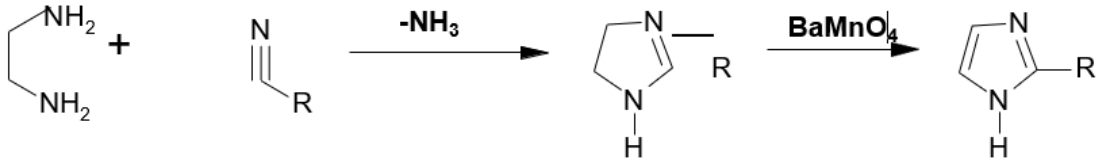
2.1. Radiszewski Synthesis [1-3]

It consist of condensing a dicarbonyl compound such as glyoxal, □- keto aldehyde or □- diketones with an aldehyde in the presence of ammonia, benzyl for instantce, with benzaldehyde and two molecule of ammonia react to yield 2,4,5-triphenylimidazole. Formamide often proves a convenient substitute for ammonia.



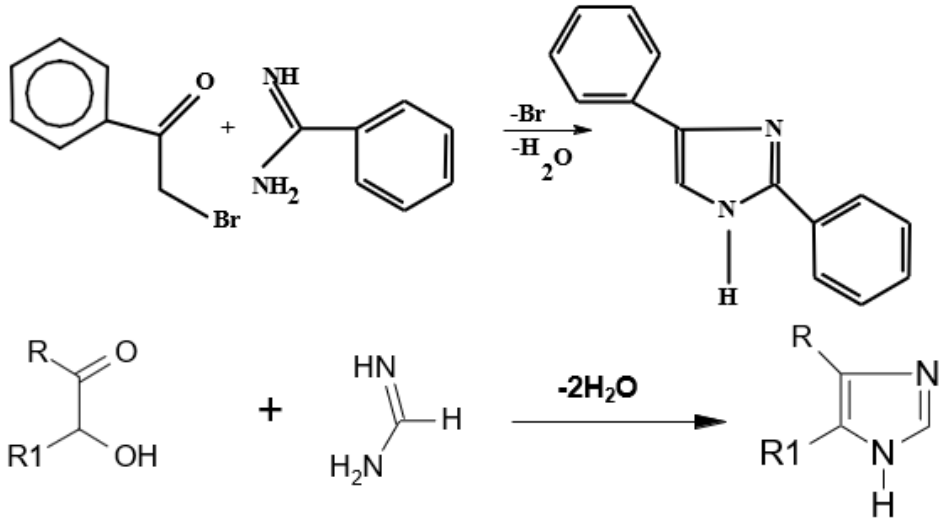
2.2. Dehydrogenation of Imidazoline [4]

Knapp and co-workers reported the use of a milder reagent, barium manganate, for the conversion of imidazolines into imidazoles in the presence of sulfur. Imidazolines synthesized from alkyl nitriles and 1,2-ethanediamine, when treated with $BaMnO_4$, undergo oxidation to afford 2-substituted imidazoles.



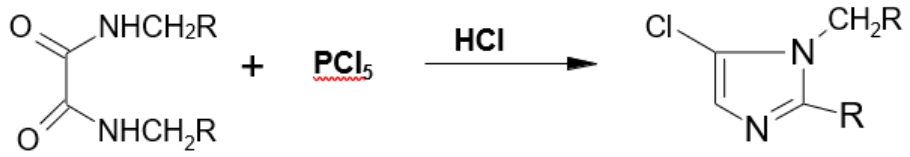
2.3. From □- Halo Ketone [4]

This reaction involves the interaction of an imidine with α-halo ketones. The method has been successfully employed for the synthesis of 2,4- or 2,5-diphenyl imidazoles. For example, phenacyl bromide reacts with benzimidine under these conditions to produce 2,4-diphenyl imidazole. In a similar manner, amidines react with acyloins or α-halo ketones to yield substituted imidazoles.



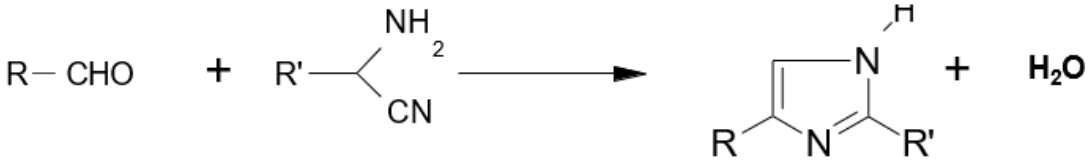
2.4. Wallach Synthesis [4 - 8]

When N, N′ -dimethyloxamide is treated with phosphorus pentachloride, a chlorine containing compound is obtained which on reduction with hydroiodic acid give N- methyl imidazole. Under the same condition N, N′ -diethyloxamide is converted to a chlorine compound, which on reduction gives 1- ethyl –2- methyl imidazole. The chlorine compound has been shown to be 5- chloral imidazole.



