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A REVIEW ARTICLE ON SYNTHESIS OF IMIDAZOLE DERIVATIVES

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ABSTRACT

Imidazoles are heterocyclic compounds that have gained greatly from the five-member ring structure, outstanding location for their exceptional pharmacological activities in recent years. The nucleus of imidazole is a major drug discovery synthesis strategy. Imidazole is a five-member planar ring structure with N atom at positions 1 and 3. This compound is systematically named 1, 3, one of the N bear a H atom and one of the pyrrol type N. Imidazole was called glyoxalin for the first time. It is amphoteric and susceptible to electrophilic and nucleophile attack. The 4- amino-imidazole- 5-carboxamide, found naturally as riboside, is a part of purine nucleus and histidine amino acid. This interesting group is characterized by a wide range of biological activities, including analgesic, inflammatory, antiviral, and anthelmintic, anticonvulsant, antimicrobial, anti-allergic, etc. This is the group of heterocyclic compounds. Distinctively large scope is given by various methods for the synthesis of the imidazole and its chemical reactions.

1. INTRODUCTION

Imidazole is a formula C3H4N2 organic compound. This aromatic "1, 3-diazole" heterocyclic is known to be an alkaloid. Imidazole[1] refers to the parent compound, while imidazoles are a

heterocyclic class of identical, but distinct, ring structures. In important blocks, such as histidin[2], and related hormonal histamine[3], this ring system is present. As a basis and a weak acid, Imidazole may be used. Many drugs, such as antifungal and nitro imidazole[4] (A.R. Katritzky) (Brown) (Grimmett.) contain an imidazole ring. Imidazole had originally been synthesized by Heinrich Debus in 1858 but as early as the 1840s various imidazole derivatives[7] had been found to form imidazole using glyoxal[5] and formaldehyde.[6] This synthesis is still used to generate C-substituted imidazoles while achieving relatively low yields.

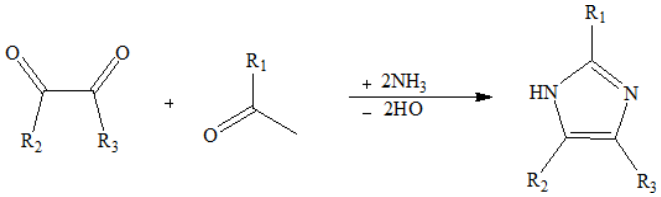
Imidazole is one of the most essential nitrogen-containing heterocyclic scaffolds, which is commonly used in natural products and medical molecules. Furthermore, in the treatment of various types of diseases, imidazole heterocyclic compounds which are of vital importance in medicinal chemicals, and new derivatives for medicinal use are developing globally.[1–5] Due to its unique structural features, it is advantageous for imidazole groups to combine with various biological system receptors and enzymes by means of different interactions with various bioactivities, thanks to the worthy electron-rich function.

2. General Methods of Preparation

Numerous methods require imidazole to be synthesized. Many of these syntheses can also be used with various replaced imidazole and imidazole derivatives simply by changing the reactants' functional groups. Different methods are available for the synthesis of imidazoles such as, debus synthesis, imidazole's dehydrogenation, wallachs synthesis, amino nitriles and aldehydes, and Marckwald synthesis (Bhatnagar A). There are also approaches available for imidazoline synthesis. Below are the descriptions of the synthetic methods.

2.1. Debus Synthesis

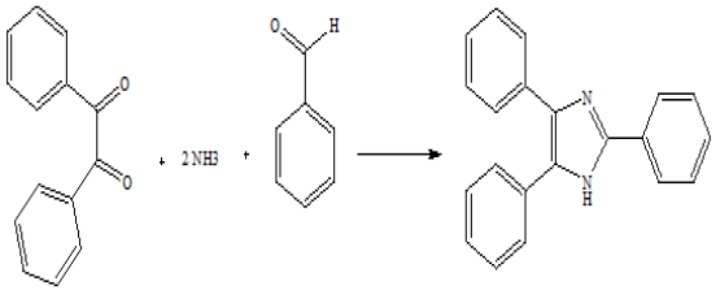
Debus Imidazole synthesized with ammonia glyoxal[9] and formaldehyde[10]. This synthesis is still used to produce C-substituted imidazoles[11], though yielding fairly low yields. (Sanchita Baroniya*).



Glyoxal[9] **Formaldehyde[10]** **C-subsituted Imidazole[11]**

2.2.Radiszewski Synthesis

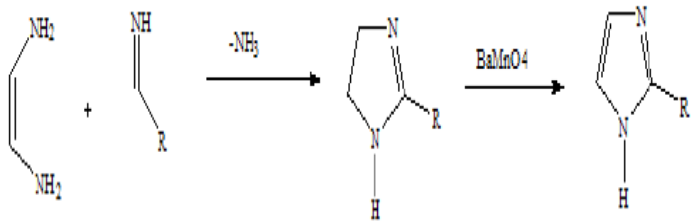
Radiszewski has shown that dicarbonyl compounds, benzyl[12] and a-caldehyde, Benz aldehyde[13] or a dike tone have condensed in presence of ammonia, yield 2, 4, 5-triphenylimidazole.[14] (E Lunt) (M.Y. Pathan)



Benzyl (12) benzaldehyde (13) 2,4,5 tri-phenyl imidazole (14)

