*Available online at* www.derpharmachemica.com

Scholars Research Library

**Der Pharma Chemica, 2012, 4 (1):116-140**
*(http://derpharmachemica.com/archive.html)*

**ISSN 0975-413X**
**CODEN (USA): PCHHAX**

# Review: A convenient approach for the synthesis of imidazole derivatives using microwaves

**[1*]Anshul Chawla, [1]Ashu Sharma and [2]Anil kumar Sharma**

*CT Institute of Pharmaceutical Sciences, Shahpur, Jalandhar(Punjab) INDIA*

---

## ABSTRACT

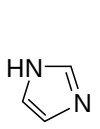
*Imidazole is the heterocyclic 5-membered ring structure, out of which three are carbon and the remaining two are nitrogen, arranged at 1 and 3 positions. It is the constituent of several natural compounds like histamine, histidine, biotin, alkaloids and nucleic acid and a very important class among the medicinal compounds. Large number of imidazole derivatives have been are being developed for different therapeutic actions, therefore this article aims to review the work reported on the synthesis of imidazole derivatives using microwave reactions as a modern method for synthesis, to get better yield, economic and environment friendly reaction.*

**Keywords** microwave techniques, green chemistry, ecofriendly, imidazole.

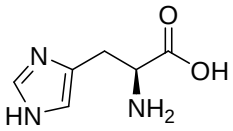
---

## INTRODUCTION

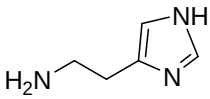
Imidazole is an organic compound with the formula $C_3H_4N_2$. This aromatic heterocyclic is a "1, 3-diazole" and is classified as an alkaloid. Imidazole (1) refers to the parent compound, whereas imidazoles are a class of heterocycles with similar ring structure, but varying substituents. This ring system is present in important biological building blocks, such as histidine (2), and the related hormone histamine (3). Imidazole can serve as a base and as a weak acid. Many drugs contain an imidazole ring, such as antifungal drugs and Nitroimidazole (4) **[1-5]**.



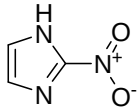

(1)




(2)

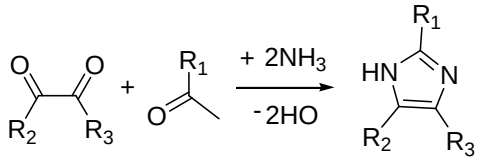



(3)




(4)

Imidazole was first synthesized by Heinrich Debus in 1858, but various imidazole derivatives (7) had been discovered as early as the 1840s, as shown below, used glyoxal (5) and formaldehyde (6) in ammonia to form imidazole **[6]**. This synthesis, while producing relatively low yields, is still used for creating C-substituted imidazoles.



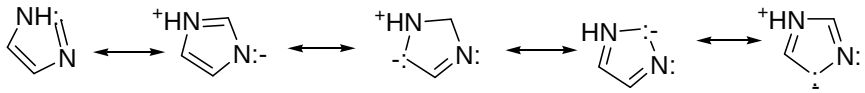

(5) (6) (7)

Synthesis Various types of 2-imidazolines are biologically and pharmaceutically very important, since many imidazoline derivatives possess antidiabetic, antihypertensive, and anti-inflammatory activity. Apart of its use for pharmaceutical purpose it also has variety of applications in industries. One of the applications of imidazole is in the purification of His tagged proteins in immobilized metal affinity chromatography (IMAC). Moreover 2-substituted imidazolines are synthetically important due to their use as a synthetic intermediates **[7]**, catalysts **[8]**, chiral auxiliaries **[9]**, chiral catalysts **[10]** and ligands for asymmetric catalysis **[11]** in various synthetic reactions. To date, there are several synthetic methods for 2-imidazolines starting mainly from aldehydes and ethylenediamine with NBS **[12]** Some methods includes synthesis from nitriles **[13]**, carboxylic acids **[14]**, esters **[15]**, ortho-esters **[16]**, hydroxy-amides **[17]** and mono or disubstituted chlorodicyanovinyl benzene **[18]**. It is also called an important synthon for the preparation of biologically active compounds **[19]**.