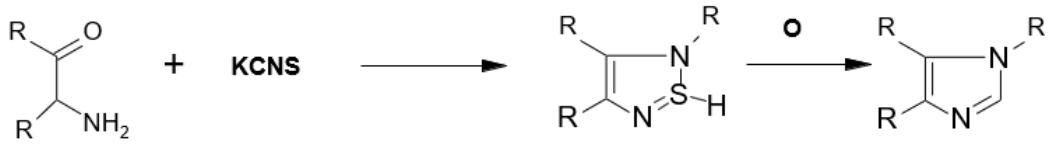
N,N-dimethyloxamide

2.5. From Aminonitrile and Aldehyde



2.6. Markwald Synthesis [4]

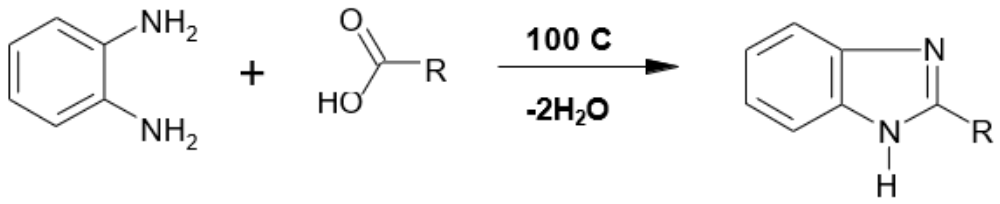
The preparation of 2- mercaptoimidazoles from □- amino ketones or aldehyde and potassium thiocyanate or alkyl isothiocyanates is a common method for the synthesis of imidazoles. The sulfur can readily be removed by a variety of oxidative method to give the desired imidazoles. The starting compounds, □- amino aldehyde or ketone, are not readily available, and this is probably the chief limitation of the Markwald synthesis.



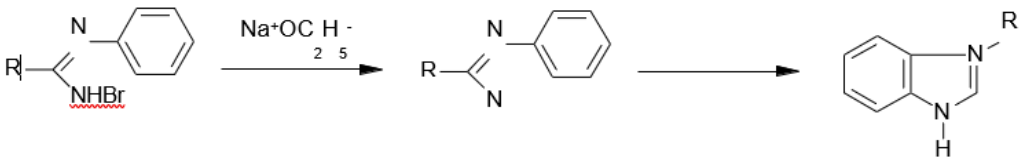
alpha-Amino ketone

2.7. Some other methods by which imidazole can be synthesized are

Benzimidazole is more important than imidazole as the former occur in Vit B12 and has been prepared by a number of methods, 1, 2-diaminobenzene condenses with a carboxylic acid on heating in an acidic medium to give benzimidazole.



The cyclization of N-haloamidines with sodium ethnoxide forms benzimidazoles through a nitrene intermediate.



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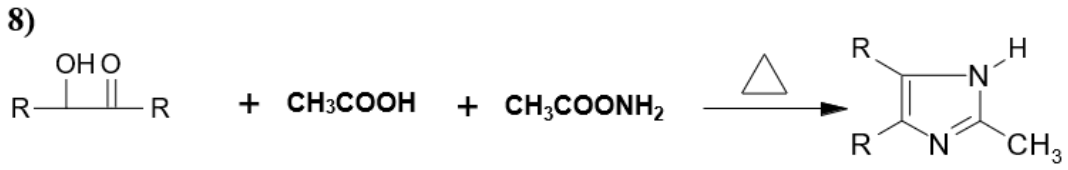
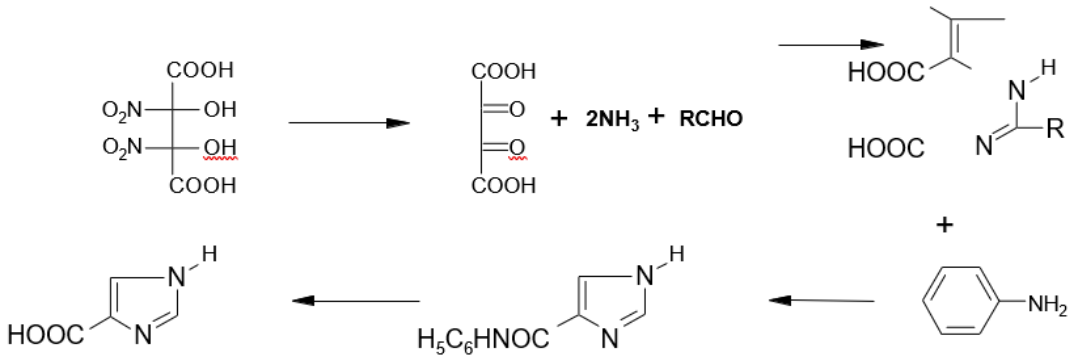
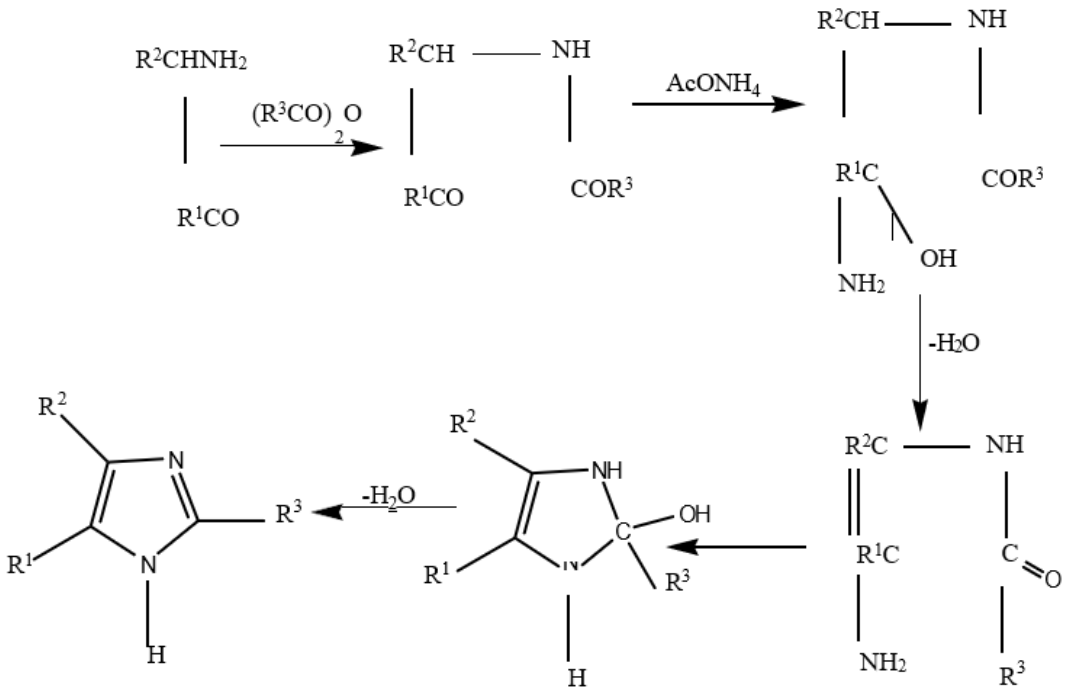