2.3. Dehydrogenation of Imidazoline

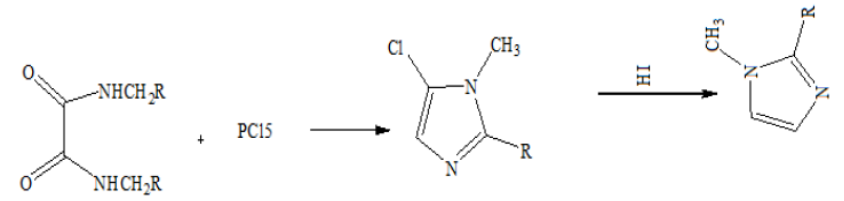
In the presence of a sculpture for the conversion of imidazolines into imidazoles, Knapp and coworkers registered mild barium manganese. Imidazolines obtained from[15] alkyl nitrates and[16] 1, 2 ethanediamins in reaction with BaMnO4NH yield[17] 2-substituted imidazols (Elderfield., Heterocyclic compounds. Vol. 5.)



1,2ethanediamine (15) Alkyl nitrile (16) 2-substitutedimidazole (17)

2.4. Wallach Synthesis

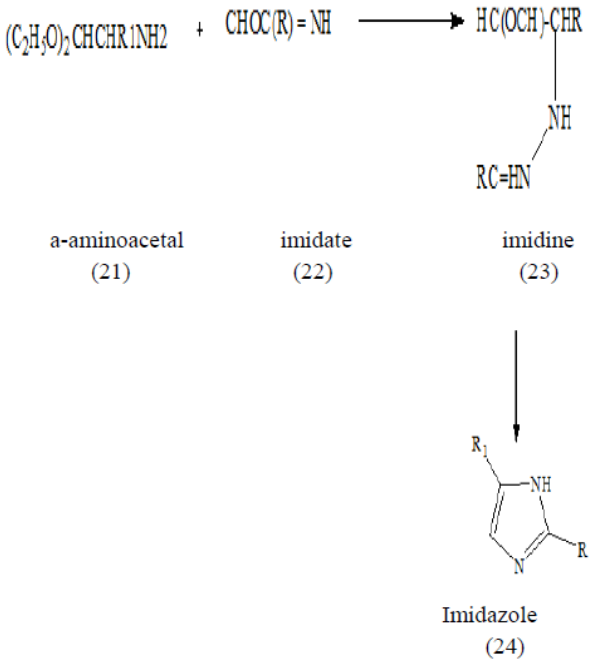
In the case of N, N-dimethyloxamide[18], Wallach reported that compounded chlorine[18], which gives N-methyl imidazole[20] after a decrease of N-methyl pent chloride, was obtained. Wallach indicated. N-diethylamide is converted to N, which lowers 1- ethyl -2- methyl imidazole, under the same condition. (Ber)



N,N-dimethyloxamide (18) Chlorine containing compound (19) N-methyl imidazole (20)

2.5. By the formation of one bond

The imidate[22] or a-aminoaldehyde or a-aminoacetal[21] binding can be established, leading to a cyclic imidine[23] to imidazole[24] The following example is if imidazole is influenced by R = R1 = hydrogen. (I.L.Finar).

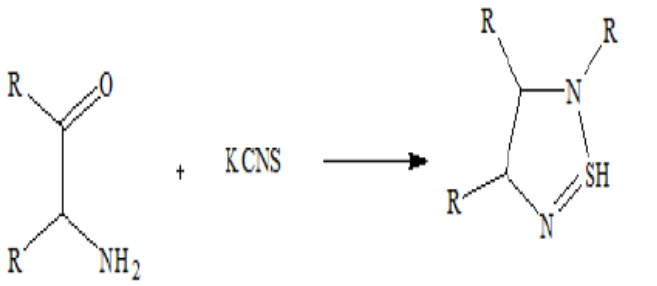


a-aminoacetal (21) imidate (22) imidine (23)

Imidazole (24)

2.6 Mark Wald Synthesis

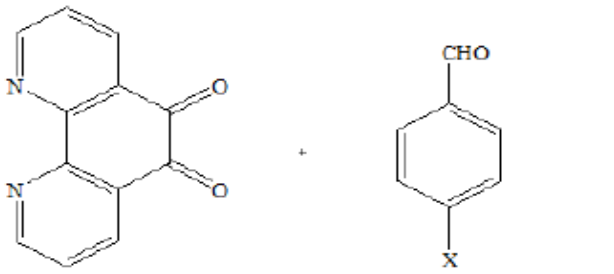
The preparation[27] 2- mercaptoimidazoles of[25] a-amino-ketones or aldehyde and[26] potassium thiocyanates or alkylisothiocyanates are a common approach for imidazole's synthesis. The sulfur can be extracted readily by a variety of oxidative methods to deliver the desired imidazole's. The starting compounds, a- amino aldehyde or ketone, are not readily available, and this is probably the Mark Wald synthesis' chief limitation. (Elderfield., Heterocyclic compounds. Vol. 5.)



