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A Review on "Imidazoles": Their Chemistry and Pharmacological Potentials

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Abstract: ***Introduction*:** Imidazole is an entity which is being synthesized in many of its derivative form from past few years; the entity is major source of interest for many of medicinal chemist to explore its various pharmacological potentials. In present article we review the chemistry of imidazole and its pharmacological actions as antihelmintics, anticancer, antifungal and anti-inflammatory agent by studying its various synthesized derivatives.

Material and method: literature study of various research papers and other publications which provide detailed work on chemistry of the imidazole and its various pharmacological actions by synthesizing its different derivatives.

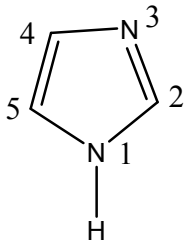
Result: Present data suggests that imidazole being hetero-atomic planar five-member ring system have diverse chemistry with varying physical and chemical properties which may be exploited via forming various derivatives having varying pharmacological actions. Results of various combinations of different moieties with imidazole and their substitutions are reviewed in present article.

Conclusion: Various methods for synthesizing imidazoles are discussed with their chemistry. Studying this chemistry different substituted and fused compounds of imidazole are analyzed here for varying pharmacological activities.

Key words: Antianthelmintic, Anticancer, Antifungal, Anti-inflammatory, Imidazole.

INTRODUCTION

Imidazole (1,3-diaza-2,4-cyclopentadiene) is a planar five-member ring system with 3C and 2N atom in 1 and 3 positions The simplest member of the imidazole family is imidazole itself, a compound with molecular formula $C_3H_4N_2$. The systemic name for the compound is 1, 3 diazole, one of the annular N bear a H atom and can be regarded as a pyrole type N. It is soluble in water and other polar solvents. It exists in two equivalent tautomeric forms because the hydrogen atom can be located on either of the two nitrogen atoms. Imidazole is a highly polar compound, as evidenced by a calculated dipole of 3.61D, and is entirely soluble in water. The compound is classified as aromatic due to the presence of a sextet of π-electrons, consisting of a pair of electrons from the protonated nitrogen atom and one from each of the remaining four atoms of the ring.Imidazole is amphoteric, *i.e.* it can function as both an acid and as a base. As an acid, the pK_a of imidazole is 14.5, making it less acidic than carboxylic acids, phenols, and imides, but slightly more acidic than alcohols. The acidic proton is located on N-1. As a base, the pK_a of the conjugate acid (cited above as pK_{BH^+} to avoid confusion between the two) is approximately 7, making imidazole approximately sixty times more basic than pyridine. The basic site is N-3.



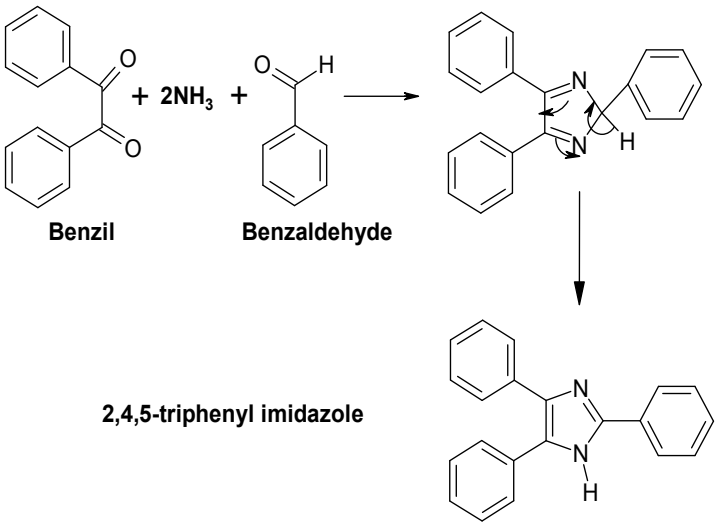
Imidazole is incorporated into many important biological molecules. The most pervasive is the amino acid "histidine", which has an imidazole side chain. Histidine is present in many proteins and enzymes and plays a vital part in the structure and binding functions of hemoglobin. Histidine can be decarboxylated to histamine, which is also a common biological compound. One of the applications of imidazole is in the purification of His tagged proteins in immobilised metal affinity chromatography (IMAC). 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. Apart of its use for pharmaceutical purpose it also have varying applications in industries, the imidazole has been used extensively as a corrosion inhibitor on certain transition metals, such as copper. Preventing copper corrosion is important, especially in aqueous systems, where the conductivity of the copper decreases due to corrosion. Many compounds of industrial and technological importance contain imidazole derivatives. The thermostable polybenzimidazole (PBI) contains imidazole fused to a benzene ring and linked to benzene, and acts as a fire retardant. Imidazole can also be found in various compounds which are used for photography and electronics. This review mainly enlights the pharmaceutical importance of the imidazole moeity.