Imidazole can best be prepared itself by action of ammonia on a mixture of formaldehyde and tartaric acid dinitrate and then heating the dicarboxylic acid in quinoline in presence of cooper [9].



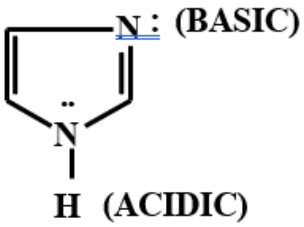
2.8. CYCLIZATION OF α-ACYLAMINOKETONES [9]

α-acylaminoketones, also behave as 1, 4-diketo compounds.



3. REACTIVITY

Imidazole can be considered as having properties similar to both pyrrole and pyridine. The electrophilic reagent would attack the unshared electron pair on N-3, but not that on the 'pyrrole' nitrogen since it is the part of the aromatic sextet. While the imidazole ring is rather susceptible to electrophilic attack on an annular carbon, it is much less likely to become involved in nucleophilic substitution reaction unless there is a strongly electron withdrawing substituents elsewhere in the ring. In the absence of such activation the position most prone to nucleophilic attack is C-2. The fused benzene ring in benzimidazoles provides sufficient electron withdrawl to allow a variety of nucleophilic substitution reaction at C-2.



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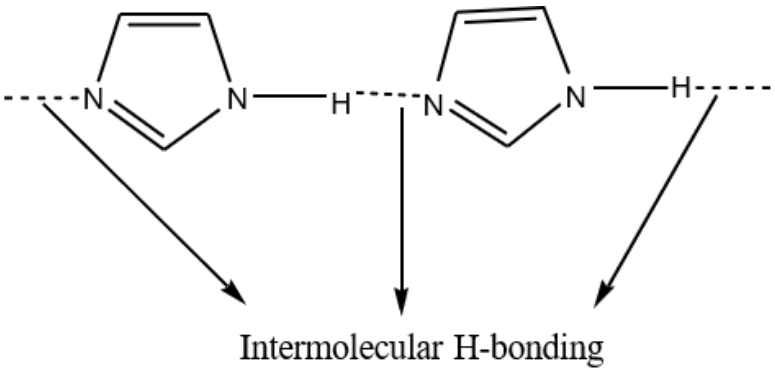
The over all reactivity of imidazole and benz imidazole is referred from sets of resonance structure in which the dipolar contributors have finite importance.

These predict electrophilic attack in imidazole at N-3 or any ring carbon atom, nucleophilic attack at C-2 or C-1 and also the amphoteric nature of the molecule. In benzimidazole the nucleophilic attack is predicted at C-2. The reactivity of benzimidazole ion at the C-2 position with nucleophiles is enhanced compared with the neutral molecule [10].

4. PHYSICAL PROPERTIES

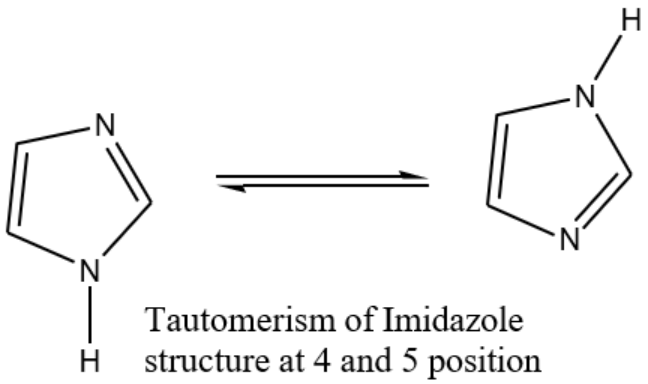
It is colourless liquid having a high B.P. of 256 oC than all other 5- membered heterocyclic compounds due to the intermolecular H-bonding, where there is linear association of molecule [11]



Imidazoles shows a large value of dipole moment of 4.8 D in dioxane. Imidazole show amphoteric properties and has pKa of 7.2 more than pyrazole and pyridine.

Imidazoles are an aromatic compound possessing a resonance value of 14.2 K cal/ mol, which is almost half the value for pyrazole. The electrophillic substitution occurs frequently in imidazole and nucleophillic substitution

happens in the presence of electron withdrawing group in its nucleus. Imidazoles have M. pt. 90 ^{0}C, it is a weak base and tautomeric substance, since position 4 and 5 are equivalent.