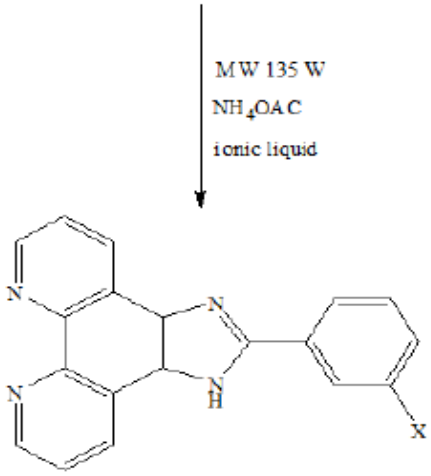
a-aminoketone (25) potassium thiocynate (26) 2-mercapto Imidazole (27)

3. Microwave Reactions Synthesis of Imidazole Derivatives

Sultan et al (S Sultan) synthesized 2-phenylimidazo [4,5-f] [1,10] phenanthrolines[30] is a type of acid catalytic acid reaction that has excellent yields in ionic neutral, 1-Methyl-3-hepstyl-tetrafluoroborate [(HeMIM) BF4] solvent-free and supported microwave, reacting with dicarbonyl compounds[28] and p-substituted benzaldehyde.[29] This specific response fits with all the merits of microwave reactions, such as fast work, stronger yield and a pleasant reaction to the environment.

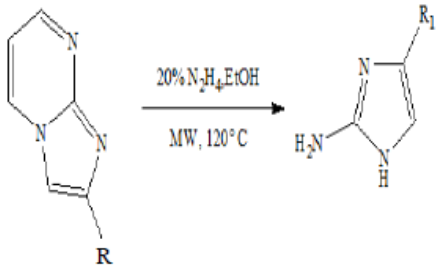


di carbonyl compounds (28) + p-subsituted benzaldehyde (29)



Phenanthroline derivatives (30)

Microwave-assisted imidazo hydrazinolysis of substituted imidazo [1, 2, a] pyrimidines[31] reported Ermolat et al (E. S. D.S. Ermolat) synthesized mono- and replaced-2-amino-1H Imidazoles.[34] This procedure avoids severe acidic conditions and is superior to the conventional cyclocondensing of N-acetyl guanidine haloketones.



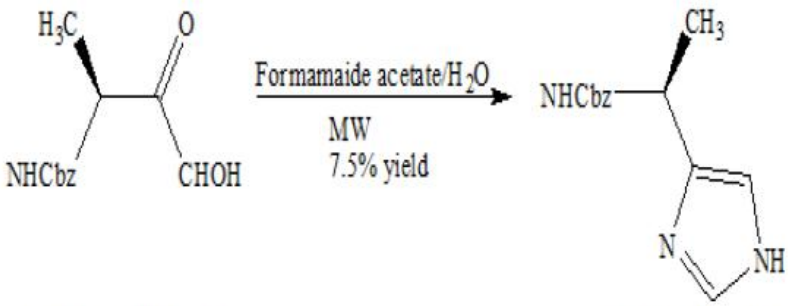
imidazo[1,2 ,a] pyrimi dines $R_1 = Ph$, $R_2 = B_r Ph$ disubstituted- 2-amino -1H – imidazole

(31) (32)

Frank et Al (P.V.Frank) synthesized nitroimidazole nitro-microwave-assisted as well as

conventionally assisted 5- substituted-2 (2-methyl 4-nitroimidazomethyl)-1, 3, 4-oxadiazole[33], which had an antibacterial , antifungal and anti-flammatory effect.

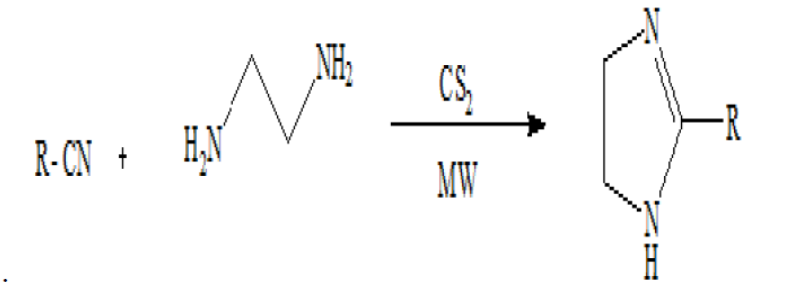
Marek et al (A.Marek) synthesized with a simple, 4-step reaction sequence based on N-Cbz amino acids, which are commercially available and cheap.[34] The condensation with formamidine acetate of the corresponding abromoketones in liquid ammonia was shown to be a useful method for the synthesis of these imidazole derivatives.[35]



N –Cbz amino acids (34)

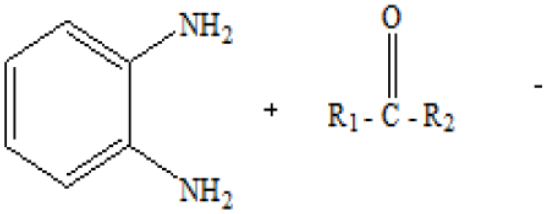
imidazole derivatives (35)

In presence of carbon disulphide 2-imidazolines[36] substituted by 2-microwaved irradiation, Pathan et al (M.Y. Pathan) reported the reaction of alkyl cyanide[36] with ethylene diamine[37] this protocol produces considerably high yields and reduces the reaction time.

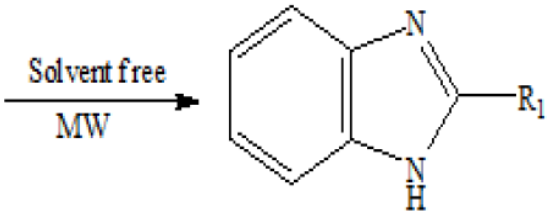


Alkyl cynide (36) ethylenediamine (37) 2-substituted2- imi dazolines (38)

Effective and fast microwave-assisted Benzimidazole and tri-substituted imidazole syntheses have been identified in Na Zhao et al (N. Zhao). As a result of 1,2phenylenediamine[39] condensation with carboxylic acid and[40] ester without catalyst, three benzimidazoles were obtained.