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:

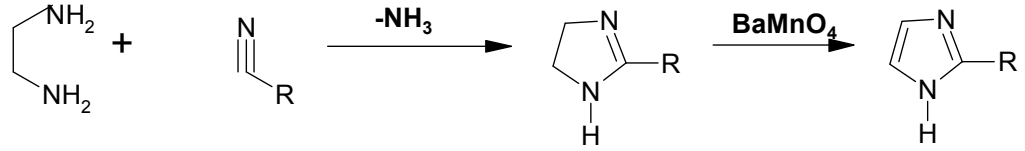
1) RADISZEWSKI SYNTHESIS [1-3]

It consist of condensing a dicarbonyl compound such as glyoxal, α- keto aldehyde or α- 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.



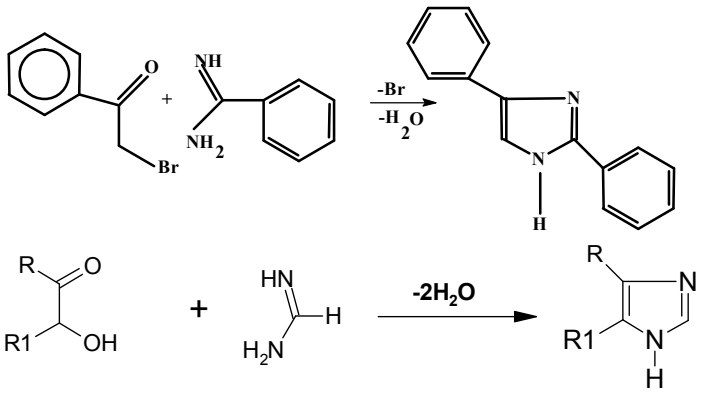
2) DEHYDROGENATION OF IMIDAZOLINE [4]

Knapp and coworkers have reported a milder reagent barium managanate for the conversion of imidazolines to imidazoles in presence of sulphur. Imidazolines obtained from alkyl nitriles and 1, 2 ethanediamine on reaction with $BaMnO_4$ yield 2-substituted imidazoles.



3) FROM α- HALO KETONE [4]

This reaction involves an interaction between an imidine and alpha halo ketones. This method has been applied successfully for the synthesis of 2, 4- or 2, 5- biphenyl imidazole phenacyl bromide and benzimidine according to this method afford 2,4-diphenyl imidazole. Similarly, amidine reacts with acyloin or alpha halo ketones to yield imidazoles.

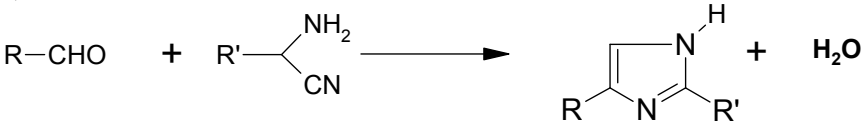


4) WALLACH SYNTHESIS [4 - 8]

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. .