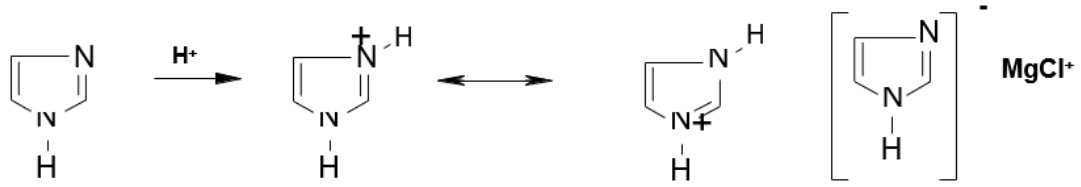
Tautomerism of Imidazole structure at 4 and 5 position

It's spectroscopic parameters are λ_{max} of 207 nm, I.R.=1550, 1492, 1451(cm^{-1}), τ = 2.30, 2.86, mass spectroscopy is studied for heterocyclic compounds containing one hetero-atom, in detail, not in case containing two or more heteroatom [11].

5. Chemical Reaction

5.1. REACTION WITH ACIDS

Imidazole is a monoacidic base and form crystalline salt with acid. It also possesses weakly acidic properties (pseudo acidic) and is even more acidic than pyrroles and thus forms salts of the following type with Grignard reagent or metal ions.



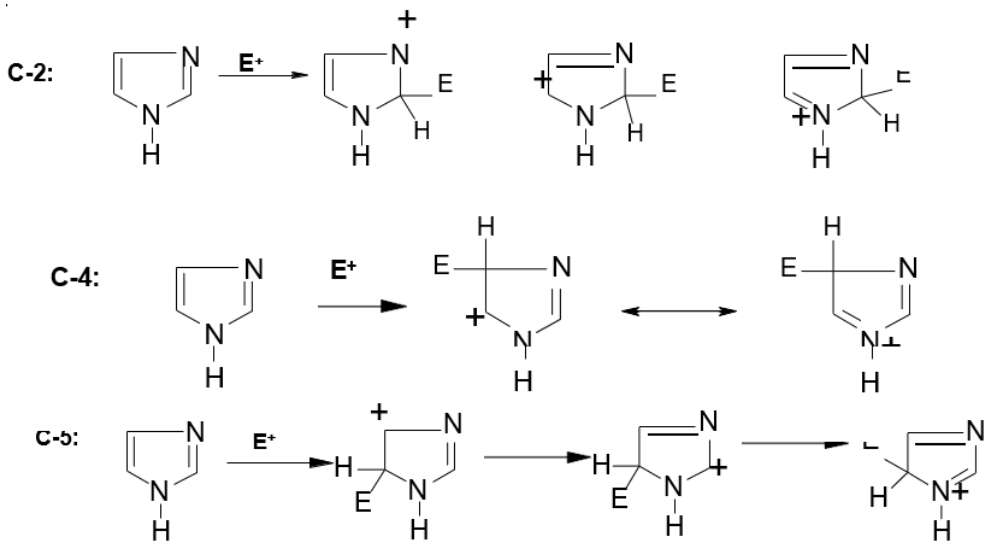
With ammonical silver nitrate imidazole form a silver salt, which is sparingly soluble in water.

5.2. Reaction with Oxidizing and Reducing Agents

Imidazole itself is stable to auto oxidation and to the action of chromic acid but is attacked by potassium permanganate. However imidazole readily opens the ring to form oxamide with H2O2 [10]. Oxygen in the presence of a sensitizer (single oxygen) reaction gives an imidazolidine derivative. Imidazolium dichromate, a mild oxidizing agent has been employed for the oxidation of allylic and benzylic alcohol to the corresponding carbonyl compound.

5.3. Electrophilic Substitution

Imidazoles posses increased reactivity towards electrophillic attack. It is more susceptible to electrophillic attack than pyrazole or thiazole and more so than from furan and thiophene also. From the following resonance structure of the intermediate ion; it is evident that the attack takes place at the 4th and 5th position in imidazole ring. It may be noticed that the attack at C-2 involves a canonical form which is highly unfavored at positive N at position 3.



Halogenations of imidazole is very complex and varies considerably depending on the substrate, reagents and reaction condition.

5.4. Pharmacological Activities of Imidazoles

Imidazole derivatives have a wide range of pharmacological activity, literature survey revealed that imidazole and its derivative are reported to have, analgesic and anti-inflammatory activity [12-15], cardiovascular activity [16,17], anti-neoplastic activity [18], anti- fungal activity [18-19], enzyme inhibition activity [20-22], anti-anthelmintic activity [23], anti-filarial agent, anti- viral activity and anti- ulcer activity.

Other then their pharmacological actions they also function as dyestuffs catalysts and polymerizing agents. 2-nitro imidazole (azomycin) and 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole (metronidazole) are anti bacterial agent with particular applications as trichomonacide. Along with metronidazole other nitroimidazoles (misonidazole, metrazole and clotrimazole) are important anti cancer drugs.

Two imidazolines, priscol and privine are valuable vasodialating and vasoconstricting drugs. 2-aminoimidazolines are among the class which are known for fungicidal action. The modern scientific searches aim at discovering more effective and better-tolerated imidazole derivatives.

5.5. Imidazoles as Anthelmintics

Imidazole derivatives have been found to be less effective against extraintestinal parasites, particularly intravascular and tissue-dwelling parasites, compared with their activity against gastrointestinal parasites. Their efficacy is generally greater against developing stages of parasites than against arrested or adult stages occupying similar habitats. In vivo studies indicate that hatching and larval development are inhibited at doses that are sub-therapeutic for adult parasites.