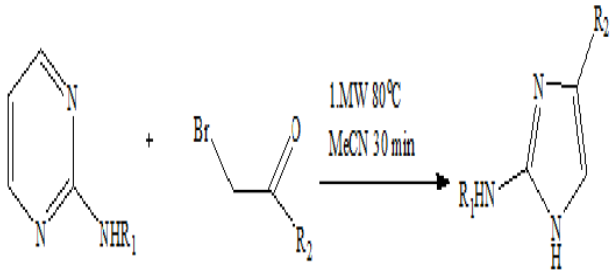


1.2phenylene diamine carboxylic acids(39) acetoacetic ester benzimi dazoles (40)



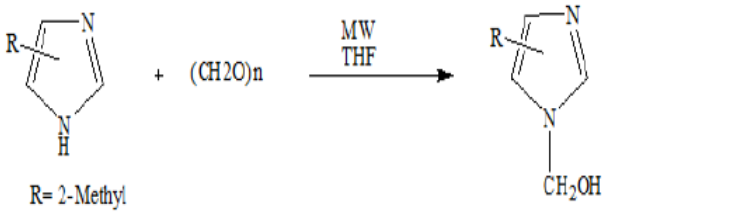
trisubstituted imidazoles
(41)

The effective, one-stop one-pot, one-step, microwave-assisted protocol to construct disused 2-amino-1H-imidazole was developed by Ermolat'ev et al (B. S. D.S. Ermolat).[46] This cycle includes concurrent formation of 2- aminopyridin[44] and a-bromoketones[45], followed by the pyrimidine ring cleavage of a hydrazine, of 2, 3- dihydro-2-hydroxy imidazo [1,2-a] pyrimidinium salts.



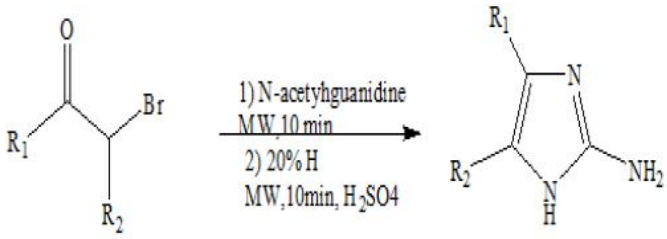
2-aminopyrimidines Bromo ketones di substituted 2 amino -1H-Imidazoles
(44) (45) (46)

Azoles[48] condensation reaction (pyrazole; imidazole; 3.5-dimethylpyrazole; 2methylimidazole; benzimidazole) with paraformaldehyde[46] was synthesized by Lupsori et al (S. lupsor) in a range of 1-hydroxymethylazoles.[50] Reaction to tetrahydrofurans (THF) and dimethyl sulfoxide (DMSO) was performed under microwave irradiation conditions as solvents. The assisted technique of microwave has substantial advantages as compared to conventional methods: increase in yield, significant reduction in response time, consumption of solvents and minimisation of waste.



Azoles (48) paraformaldehyde (49) 1-hydroxymethylazoles (50)

In the case of di- and monosustituted di-AminoIidazoles, Soh et al (M.D.Le Bas) have developed a microwave- assisted protocol. The two-stadium reaction involves the synthesis of N-(1Himidazol-2-yl) acetamides[52] from readily accessible alpha-significant rate increase was observed and the total reaction time was reduced to 20 minutes, as compared with 48 hours in conventional procedures. Using commercially available parallel reactors a representative set of 2-aminoimidazoles di- and mono-substantiated was developed.



alpha–haloketones N–(1Himidazo1-2-y1)acetarnides

(51) (52)

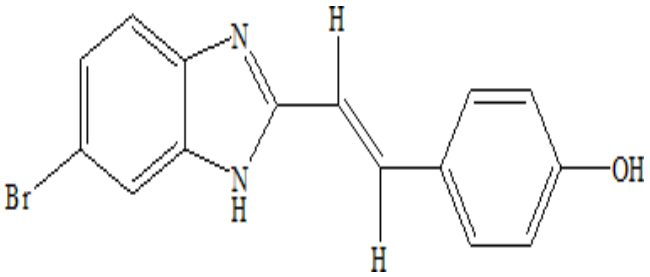
4. Pharmacological Activities

Imidazole derivatives have a broad variety of pharmacologically active products and the survey found that imidazole and its derivatives have been reportedly used, analgesic activity and anti-inflammatory activity (M. Suzuki) (F Suzuki) (S.A. El – Feky) (L.Isikdag), cardio-vascular activity (D.W. Robertson) (P.W. Erhardt) (R.A. Johnson), anti-neoplastic activity, anti-fungal activity (M.D. Brewer) (Nathanson). They also function as catalysts and polymerizing agents other than their pharmacological activities. The anti-bacterial agents are 2-nitro-imidazol (Zomycin) and 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazol (metronidazole) with a common applications such as trichomonacin. Certain anti-cancer drugs (misonidazole, metrazole and clotrimazole) are effective in conjunction with metronidazole. There are useful vasodializing and constricting therapeutic drugs in two imidazolines, priscol and privine. The class known for fungicidal actions includes 2-

aminoimidazolines. The goal of modern scientific research is to discover new and more reliable derivatives of imidazole.