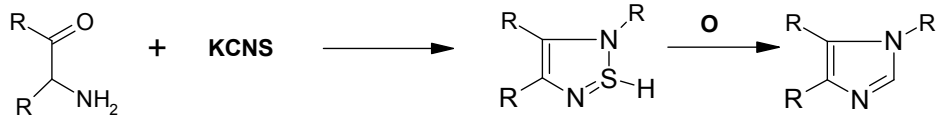
N,N-dimethyloxamide

5) FROM AMINONITRILE AND ALDEHYDE



6) MARKWALD SYNTHESIS [4]

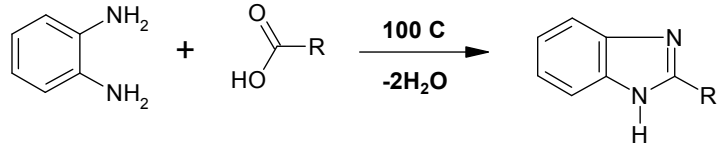
The preparation of 2- mercaptoimidazoles from α- amino ketones or aldehyde and potassium thiocyanate or alkyl isothiocyanates is a common method for the synthesis of imidazoles. The sulfur can readily be removed by a variety of oxidative method to give the desired imidazoles. The starting compounds,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



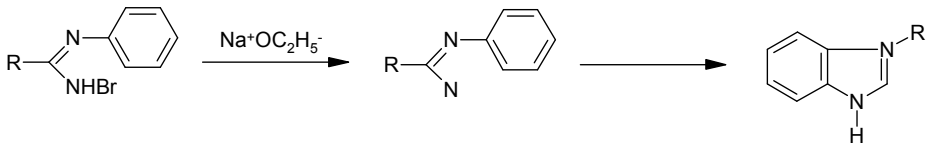
alpha-Amino ketone

Some other methods by which imidazole can be synthesized are

7) Benzimidazole is more important than imidazole as the former occur in Vit B_{12} 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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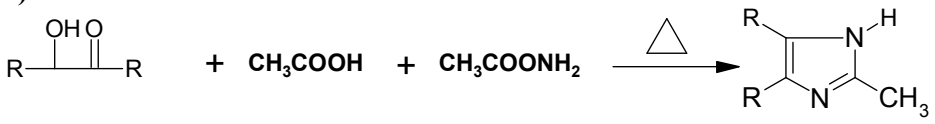
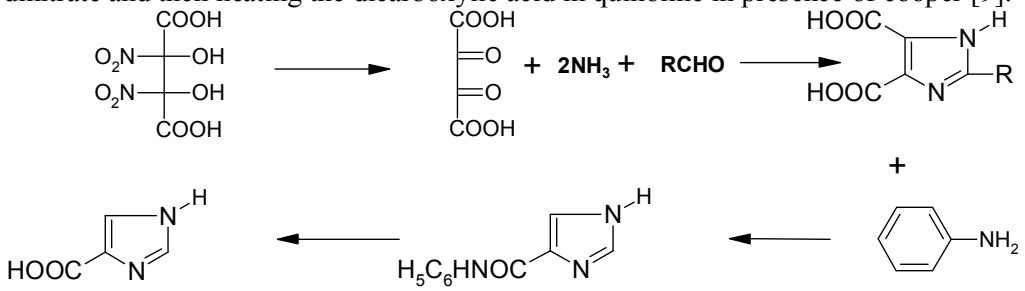
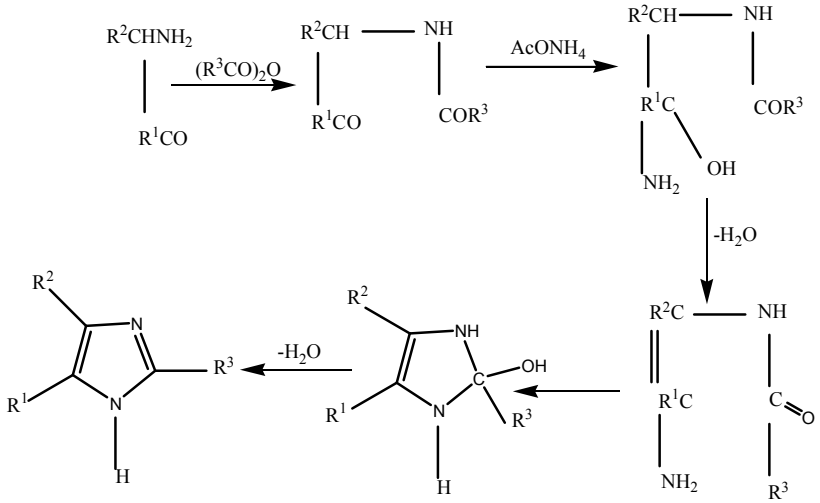


9) Imidazole can best be prepared itself by action of ammonia on a mixture of formaldehyde and tartaric acid dinitrate and then heating the dicarboxylic acid in quinoline in presence of cooper [9].