Lower drug doses are required to achieve efficacy against nematodes compared with those needed for the control of cestodes and trematodes. In the case of cestode and trematode infections, higher doses or repeated treatments are usually necessary to obtain satisfactory therapeutic outcomes.

Members of the 2-alkyl benzimidazole class have been reported to eliminate a wide range of nematode and trematode species from various hosts. Among these, 4,5,6,7-tetrachloro-2-trifluoromethyl benzimidazole has shown high activity against nematodes such as *Ancylostoma caninum*, *Haemonchus contortus*, and *Ascaris suum*, as well as against the trematode *Fasciola hepatica*. Several 2,5-disubstituted benzimidazoles, originally developed for their strong activity against intestinal nematodes, have also demonstrated efficacy in the treatment of cestodiasis in both humans and animals. Mebendazole, administered at a dose of 100 mg/kg, has been reported to successfully cure infections caused by *Taenia solium* and *Taenia saginata*.

5.6. 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.

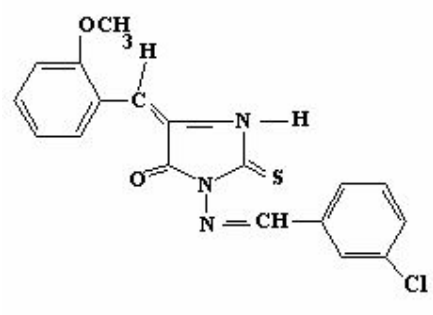
Amino acids are reported to posses' anti-inflammatory activity [24-25] and bearing this in mind Kumar et al [26] prepared various heterocyclic derivatives having both carboxylic and amino group. The structure activity relationship studies indicated the conversion of the carboxylic group into a heterocyclic ring usually potentiated the inhibition of edema. Conversion into benzimidazole and 1, 2, 3, 4-tetrahydroquinoline ring resulted in compounds possessing better activity then 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 [27] and substituted imidazolone [28] have been found to be active. Among a series of 3-[substituted phenyl methylene] amino-5- (substituted phenyl methylene –2 -thioxo- imidazolidinone) compound (I) was found to be most potent inflammation inhibitor and

superior to phenyl butazone [29]. Activity has also been observed among some 1-(thiadiazolyl substituted phenyl) - 2-methyl-4- (substituted) methylene imidazol- 5-ones [30].

Some active 2-(5-aryl –4-5dihydro pyrazol-3-yl) and 2-(2-amino-6 aryl pyrimidin-4yl) benzimidazoles [31] and benzimidazoles derivatives [32] with 6-aryl-4, 5- dihydro-3 (2H) - pyridazinone moiety attached at position 2 have been prepared.

2-substituted benzimidazole with different aryl alkyl moiety such as (4-isobutyl phenyl) ethyl, (6-methoxy naphthyl ethyl) and (3- benzoylphenyl ethyl) have shown anti-inflammatory activity [33].



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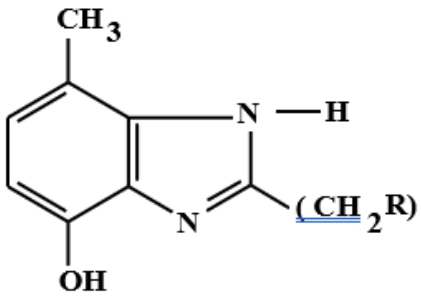
It was shown by the early work of Vane and others that the non-steroidal anti-inflammatory drugs owed their activity to the inhibition of cyclooxygenase and the consequent reduction in the formation of thromboxane and prostaglandins, little interest was shown in other oxidative pathways.

It was characterization of the slow reacting substance of anaphylaxis (SRS-A) a potent bronchoconstructor, as a mix of the leukotrienes LTC4 and LTE4, LTB4 a potent chemo toxin that focused attention on the 5-lipooxygenase pathway of arachidonic acid metabolism this increase awareness of the arachidonic acid cascade and the enzyme involved lead to the development of novel 1H-2-substituted benzimidazole-4-ols with potent 5-lipooxygenase inhibitory activity. In the series of 7- methyl-1H-benzimidazole –4-ols (I) the compound (A) having constituent as (R=C6H5) showed potent inhibition of 5- lipooxygenase in vitro.



[A] = R=C6H5

The compounds bearing a variety of substituents in benzimidazole ring were prepared and it was found that:

[1] A free hydroxyl group appeared essential for good activity, as did the presence of an alkyl group at C-7.

[2] *In vivo* result suggested that the C-2 benzyl moiety were preferred.

[3] Potency was retained by replacement of the benzenoid ring at C-2 by both thiophene and pyridine.

[4] The 4- hydroxy compound (B) and the multiple methoxylated analogues (C) and (D) were also active where as the (methoxyphenyl) benzimidazole – 4-ol was inactive at the doses tested.

(B) R = 4-OH-C_6H_5

(C) R = 3,4-$(CH_3O)_2$ C_6H_3

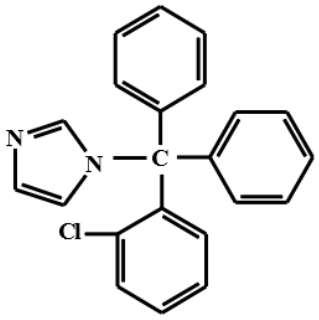
(D) R = 3, 4, 5-$(CH_3O)_3$ C_6H_2

Several heterocyclic systems such as pyrazolo, isoxazolo, 2-aminothiazolo, oxadiazolo and mannic bases have been synthesized and screen for anti-inflammatory activity.