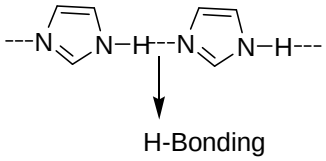
Advent of microwaves, the magnetron a remarkable device for generating fixed-frequency microwaves, was designed by Randall and Booth at the University of Birmingham **[20]**. A magnetron is a vacuum device which converts DC electrical energy into microwaves. In early days, it was recognized that microwaves could heat water in a dramatic fashion. Domestic and commercial appliances for heating and cooking of foods began to appear in the 1950s. The first microwave oven was introduced by Tappan in 1955 but the widespread use of domestic microwave ovens occurred during the 1970s and 1980s. The first application of microwave irradiation in chemical synthesis was published in 1986 **[21]**. A microwave (MW) is a form of electromagnetic energy that falls at the lower frequency end of the electromagnetic spectrum (300-300000 MHz). Microwave heating (dielectric heating) is a very efficient process due to the microwave couple directly with the molecules that are present in the reaction mixture, leading to a fast rise in temperature, faster reactions and cleaner chemistry. The two fundamental mechanisms for transferring energy from microwaves to the substance are dipole rotation and ionic conduction. Dipole rotation is an interaction in which polar molecules try to align themselves with the rapidly changing electric field of the microwave. Ionic conduction mechanism consists in the instantaneous superheating of the ionic substance due to the ionic motion generated by the electric field **[22]**. When the temperature increases, the transfer of energy becomes more efficient. Since their ionic character, ionic liquids absorb microwave irradiation extremely well and transfer energy quickly by ionic conduction.

**Structure and properties**

Imidazole is a monoacidic base having the ability to form crystalline salts with acids. The melting point of number of characteristic imidazolium salts **[23]**. Imidazole is a 5-membered planar ring, which is soluble in water and other polar solvents. It exists in two equivalent tautomeric forms, 1*H*-imidazole and 3*H*-imidazole, 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. Some resonance structures of imidazole are shown below **[24]**



Imidazole is amphoteric. That is, it can function as both an acid and as a base. As an acid, the p$K_a$ of imidazole is 14.5. As a base, the p$K_a$ of the conjugate acid is approximately 7, making imidazole approximately sixty times more basic than pyridine. Being a polar and ionisable aromatic compound, it improves pharmacokinetic characteristics of lead molecules and thus used as a remedy to optimise solubility and bioavailability parameters of proposed poorly soluble lead molecules. It is a colourless organic compound having melting point 89-91 °C and boiling point is 256 °C. It has high boiling point as compared all other five membered heterocyclic compounds **[25]**. It demonstrates that hydrogen bonding exists in imidazole ring.

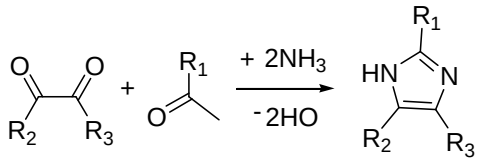



**General Methods of Preparation**

Imidazole can be synthesized by numerous methods. Many of these synthesis can also be applied to different substituted imidazoles and imidazole derivatives simply by varying the functional groups on the reactants. Several approaches are available for synthesis of imidazoles as, Debus synthesis, Radiszewski synthesis, dehydrogenation of imidazolines, from alpha halo ketones, Wallach synthesis, from aminonitrile and aldehyde and Marckwald synthesis **[24]**. Details of the synthetic procedures are given below.

**1) Debus Synthesis [6]**

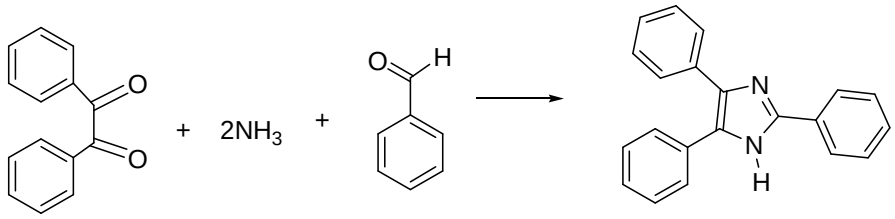
Debus Synthesised imidazole by using glyoxal (5) and formaldehyde (6) in ammonia. This synthesis, while producing relatively low yields, is still used for creating C-substituted imidazoles (7).