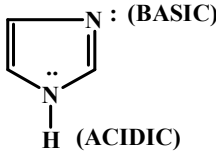
10) CYCLIZATION OF α-ACYLAMINOKETONES [9]

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



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.



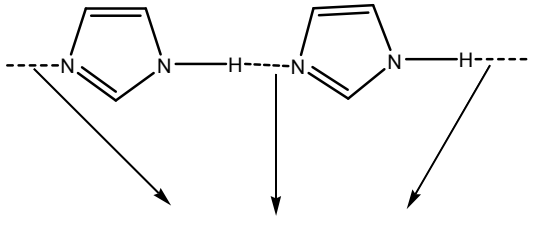
(I)

The overall reactivity of imidazole and benzimidazole 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].

PHYSICAL PROPERTIES

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

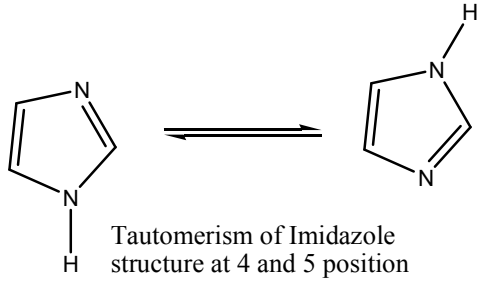


Intermolecular H-bonding

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.



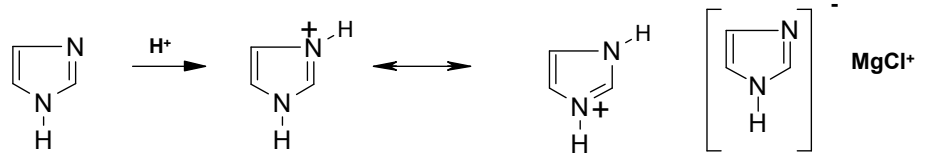
Tautomerism of Imidazole
structure at 4 and 5 position

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].

CHEMICAL REACTION

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.



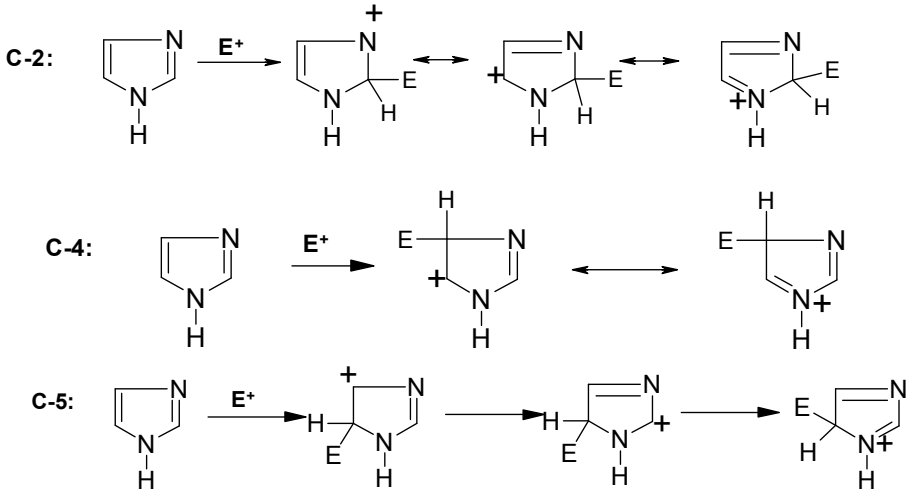
With ammonical silver nitrate imidazole form a silver salt, which is sparingly soluble in water.

REACTION WITH OXIDISING 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 H_2O_2 [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.

ELECTROPHILLIC 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.

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.