5.7. Imidazoles as Anti-Fungal Agents [34]

The search for new anti fungal in recent years has concentrated principally on the imidazole and triazole area of chemistry. The group of drug known collectively as the azoles, comprising a number of 1-substituted imidazole and triazole compounds undoubtedly represents the modern approach to both topical and systemic treatment of fungal disease. The imidazole as anti fungal has pronounced pharmacological and biochemical activities.

The lipophilic imidazoles such as clotrimazole (I), econazole (II) and miconazole (III) 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.



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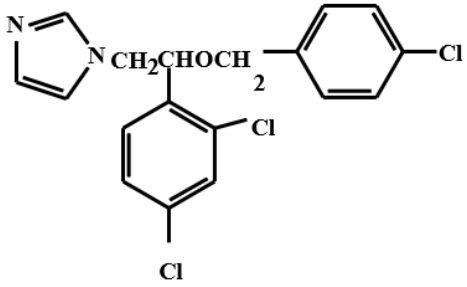

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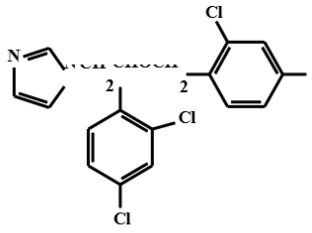

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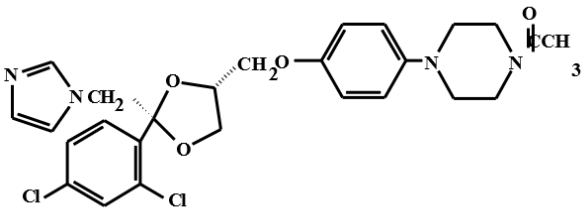

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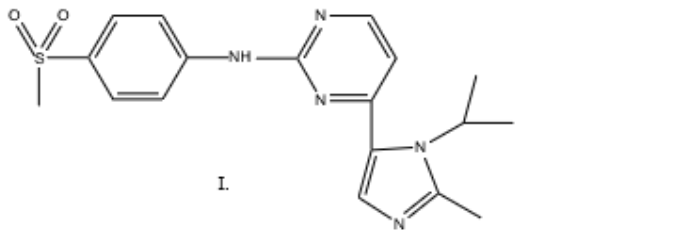
5.8. IMIDAZOLES AS ANTI-CANCER AGENTS

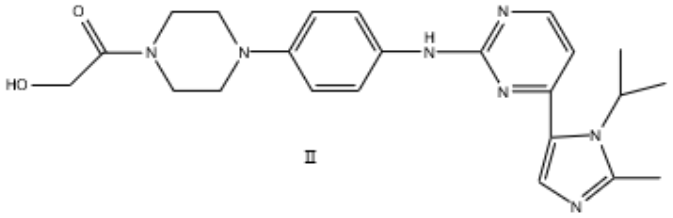
Past few years imidazole moiety is exclusively studied as an important structure as an anticancer or antineoplastic agent. Principally importance is given at the various substitutions at different positions in the moiety.

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

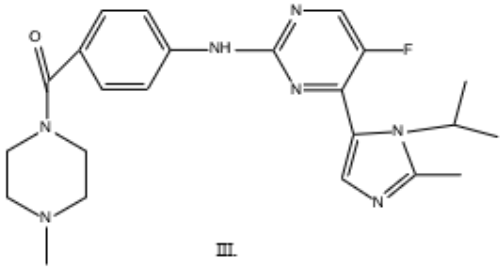
regulation of the cell cycle and the observed expression/activity pattern in most human cancers, considerable effort has been focused on the development of small molecule CDK cell cycle inhibitors as potential therapeutic agents [35]. Incorporation of a basic group into CDK imidazole pyrimidine amide 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 [36]. Many secondary amides, like the 5-fluoro pyrimidine ortho-fluoro amide substitution gives the highest levels of enzyme potency against both CDK1 and CDK2, this highly potent CDK1/2 inhibition resulted in extremely potent inhibition of cellular proliferation in cancer cell lines. The chiral, non-racemic pyrrolidines (both S and R forms) also displayed excellent potency against CDK1 and CDK2, again with potent anti-proliferative activity. In contrast to the piperazine amides, the corresponding homopiperazine (III) gave much improved properties with significant increases in both enzyme and cellular potency. The increased basicity of the homopiperazine (measured pKa 8.1 for comp.III) also resulted in much improved solubility which altogether proved to be potent *in vitro* anti-proliferative effects against a range of cancer cell lines [37]



I.



II



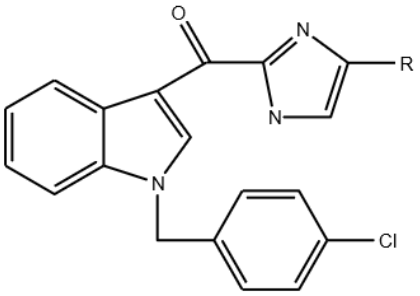
III.

A series of indole–imidazole compounds have been developed that exhibit significant in vitro antiproliferative activity against a variety of cancer cell lines, including those displaying multidrug resistance (MDR) phenotypes. Prolonged exposure of cancer cells to certain chemotherapeutic agents often leads to the development of resistance to multiple drugs, a phenomenon known as MDR [38]. The cytotoxic effects of these compounds have been demonstrated against a broad range of tumor types, encompassing both hematological and solid malignancies such as leukemia, breast, colon, and uterine cancers. MDR is commonly associated with the overexpression of ATP-binding cassette (ABC) transporters [39]. Additional mechanisms contributing to MDR include increased expression of anti-apoptotic genes with concurrent suppression of pro-apoptotic genes [40], overexpression of specific tubulin isotypes [41], reduced expression of topoisomerases [42], and elevated levels of major vault protein [43].