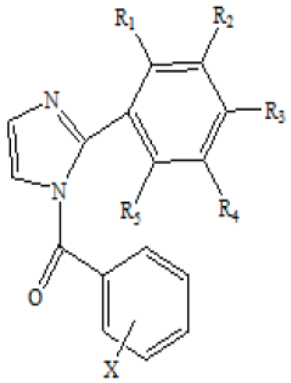
4.1. Antifungal and anti-bacterial activity

Sharma et al (D. Sharma) encapsulated up the series of[53] unique 5-(nitro / bromo)-styryl-2-benzimidazole derivatives tested for antibacterial activity of Candida albicans, Aspergillus fumigates and for staphylococcus aureus, Escherichia coli, Enterococcus facalis, Klebsiella pneumoniae. It was similar to ciprofloxacin.



(E)-4(2-(6-bromo-1H –benzo[d]imi dazol-2-y1) viny1)phenol (53)

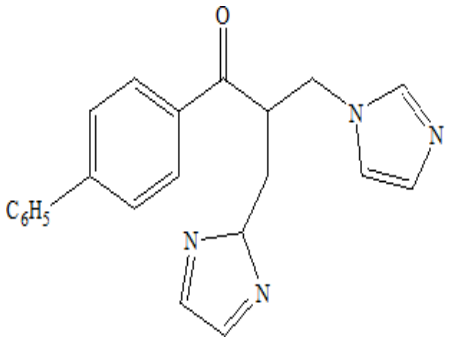
Deepika Sharma et al synthesized and examined the gram positive, gram negative and fungal antimicrobial activity of[54] 2- (substituting phoenyl)–1H-imidazole and (substituted phenyl)—[2-(substitute phenyl)–imidazol—1-yl]- menthanine analogs. Norfloxacin is the most potent drug used as normal and following.



For compounds: 1. $R_1 = C1, R_2$=H, $R_3 = H, R_4 = H, R_5 = H, X = 4 - NO_2$
2. $R_1 = COOH, R_2 = H, R_3 = H, R_4 = H, R_5 = H, X = 4 - NO_2$
3. $R_1 = H, R_2 = H, R_3 = C1, R_4 = H, R_5 = H, X = 2 - Br$
4. $R_1 = H, R_2 = H, R_3 = NO_2, R_4 = H, R_5 = H, X = 2 - Br$

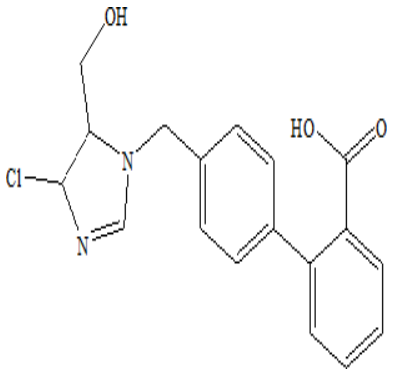
2-(substitu ted pheny1)-1H-imidazole and (substituted Pheny1)-[2-(sudstituted pheny1)-menthanoneanalogues (54)

zanti-hydrocarbon and anti-mycobacterial activity[55] to imidazole derivatives. The operation against Candida albicans and Candida glabrata was fair too strong for all components. As a reference drug, miconazole is used.



2-((1H- imidazole-1-y1)-1-(bipheny1-4-y1)-3-(2H-imidazol-2-y1) propan-1-one (55)

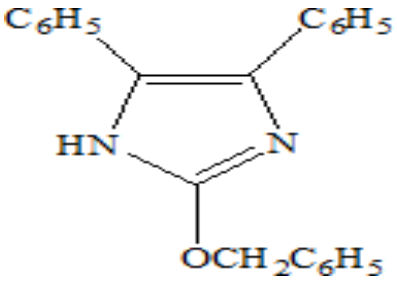
The in-vitro antibacterial activity of Shreenivas et al (M.T. Shreenivas) Compounds was screened for S. Aura and B. Aura. subtilisemploying the cup-plate method in nutrient agar media with a concentration of 100µg / ml and in vitro antifungal activities against C.albicnsand. A. Niger with 100µg / ml cup plate method. Savouraud-dextrose agar concentration. For antimicrobial action, DMSO was used as solvent regulation. The antimicrobial norm was Streptomycin. Zone estimated in cm region of inhibition.[56]



4'-((4-chloro-5-(hydroxymethy1)-4,5-dihydro-1H- imidazole-1-y1)methyeny1)bipheny1-2-carboxy1icacid (56)

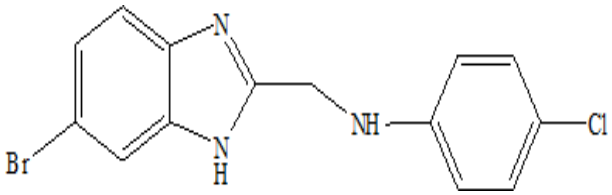
4.2. Anti -inflammatory and analgesic activity

Puratchikody A. et al (Doble)[57] 2-substituted-4) studies of five-diphényl-1H-imidazoles, and the carrageenan- induced paw edema process to test anti-inflammatory activity. The maximal activity and indomethacin used as reference drugs in this compound is shown.