(5) (6) (7)

**2) Radiszewski Synthesis [26-28]**

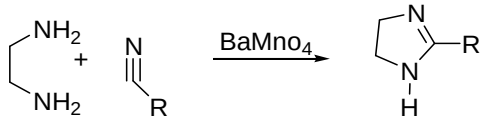
Radiszewski reported the condensation of a dicarbonyl compound, benzil (8) and α- keto aldehyde, benzaldehyde (9) or α-diketones in the presence of ammonia, yield 2, 4, 5-triphenyl-imidazole (10).




(8) (9) (10)

**3) Dehydrogenation of Imidazoline [29]**

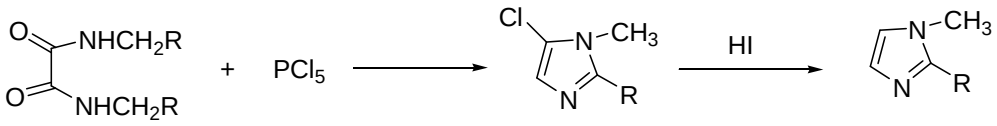
A milder reagent barium managnate to convert imidazolines to imidazoles in the presence of sulphur. Imidazolines obtained from 1, 2 ethanediamine (11) and alkyl nitriles (12) on reaction with $BaMnO_4$ yield 2-substituted imidazoles (13).




(11) (12) (13)

**4) Wallach Synthesis [30-33]**

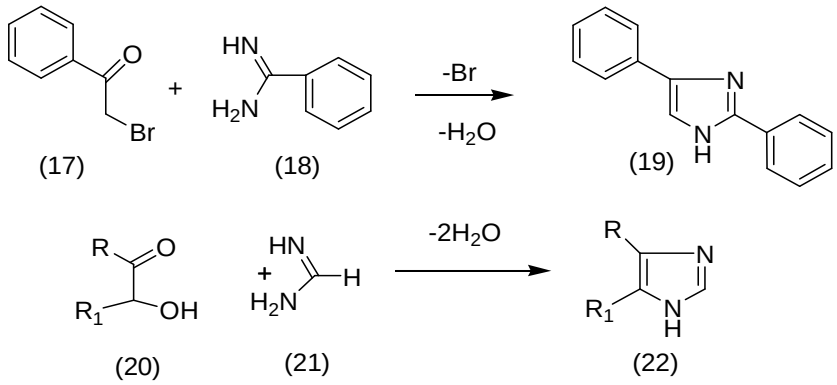
Wallach reported that when N, N- dimethyloxamide (14) is treated with phosphorus pentachloride, a chlorine containing compound (15) is obtained which on reduction with hydroiodic acid give N- methyl imidazole (16). Under the same condition N, N-diethyloxamide is converted to a chlorine compound, which on reduction gives 1- ethyl –2- methyl imidazole.




(14) (15) (16)

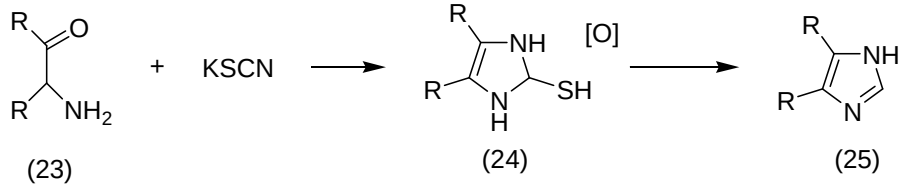
5**) From α- Halo Ketone [29]**

This method is based on an interaction between an alpha halo ketones (17) and imidine (18). This method has been applied successfully for the synthesis of 2, 4- or 2, 5- biphenyl imidazole (19). Similarly, acyloin (20) reacts with amidine (21) or alpha halo ketones to yield imidazoles (22).