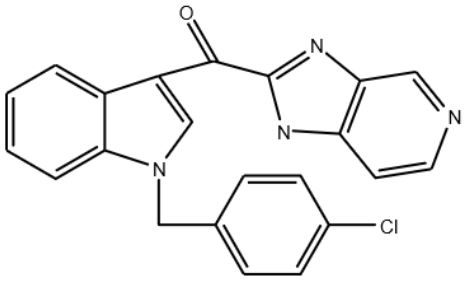
Various strategies have been explored to overcome MDR, most notably the inhibition of P-glycoprotein (P-gp) and related efflux transporters to prevent drug extrusion from cancer cells [44]. Although numerous MDR-reversal agents have been reported, many are limited by undesirable side effects such as toxicity. In contrast, indole–imidazole derivatives have demonstrated considerable cytotoxic activity against both sensitive and MDR cancer cell lines through strategic substitutions at different positions on the molecular scaffold. For instance, substitution with a 2-pyridyl group in compound (IV) resulted in potent activity, while introduction of a

conjugated ketone group maintained activity in compound (V). Another derivative, compound (VI), containing a methyl ester substitution, showed strong cytotoxicity against the Taxol-resistant HL60/TX1000 cell line [45,46]. Notably, the indole–pyridoimidazole compound exhibited approximately a tenfold increase in potency compared with the indole–imidazole derivatives (IV, V, and VI).

The indole–pyridoimidazole compound was effective against all tested cell lines, including Taxol-resistant MDR lines MES-SA/DX5 and HL60/TX1000 [45,47]. Further studies on various substitutions provided insights for designing future drugs targeting MDR cancer cells [48].



Indole-Imidazole compound
(IV) R=2-pyridyl
(V) R=COEt
(IV) R=$COOCH_3$

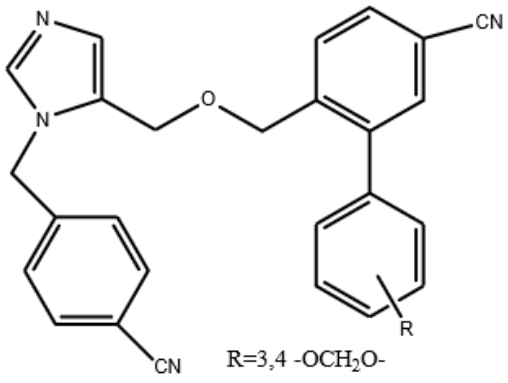


Indole-pyrido imidazole compound

Imidazole derived compounds are also emerging as potent agents against many cancer cell lines. Farnesyltransferase inhibitors (FTIs) have emerged as a novel class of anti-cancer agents. Analogs of the FTI, 1-benzyl-5-(3-biphenyl-2-yl-propyl)-1H-imidazole, had been synthesized and tested *in vitro* for their inhibitory activities.

In normal human body GTP-bound Ras proteins are responsible for initiating an intracellular phosphorylation cascade, and consequently play an important role in normal cellular physiology and pathophysiology [49]. Thus the antitransforming properties of farnesyltransferase inhibitors (FTIs), has emerged as a novel class of cancer therapeutics, in the past decade [50–54]. FTIs were initially formed with the aim of inhibiting the posttranslational prenylation and oncogenic activity of Ras. But it is seen that inhibition of Ras prenylation is not necessary for these compounds to exhibit antitumor activity, instead inhibition of Rho-B and possibly other cellular proteins might also account for the efficacy against malignant tumors [55–58].

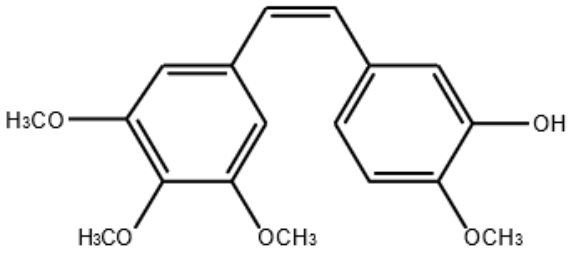
The 3,4-methylenedioxy analog was found to be the most potent FTase inhibitor in the series of substituted 1-benzyl-5-(3-biphenyl-2-yl-propyl)-1H-imidazole compounds ,consequently having more than 15,000-fold selectivity in favor of FTase inhibition and Ras processing. This analog has oral bioavailability of 11.3% in rat compared with the complete lack of bioavailability observed in the other analogs of the series of 1- benzyl -5 -(3- biphenyl-2-yl-propyl) - 1H- imidazole. Studying the various analogs, it was observed that analogs having the ether linkage possessed potent inhibitory activities against the FTase enzyme. The highest selectivity for FTase inhibition over GTase-1 was observed in compound (VII). This compound is more potent in inhibition of FTase enzyme and possesses better selectivity. It also has reasonable bioavailability [59].