2-(benzy1oxy)-4,5-dipheny1-1H –imidazole (57)

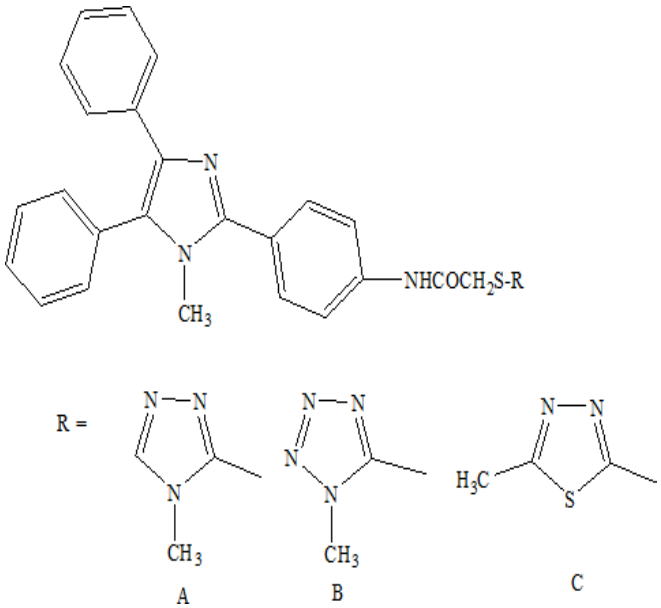
Kavitha C.S.et al (K. C.S. Achar) has analgesics and anti-inflammatory behaviors investigated in a sequence of[58] 2-methylaminibenzimidazole derivatives. This compound displays painkillers and compares them to normal nimesulide products.



N-((6-bromo-1H-benzo[d]imidazo1-2-y1)methy1)-4-chloroaniline (58)

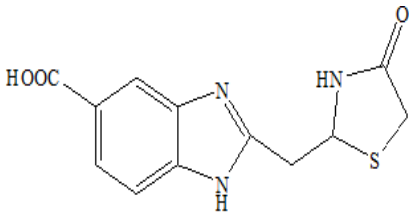
4.3. Anticancer activity

In order to study the development of cancer, Yusuf Ozkay et al (Y. Özkay) summarized several novels[59] imidazole-(Benz) azole and epiperazine derivatives of imidazole. Screening tests of the anti-cancer activity showed that the active compounds in the sequence were the most active. As a reference drug, cisplatin was used.



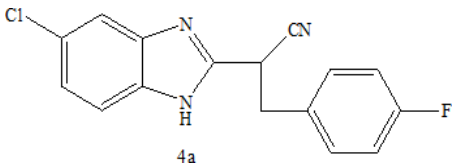
Imidazole-(Benz) azole and imidazole epiperazine derivatives (59)

The two substituted series of benzimidazole were synthesized by Hanan M. Refaat (Refaat). Some of the synthesized drugs were tested for anti-cancer and demonstrated antitumor activity against human hepatocellular carcinoma, breast, adenocarcinoma, and human colon carcinoma in the tested compounds. The maximum potency against human hepatocellular carcinoma was shown by 3a[60] and 4a[61]



3a

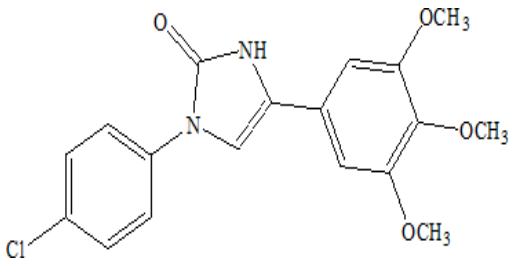
2-((4-oxothiazolidin-2-yl)methyl)-1H-benzo[d]imidazole-5-carboxylic acid (60)



4a

2-(5-chloro-1H-benzo[d]imidazole-2-yl)-3-(4-fluorophenyl)propanenitrile (61)

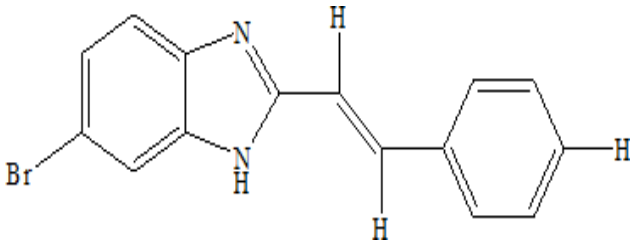
Cenzo congiu et al (C. Congiu) synthesized and evaluated the behavior of antitumours, including the sequence[62]1, 4-diarylimidazole-2(3H)-one derivatives, and their 2-thione analogues. The anti-tumor activity of this compound is potent.



1-(4-chlorophenyl)-4-(3,4,5-trimethoxyphenyl)-1H-imidazole2-(3H)-one (62)

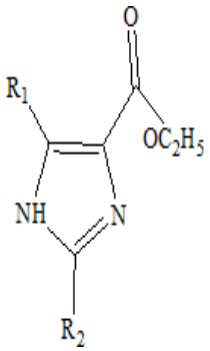
4.4. Antitubercular activity

Ramya V et al (R. V. Shingalapur) synthesized the series of in vitro, in vitro tuberculosis anti-tubers against mycobacterium tuberculosis and synthesized derivatives[63]5-(nitro / bromo)-styryl-2-benzimidazoles (1–12). Streptomycin is a reference medicinal medicine.



(E)-6-bromo-2-styryl-1H-benzo[d]imidazole (63)

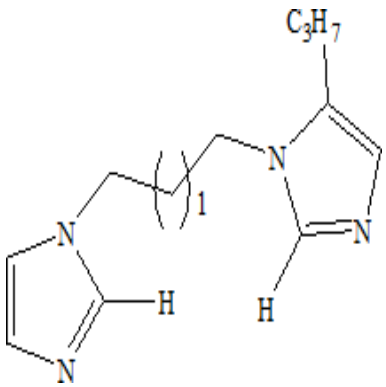
Preeti Gupta et al (P. Gupta) describe anti-mycobacterium tuberculosis activities of ring substituted[64] 1H imidazole-4-carboxylic acid derivatives and 3-(2-alkyl-1H-imidazole-4-yl)-propionic acid derivatives against drug- sensitive and drug- resistant M. tuberculosis strains. The most active compounds were 2f and 2h compounds.