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. 4, 5, 6, 7-tetra chloro-2-trifluoromethyl benzimidazole show high activity against the nematodes *Ancylostoma caninum, Haemonchus contrtus, ascarissuum* and trimatodes *Fasciola hepatica* several 2-5 disubstituted benzimidazole, with proven potentials to kill various species of intestinal nematodes have also been found to posses activity against cestodiasis of man and animal. Mebendazole at the dose of 100 mg/kg cure patient suffering with *T. Solium* and *T. Saginata.*

The pharmacological principle affecting *in vivo* efficacy are -

1. Host toxicity is low at efficacious anthelmintics doses, however adverse reactions at higher doses are observed.
2. Benzimidazoles are extensively metabolized in host species usually to less potent anthelmintics. The rate of metabolism for each benzimidazole is similar for all hosts. First pass metabolism by soluble liver enzyme (reductase & oxidase) constitutes a rapid pathway for deactivation for several benzimidazoles notably Mebendazole & Albendazole.
3. Benzimidazoles are hydrophobic and water insoluble and therefore bioavailability and pharmacodynamics and thus efficacy can be altered by formulation and presentation.

Thus there are three aspect of benzimidazole pharmacology *in vivo*, the role of host pharmacodynamics, host-parasite interaction and biochemical pharmacology of benzimidazole. For maximum efficacy of the drug its bioavailability is also to be considered.

The factors that influence the bioavailability of anthelmintic include host biology (e.g. site and kinetics of absorption, drug metabolism, and disease state), parasite biology (e.g. site of predilection, absorption kinetics) and physicochemical properties of the drug (e.g. lipophilicity, pKa, molecular size).

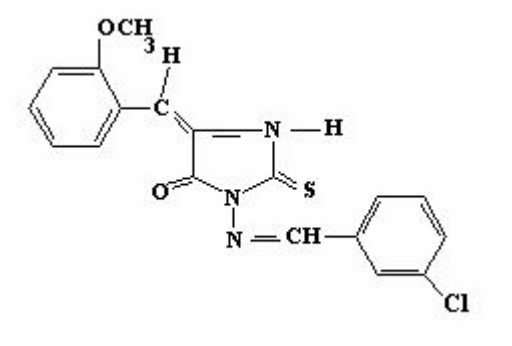
IMIDAZOLES AS ANTI-INFLAMMATORY AGENTS

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.

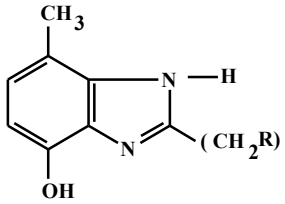
Though imidazole and benzimidazole derivative are associated with a broad spectrum of biological activities they also have anti inflammatory activity, various N-substituted imidazoles [27] and substituted imidazolone [28] have been found to be active. Among a series of 3-[substituted phenyl methylene] 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.



(I)

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].
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 LTC_4 and LTE_4, LTB_4 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 ($R=C_6H_5$) showed potent inhibition of 5- lipooxygenase *in vitro*.



[A] = $R=C_6H_5$

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.

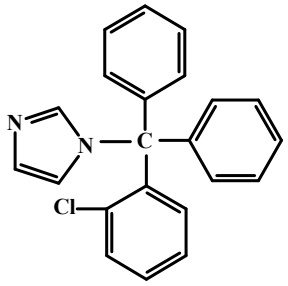
(B) R = 4-OH-C_6H_5
(C) R = 3,4-$(CH_3O)_2$ C_6H_3
(D) R = 3, 4, 5-$(CH_3O)_3$ C_6H_2

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

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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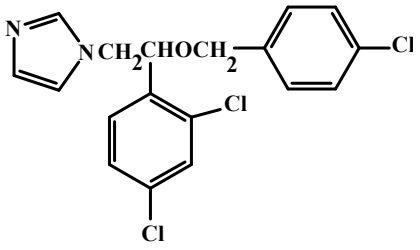

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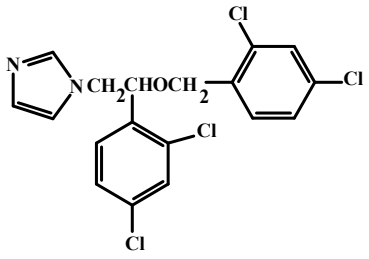