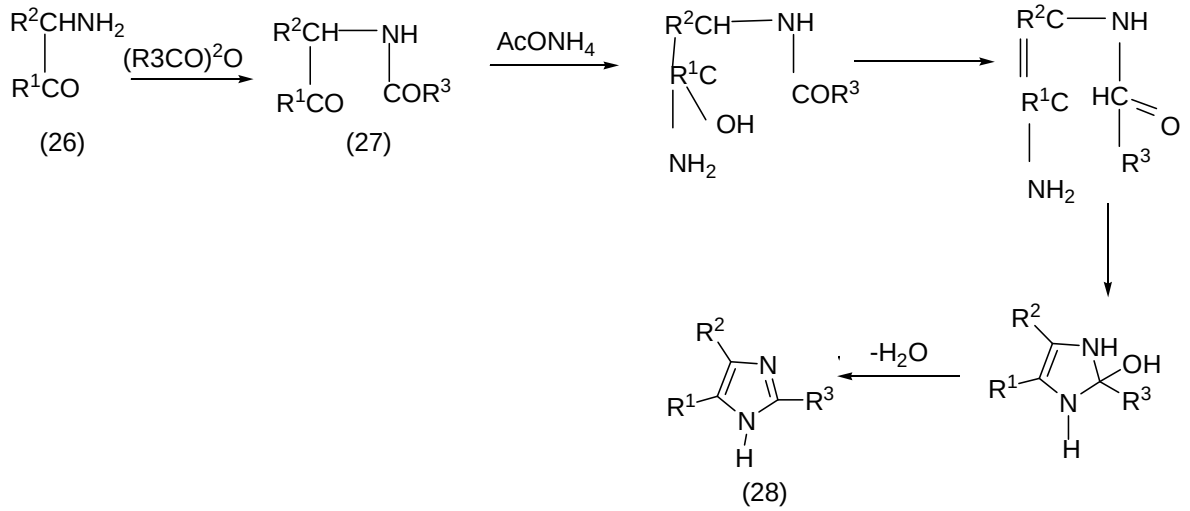

**6) Markwald Synthesis [29]**

The preparation of 2- mercaptoimidazoles from α-amino ketones (23) or aldehyde and potassium thiocyanate are used for the synthesis of 2-thiol substituted imidazoles (24). The sulfur can readily be removed by a variety of oxidative method to give the desired imidazoles (25).



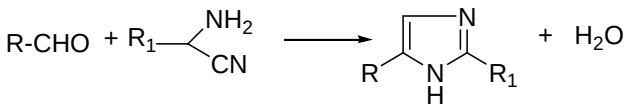

**7) Cyclization of α-Acylaminoketones [34]**

α-acylaminoketones (26), also behave as 1, 4-diketo compounds (27). This compound lead to ready cyclization (28), in the presence of anhydride followed by presence of ammonium acetate.




**8) From Aminonitrile and Aldehyde [24]**

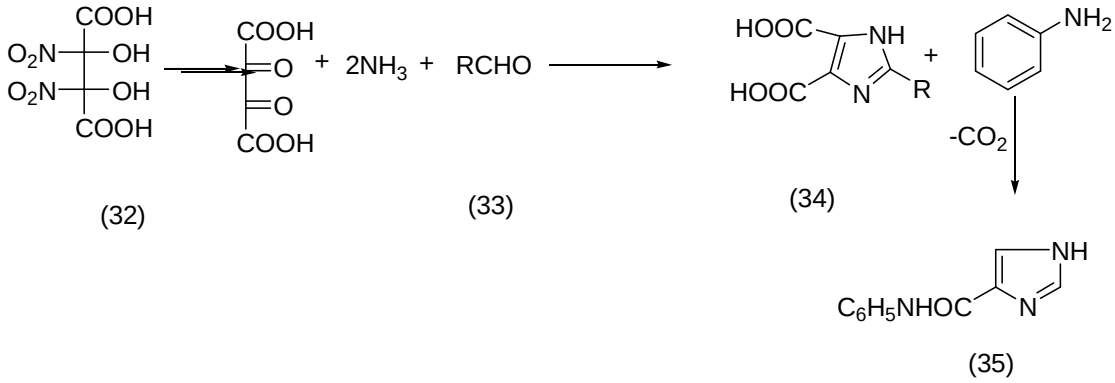
Mixture of an aldehyde (29) and aminonitrile (30) both condensed under suitable reaction condition to give substituted imidazole (31) as shown below




(29) (30) (31)

**9) From formaldehyde and tartaric acid dinitrate [34]**

Imidazole can best be prepared itself by action of ammonia on a mixture of tartaric acid dinitrate (32) and formaldehyde (33) then heating the dicarboxylic acid with quinoline in the presence of copper to give 2-alkyl substituted 4,5- dicarboxylic acid imidazole (34) further which is reacted with aniline to give 4- substituted benzamide (35)

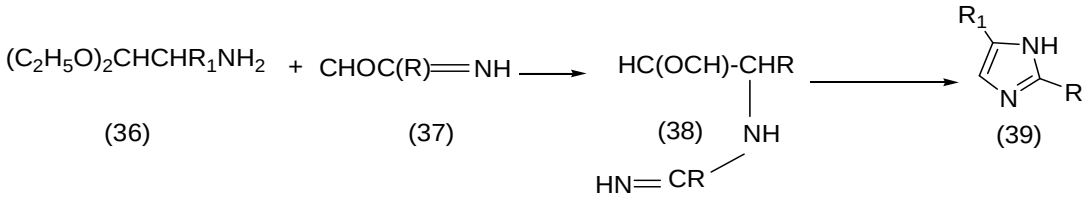



(32) (33) (34) (35)

.