R=3,4 -OCH_2O-

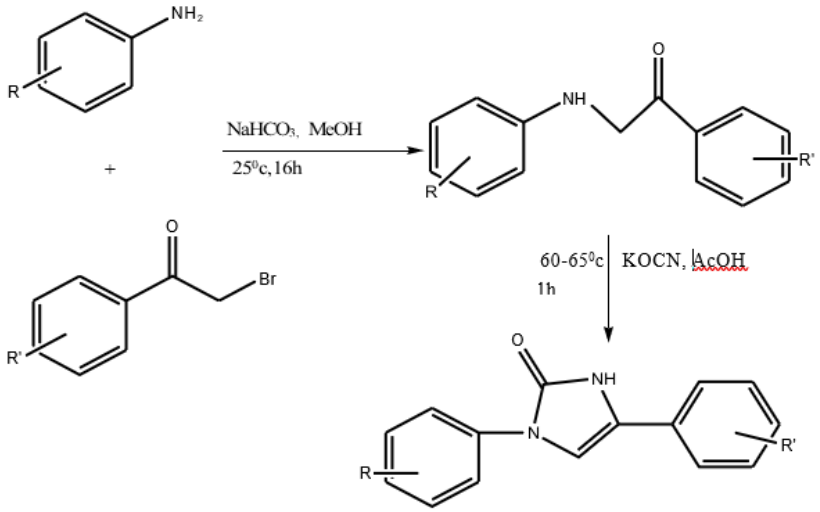
(VII). 3,4 methylene dioxy analog

The discovery of anticancer properties of the combretastatins, a group of antimitotic agents isolated from the bark of the South African willow tree Combretum caffrum Kuntz[60] has attracted considerable interest in designing series of new compounds against various tumors cell lines, mainly Combretastatin A-4 (CA-4), appears to be the most active compound in the group, showing potent inhibitory activity against a variety of human cancer cells, including multi-drug resistant cell lines [61].



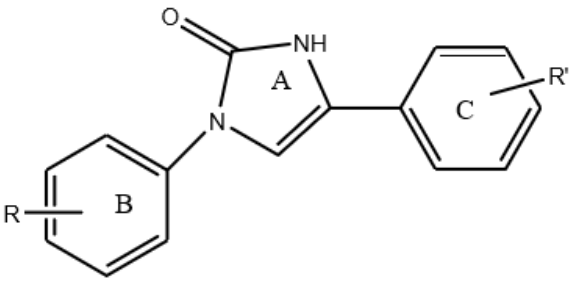
CA-4(combretastatin)
{3-atom bridged structure}

CA-4 is one of the most potent antimitotic agents and binds to tubulin on the colchicine binding site which is it's mode of action as antimitotic agent [62] thus, series of new 1,4-diarylimidazol-2(3H)-one derivatives and their 2- thione analogues had also been prepared and evaluated in vitro for antitumor activity against the NCI human cancer cell lines. It was observed, compounds having a 3, 4, 5-trimethoxyphenyl ring linked to either N-1 or C-4 position of the imidazole entity gave an interesting profile of cytotoxicity with specific activity against leukemia cell lines, the synthesis and preliminary anticancer activity of new imidazolone derivatives, and their 2-thione analogues and 1, 4-diaryl-1H-imidazol-2(3H)-ones is studied with the help of mentioned scheme: [63]

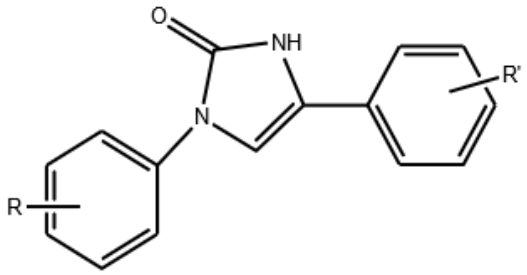


R=4-Cl
R'=3,4,5-(MeO)3

These compounds have been designed with the strategy of three-atom bridgehead 1, 3-oriented CA-4 (Combretastatin A-4) analogues, where the imidazole core (ring A) serves as a linker between functionalized B and C rings.



It was observed after meticulous studies that a 3, 4, 5-trimethoxyphenyl ring was essential for potent antitumor activity. A trimethoxyphenyl group is considered a structural feature typical for inhibitors of tubulin polymerization [64].



R=4-Cl
R'=3,4,5-(MeO_3)

Many other amino substituted xantheno[1,2-d]imidazoles derivatives had also been synthesized with cell growth inhibitory activity specifically against breast cancer cell lines, insertion of two basic side chains at 2- and 5-positions in this moiety ,exhibited a strong dose-dependent antiproliferative activity [65].

Again some specific moiety like 5-Arylamino-1H-benzo[d]imidazole-4,7-diones were synthesized for their inhibitory activities on the proliferation of human umbilical vein endothelial cells (HUVECs) and the smooth muscle cells (SMCs). Among them, several 1-H benzo[d]imidazole-4, 7-diones exhibited the selective antiproliferative activity on the HUVECs [66].

6. CONCLUSION

Imidazole is a widely studied pharmacophore with unique physicochemical properties that have been extensively exploited for the development of compounds with diverse pharmacological activities. Numerous imidazole derivatives have shown promising anticancer, antihelmintic, anti-inflammatory, and antifungal effects, depending on the nature and position of substitutions on the imidazole ring. Structural modifications such as trimethoxyphenyl, indole, amino acid, and triazole substitutions have resulted in enhanced cytotoxic, antiproliferative, anti-inflammatory, and antifungal activities. In particular, 2-alkyl benzimidazoles have demonstrated strong efficacy against gastrointestinal nematodes and trematodes, while other substituted imidazoles have shown potential as antineoplastic agents. Overall, the versatility of the imidazole nucleus continues to make it an important scaffold for the design and development of novel therapeutic agents for various pathological conditions.

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[47] Cell lines (tissue origin in parentheses) were all purchased from ATCC: MDA435 (breast), HL60 (leukemia), P388 (murine leukemia), DU145 (prostate), MES-SA (uterine) and MES-SA/DX5 (MDR uterine).

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