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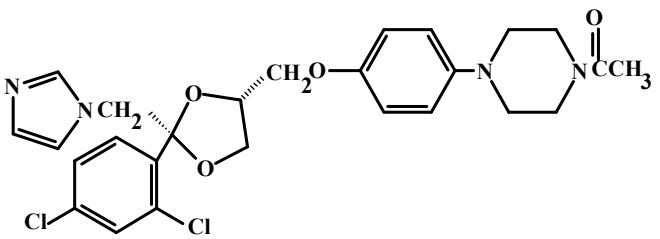

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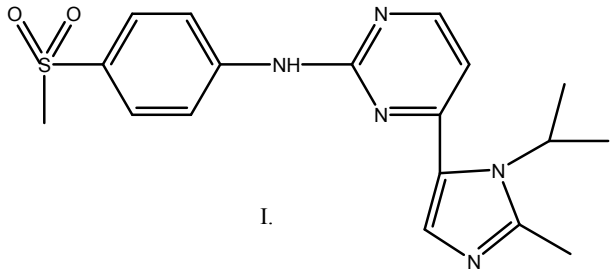
IMIDAZOLES AS ANTI-CANCER AGENTS

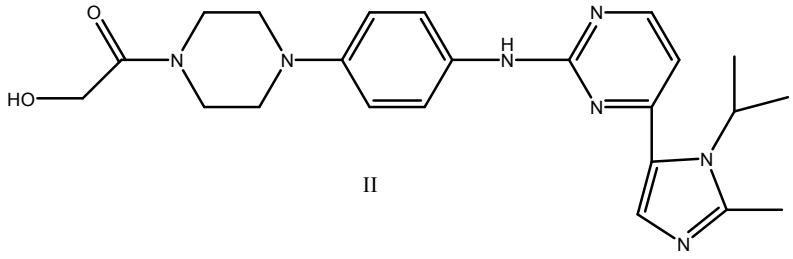
Past few years imidazole moiety is exclusively studied as an important structure as an anticancer or antineoplastic agent. Principally importance is given at the various substitutions at different positions in the moiety.

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

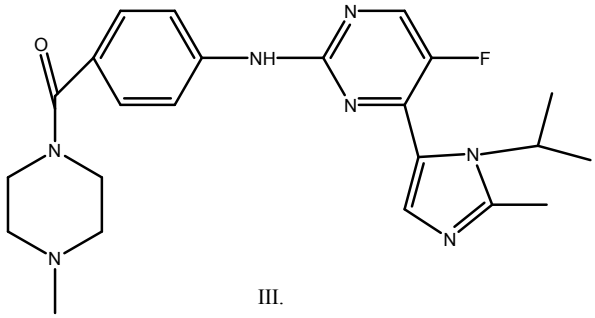
and CDK2, this highly potent CDK1/2 inhibition resulted in extremely potent inhibition of cellular proliferation in cancer cell lines. The chiral, non-racemic pyrrolidines (both S and R forms) also displayed excellent potency against CDK1 and CDK2, again with potent anti-proliferative activity. In contrast 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.



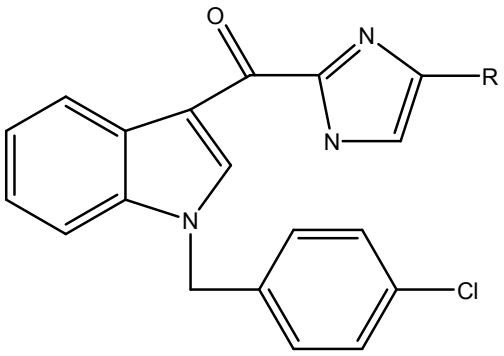
II



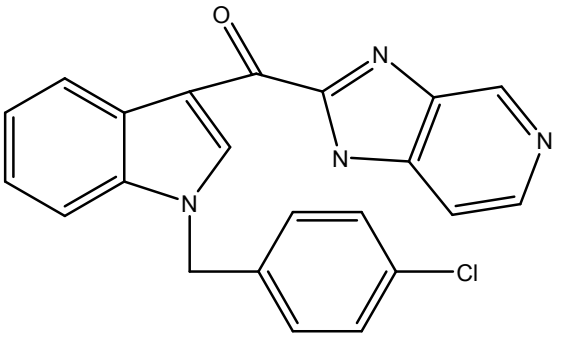
III.