**10) By the formation of one bond**

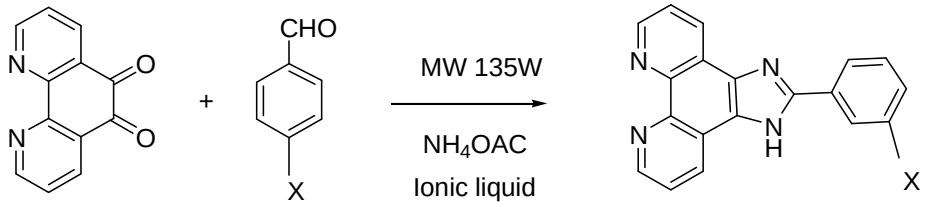
The (1,5) or (3,4) bond can be formed by the reaction of an imidate (37) and an α-aminoaldehyde or α-aminoacetal (36), resulting in the cyclization of an imidine (38) to imidazole (39). The example below applies to imidazole when R=$R_1$=Hydrogen.




(36) (37) (38) (39)

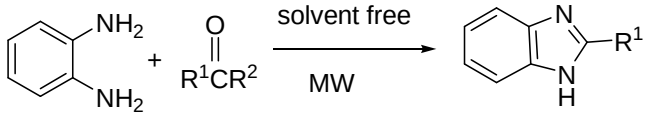
**Synthesis of imidazole derivatives by microwave reactions**

**Qasim *et al* (2011)** synthesized 2- phenylimidazo [4,5-f] [1,10] Phenanthroline derivatives (42), by reacting dicarbonyl compound (40) and *p*-substituted benzaldehyde (41), this is a type of acid catalyzed reaction with excellent yields in a neutral ionic liquid, 1-methyl-3-heptyl-imidazolium tetrafluoroborate [(HeMIM) $BF_4$], under solvent free and microwave assisted conditions. This particular reaction accompanies all the merits of microwave reactions like easy workup, better yield, environment friendly reaction **[35]**.




(40) (41) (42)

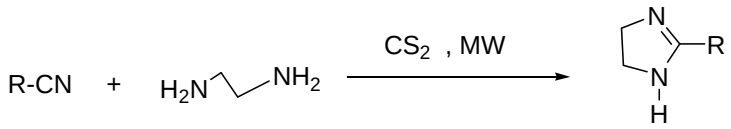
**Na Zhao *et al* (2005)** reported an efficient and a quick microwave-assisted synthesis of benzimidazoles and trisubstituted imidazoles (45). Three benzimidazoles were obtained as a result of the condensation of 1,2phenylenediamine (43) with carboxylic acids and acetoacetic ester (44) without catalyst **[36]**.




(43) (44) (45)

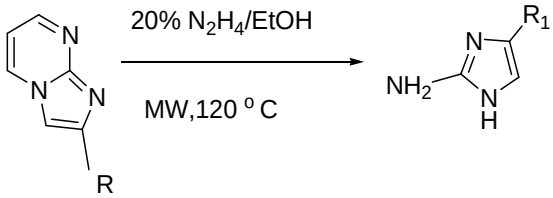
a) $R^1$= $C_6H_5OCH_2$- , $R^2$=OH
b) $R^1$=2,4-$(Cl)_2$ $C_6H_3OCH_2$ - , $R^2$ = OH
c) $R^1$=-$CH_3$ ,$R^2$ =-$CH_2COOEt$
d) $R^1$=$C_6H_5$- ,$R^2$ =OH
e) $R^1$= -$CH_3$ ,$R^2$=OEt

**Pathan *et al* (2006)** reported the reaction of alkyl cyanide (46) with ethylenediamine (47) in the presence of carbon disulphide give 2-substituted 2-imidazolines (48) under microwave irradiation. The yields of product obtained using this protocol is significantly high and the reaction time is reduced **[37]**.