For compound: 2f=R_1=R_2=C_5H_9, 2h=R_1=R_2=C_6H_{11}

1H imidazole-4-carboxylic acid derivatives and 3-(2-alkyl-1H-imidazole-4-yl)-propionic acid derivatives (64)

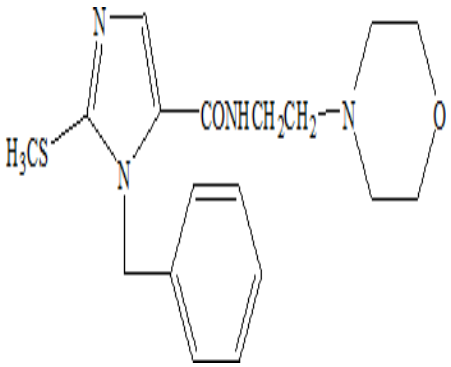
Jyoti Pandey et al (P. jyoti) synthesized a series of[65] imidazole derivatives and the compounds were screened against M.tuberculosis where this compound showed strong anti-tuberculosis activity.



1-(3-(1H-imidazole-1-yl)propyl)-5-propyl-1H-imidazole (65)

4.5. Antidepressant activity

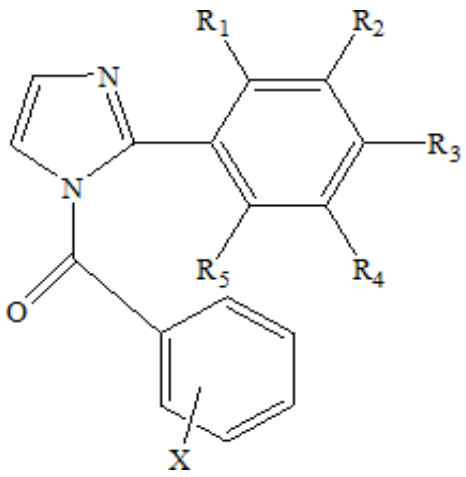
FarzinHadizadeh et al (F.Hadizadeh) synthesized[66] moclobemide analogues, by using a forced swim test to replace the ring moclobemide by substituted imidazole. Analogs 7a-c were stronger than moclobemide.



1-benzyl-2-(methyl thio)-N-(2-morpholinoethyl)-1H-imidazole-5-carboxamide (66)

4.6. Antiviral activity

Deepika Sharmaet al (D. Sharma) synthesized imidazole derivatives and antiviral screening of[67] (substituted phenyl)-[2-(substituted phenyl)-imidazole-1-yl]-methanones against viral strains indicated that A and B compounds were selected as the most potent antiviral agents. As a standard drug, ribavirin was used.

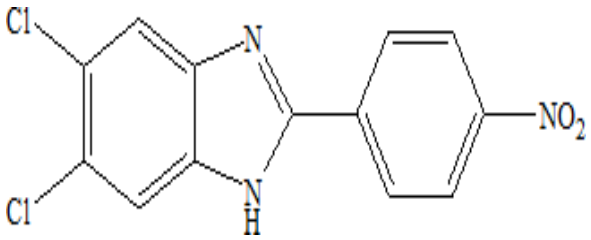


(substituted phenyl)-[2-(substituted phenyl)-imidazole-1-yl]-methanones For Compounds R_1=H, R_2=H, R_3=Cl, R_4=H, R_5=H, X=4-NO_2

R_1=H, R_2=H, R_3=NO_2, R_4=H, R_5=H, X=4-NO_2 (67)

Michele Tonelli et al (M. Tonelli) summarized 76 2-phenylbenzimidazol derivatives, tested against a panel of RNA and DNA viruses for cytotoxicity and anti-viral activity.

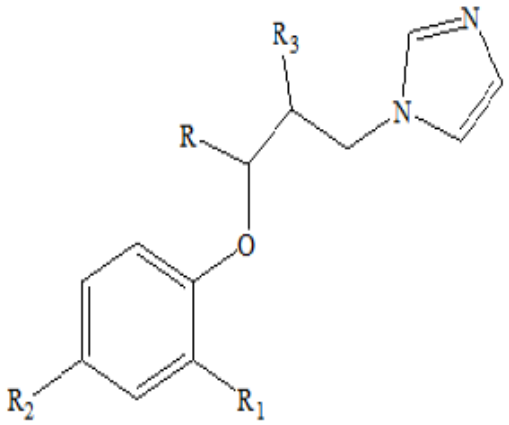
(68)Compound ([5,6-dichloro-2-(4-nitrophenyl) benzimidazole]) exhibited high activity Resulting more potent than reference drugs for smycophenolic acid and 6- azauridine.



5,6-dichloro-2-(4-nitrophenyl)-1H-benzo[d]imidazole (68)

4.7. Antilishmanial activity

Kalpana Bhandari et al (K. Bhandari) have synthesized and tested in vitro (as anti-leishmanial), a sequence of[69] substituted aryloxy alkyl alkyl and imidazol aryloxide. Inhibition of 94–100 percent of all compounds occurred.