A series of indole -imidazole compounds also formed that demonstrated substantial *in vitro* antiproliferative activities against cancer cell lines, including multidrug resistance (MDR) phenotypes, prolonged treatment of cancer cells with certain drugs can result in an acquired resistance of these cells toward multiple drugs. This phenomenon is known as multidrug resistance (MDR) [38]. The *in vitro* cytotoxic effects have been demonstrated across a wide array of tumor types, including hematological and solid tumor cell lines of various origins (e.g., leukemia, breast, colon, and uterine). MDR is often associated with an over expression of ATP-binding cassette (ABC) transporters [39] .Other mechanisms believed to be associated with MDR in cancer cells include: increased expression of anti-apoptotic genes and decreased expression of pro-apoptotic genes, [40] over expression of specific tubulin isotypes, [41] decreased expression of topoisomerases [42] and overexpression of major vault protein [43]. Various strategies have been employed to overcome MDR, the most common being inhibition of P-gp and related proteins to effectively block the efflux of the drug [44] .Numerous MDR-reversal agents have been reported but most have undesirable side effects such as toxicity, but indole -imidazole moiety have shown considerable against the cell lines including MDR phenotypes, via various substitutions at different positions. Substitution with a 2-pyridyl group in compound (IV) produces potent activity. When a conjugated ketone group is introduced activity is maintained by compound (V). Another compound (VI) with methyl ester substitution displayed strong cytotoxicity against the Taxol-resistant HL60/TX1000 cell line [45, 46]. The indole-pyridoimidazole compound showed a 10-fold increase in potency compared to any of the indole-imidazole derivatives (IV, V and VI).

Indole-pyridoimidazole compound has been found effective against all cell lines including the multidrug resistant cell lines MES-SA/DX5 and HL60/TX1000 which were resistant to treatment with Taxol [45, 47]. Further studies were conducted to determine the various substitutions effects which affect the mode of action of these compounds which can provide an insight into the design of future drugs active against MDR-carcinoma cells [48].



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

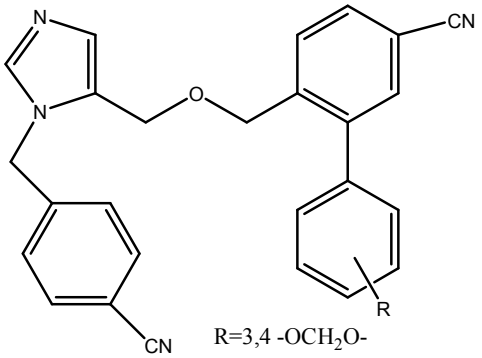


Indole-pyrido imidazole compound

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].

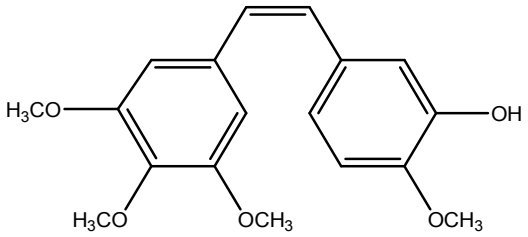
The 3,4-methylenedioxy analog was found to be the most potent FTase inhibitor in the series of substituted 1-benzyl-5-(3-biphenyl-2-yl-propyl)-1H-imidazole compounds ,consequently having more than 15,000-fold selectivity in favor of FTase inhibition and Ras processing. This analog has oral bioavailability 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-