(46) (47) (48)

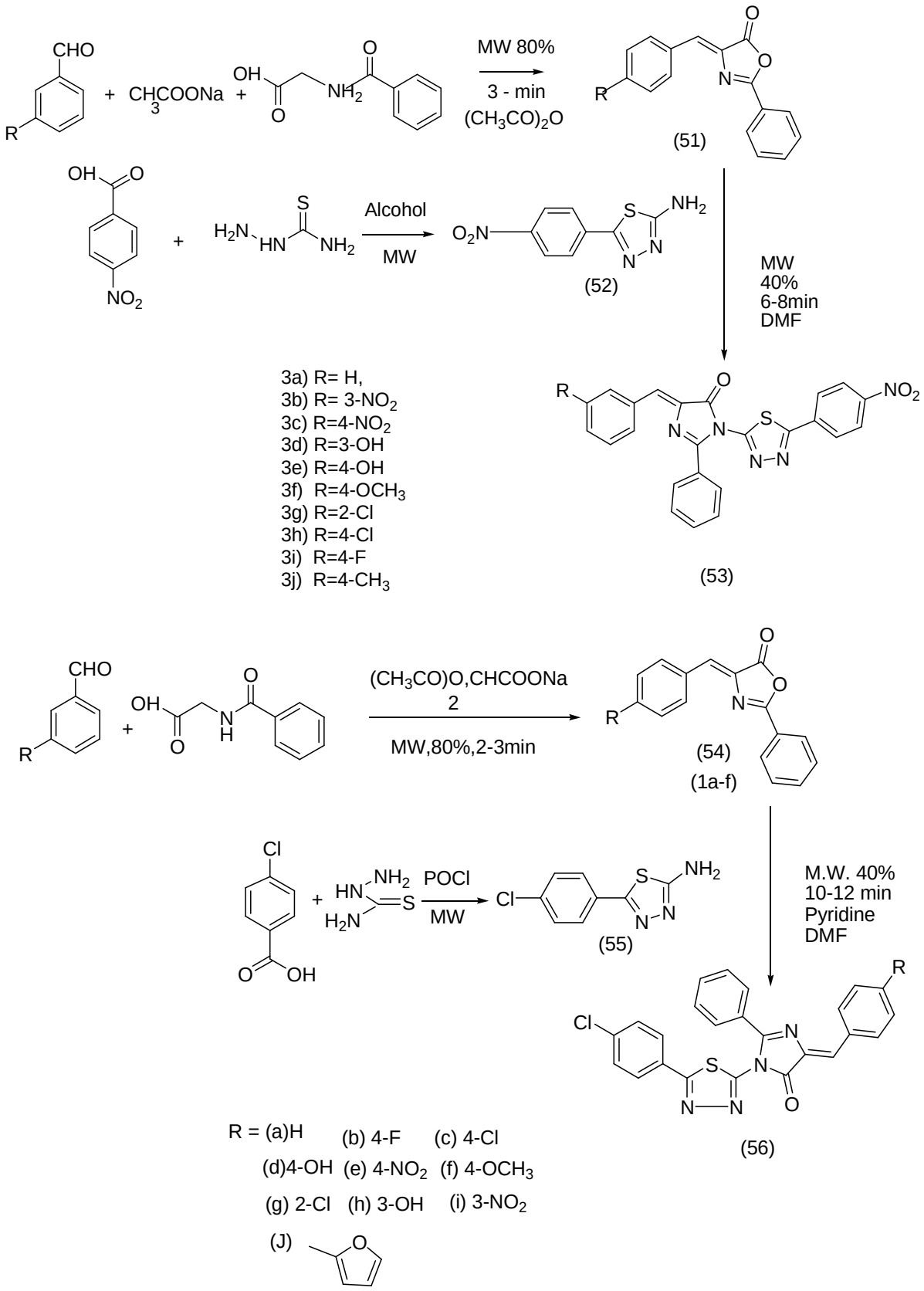
**Ermolat *et al* (2009**) synthesized mono and disubstituted-2-amino-1H imidazoles (50) via microwave assisted hydrazinolysis of substituted imidazo [1, 2 a] pyrimidines (49) is reported. This method avoids strong acidic conditions and is superior to the conventional cyclocondensation of a haloketones with N-acetyl guanidine **[38]**.