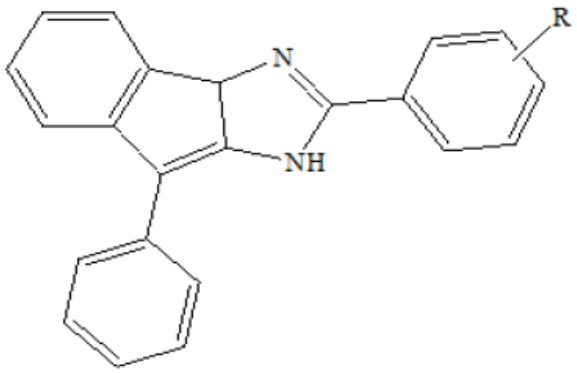
Substituted aryloxy alkyl and aryloxy ayl alkyl imidazole
(69)

Compounds	R	R_1	R_2	R_3
A	Ph	H	CF_3	H
B	CH_3	H	CF_3	H
C	CH_3	H	NO_2	H
D	CF_3	H	NO_2	H
E	CH_3	NO_2	H	H
F	CH_3	CH_3	NO_2	H

4.8.Anticonvulsant Activity

The Maximal Electroshock Process (MES) has been tested by Bhragual et al (D.D. Bhragual).

The 2nd position replacement in the replaced ring of chlorine and nitro group[70] showed considerable anticonvulsant activity without neurotoxicity, with no involvement of anticonvulsant hydrogen and 4-nitro replacement. Many other amino placed derivatives of xanthene[1,2-d]emidazoles also show a strong dose-dependent ant-proliferative activity in this movement, and were synthesized with cell growth inhibitory activity specifically for the breast-cancer cell lines. (I.K. Kostakis) Some unique motive has once more been synthesized for its inhibitorous activities in the proliferation of endothelial human umbilical vein cells (HUVECs) and Smooth Muscle Cells (SMCs) for 5- Arylamino-1h-benzo[d]imidazazel-4,7-diónes.



R=H, 2-Cl, 2-NO_2, 4-NO_2
Substituted Imidazole derivatives
(70)

Some of them demonstrated the selective anti-proliferative effect on HUVECs, including 1-H benzo-d]imidazole-4, 7-diones. (K.H. Chung).

5. Applications of Imidazoles

One of Imidazol applications in cleansing his tagged proteins in chromatographical immobilized metal affinity (IMAC). Imidazole is used to elute tagged proteins bound to NIs in the column of the chromatography bound to the beads surface. There is an excess of imidazole passing through the column, removing the His marked nickel coordination and releasing the His marked proteins. Imidazole may be used to prepare buffers at room temperature between 6.2-7.8 pH ranges. It is recommended for testing horseradish peroxides as a buffer component. This is also used to bind the various divalent cations as a chelator. (B. Storrie) The study was not released.

In oral imidazole administration, psoriasis and seborrhoea dermatitis have beneficial effects. After one and a half to three months, improvement begins in psoriasis. Patients continue with less redness, itchiness, and scaling in seborrhea dermatitis within four to six weeks. The benefits of this procedure come without the need for ointment or other topical treatments.

The nucleus of imidazole is a key synthetic drug discovery strategy. As pharmacological agents Azomycin, Clotrimazazole, Miconazole, Ergothionine, Clonidine and Moxonidine, several imidazoles are prepared. One of the key uses of imidazole derivatives is to treat dental stomatisms as a drug. Imidazole is an important component of many drugs. Some fungicides and antifungal, anti-protozoal and antihypertensive drugs contain synthetic imidazoles. Imidazole is part of a theophylline complex, which activates the central nervous system, present in tea leaves and coffee beans. It is found in anti-cancer medicines called captopurine that interact with DNA activities in leukemia. Imidazole is also used as a corrosion agent in industry for other transition metals, including copper. Owing to corrosion, copper conductivity decreases. Many industrial and technological compounds contain derivatives of imidazole. The polybenzimidazole imidazole thermostable fuses to a benzene ring and acts as an ignition retardant. In various compounds used in photography and electronics, imidazole can also be found. (Ü. Uçucu).

6. CONCLUSION

A broad variety of imidazole compounds for their biological function have been reviewed and evaluated. Thanks to their ability to boost area and/or chemoselectivity, and eco and less time-reaction, microwave reactions are highly appealing to plastics organic chemists. Therefore, the synthesis of imidazole derivatives which have proven to have an enormous potential for the various pharmacological activities is further advantageous through the application of microwave techniques.

Imidazole mobility has been studied most frequently, and several analogical pathologies are present in this study, in response to different pathological conditions. Imidazole is an entity that has interesting physical and chemical properties and the analysis of these effects is the focus of the present article, which can also be used for various pharmacological activities such as compounds with a three-dimensional ring connected with N-1 or C-4 of the imidazole entity. Replacements as an anti-neoplastic agent are discussed in pharmacological behavior.

Diverse activity against antibrovascular, anti-informational, analgesic, antitumor, anticancer, etc. is indicated by a literature survey of imidazole derivatives. Slight modifications in the supplants in the fundamental imidazole nucleus can also be used to achieve potential improvements of the activity. Structure similarities can easily bind to protein molecules compared to some other heterocyclic moieties with histidine imidazole compound. Imidazole thus has improved pharmacodynamics. In addition, at high concentrations, other imidazole drugs may have direct inhibitory effects on membranes without interacting with sterols and sterol esters. Several recent new drug developments show improved effect and less toxicity in imidazole derivatives.

Imidazole can therefore be said to be a community which has been used in recent years to synthesize specific substances with various pharmacological activities and yet can still be used more in the future against a range of pathological conditions and other uses.

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