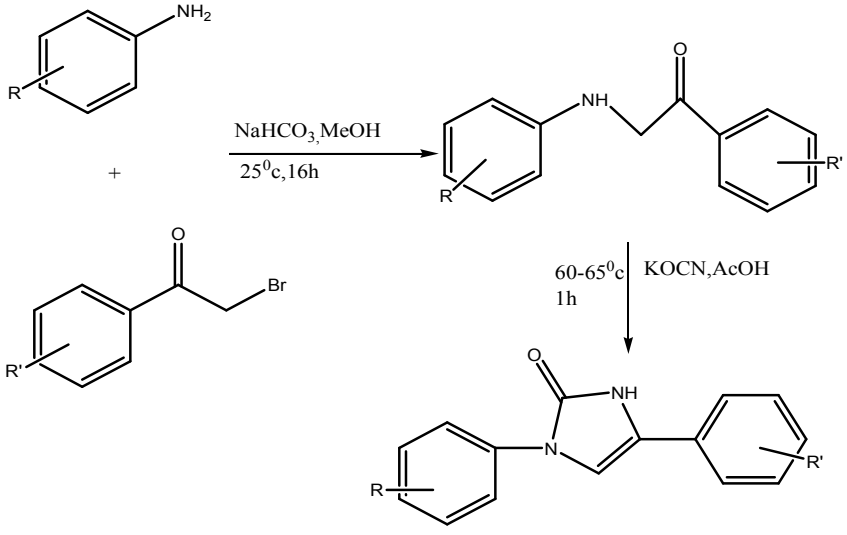
(VII). 3,4 methylene dioxy analog

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].



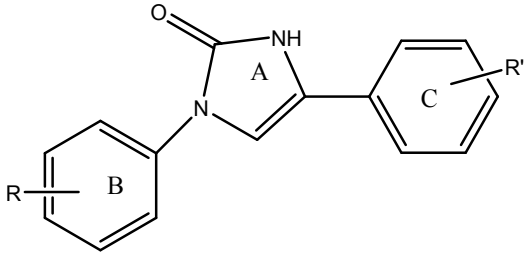
CA-4(combretastatin)
{3-atom bridged structure}

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]

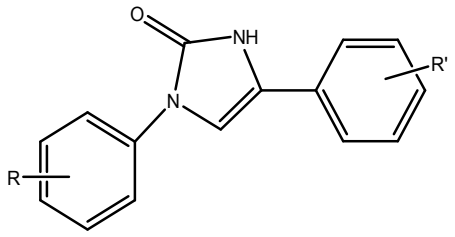


R=4-Cl
R'=3,4,5-$(MeO)_3$

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].

CONCLUSION

Imidazole moiety have been most frequently studied, many of its analogs are active against various pathological conditions, which are discussed in brief in this article. Imidazole is an entity which has interesting physical and chemical properties, in the present article focus lies on analysis of these properties which in turn may be exploited for different pharmacological activities, like 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, combination of indole-imidazole compounds formed demonstrated substantial *in vitro* anti proliferative activities against cancer cell lines, effective substitutions are also made in the entity which resembles structures of various natural compounds whose anti cancerous activity has already been examined. Substitutions are discussed in pharmacological actions as anti neoplastic agent.

Imidazoles are less sensitive in extra intestinal parasites particularly intravascular and intestinal dwelling parasites than gastrointestinal parasites. The members of class 2-alkyl benzimidazole are believed to be the most effective ones, had been found to remove various species of nematodes and trematodes from different hosts thus various compounds had been synthesized keeping 2-alkyl benzimidazole as basic moiety.

One of the other potential activities which are studied in this article is anti inflammatory activity; amino acids are believed to be potent for any sort of inflammations or edema associated with it. Study is done in regards to develop imidazole substituents having both amino and carboxylic group. Various compounds had been developed, which are analyzed clinically to check their efficacy, a detailed review is present on such compounds, with help of peer review and published research papers.

Anti fungal activity is also been discussed, imidazole and triazoles are principal areas where substituted compounds had been developed and synthesized. Here we present some of the compounds synthesized with these moieties as their structural back bone.
Thus can say imidazole is a moiety which had been exploited in the past years for synthesizing various compounds having diverse pharmacological activities, and still it can be further utilized for future prospective against various pathological conditions and other uses.

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[46].The cell line HL60/TX1000 was a gift from Dr. Bhalla of Emory University School of Medicine. HL-60/TX1000 was isolated in vitro by subculturing HL-60 in progressively higher concentration of Taxol. HL-60/TX1000 cells overexpress MDR1 mRNA and P-glycoprotein, as determined by Western blot and immunoflourescence labeling with anti-P-gp antibodies.
[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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