(49) (50)

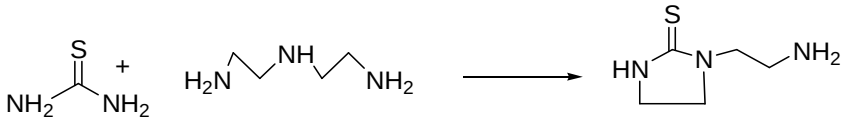
$R^1$ - Ph
$R^1$ - BrPh

**Bharadwaj *et al* (2010**) performed the condensation of different oxazolones (1a-f) (51) with 5-(4-nitrophenyl)-1, 3, 4-thiadiazol-2-amine (52) under microwave oven. The structures of the synthesized compounds (53), 3a-3j were confirmed on the basis of spectral and elemental analysis. The synthesised compounds were found in better yield than in conventional methods and also screened for *in vitro* antimicrobial study **[39]**.


CHO
R
+ CH3COONa +
OH
O
NH2
O
MW 80%
3 - min
(CH3CO)2O
R
O
O
N
(51)
OH
O
NO2
+
H2N
HN
S
NH2
Alcohol
MW
O2N
S
NH2
N
N
(52)
MW
40%
6-8min
DMF
3a) R= H,
3b) R= 3-NO2
3c) R=4-NO2
3d) R=3-OH
3e) R=4-OH
3f) R=4-OCH3
3g) R=2-Cl
3h) R=4-Cl
3i) R=4-F
3j) R=4-CH3
R
O
N
N
S
N
N
NO2
(53)
CHO
R
OH
+
O
N
H
O
(CH3CO)O,CHCOONa
2
MW,80%,2-3min
R
O
O
N
(54)
(1a-f)
Cl
O
OH
+
HN
NH2
H2N
S
POCl
MW
Cl
S
NH2
N
N
(55)
M.W. 40%
10-12 min
Pyridine
DMF
R
Cl
N
S
N
N
N
O
(56)
R = (a)H (b) 4-F (c) 4-Cl
(d)4-OH (e) 4-NO2 (f) 4-OCH3
(g) 2-Cl (h) 3-OH (i) 3-NO2
(J)
O

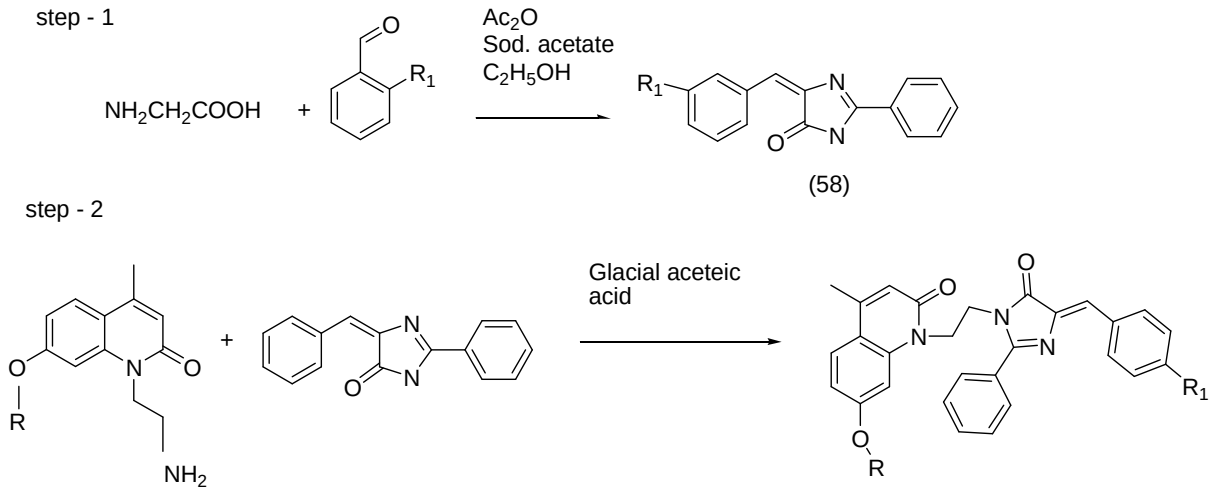
**Bhanat *et al* (2011)** Various 4-(Substituted benzylidene)-1-(5-(4-chlorophenyl)-1, 3, 4-thiadiazol-2-yl)-2-phenyl 1H-imidazol-5 (4H)-one (56) have been synthesized by the condensation of different oxazolones (54) (1a-f) with 5-(4-chlorophenyl)-1, 3, 4-thiadiazol-2-amine (55) under microwave irradiation technique. The structure of the synthesized compounds 4-(Substituted benzylidene)-1-(5-(4-chlorophenyl)-1, 3, 4-thiadiazol-2-yl)-2-phenyl-1H-imidazol-5(4H)-one was confirmed on the basis of spectral and elemental analysis. The synthesized compounds were screened for *in vitro* antimicrobial study against *E. coli, S. aureus, C. albicans* and *A. niger* using cup plate and agar well diffusion technique **[40]**

**Hopfl *et al* (2005)** 1-(2-aminoethyl)-2-imidazolidinethione (57) synthesis was described. The crystal and molecular structure was determined. The combination of an X-ray crystallographic study and theoretical calculations (DFT) provided insight into the understanding of the high performance of this compound as low toxicity corrosion inhibitor **[41]**.



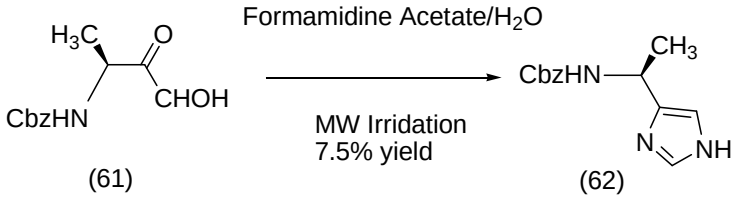
(57)

**Raghavendra *et al* (2011)** A Series of 1-(2-((18Z)-4-substituted benzylidene-4, 5-dihydro-5-oxo-2-phenylimidazol-1-yl) ethyl)-1, 2-dihydro-4-methyl-2-oxoquinolin-7-yl (60) imidazolo quinoline analogs were synthesized by condensation of substituted imidazole (58) and substituted quinoline (59). The title compounds were investigated for anti-inflammatory and its ulecerogenicity activities. All the lead compounds were assessed by QSAR and molecular modeling (CADD) studies to predict best physicochemical, pharmacokinetic, toxicological properties and best fit with targets like COX-1 and COX-2. The result indicated that the compounds have convincing activities against inflammation when compared with standard drug (Ibuprofen) **[42]**.



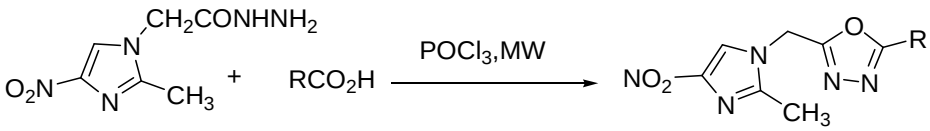

(59) (58) (60)

**Marek *et al* (2007)** synthesized via a facile 4-step reaction sequence starting from commercially available and inexpensive N-Cbz amino acids (61). The condensation of the corresponding α-bromoketones with formamidine acetate in liquid ammonia was revealed to be a useful method for the synthesis of such imidazole derivatives (62), derivatives thus prepared are structurally-related to histamine **[43]**.



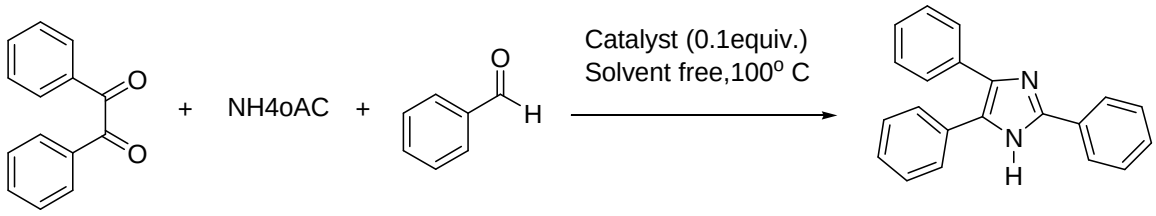

(61) (62)

**Frank *et al* (2007)** synthesized 5-substituted-2-(2-methyl-4-nitroimidazomethyl)-1, 3, 4-oxadiazoles (63) containing the nitroimidazole moiety by microwave-assisted as well as conventional method was carried out and their antibacterial, antifungal and anti-inflammatory activity was reported **[44]**.



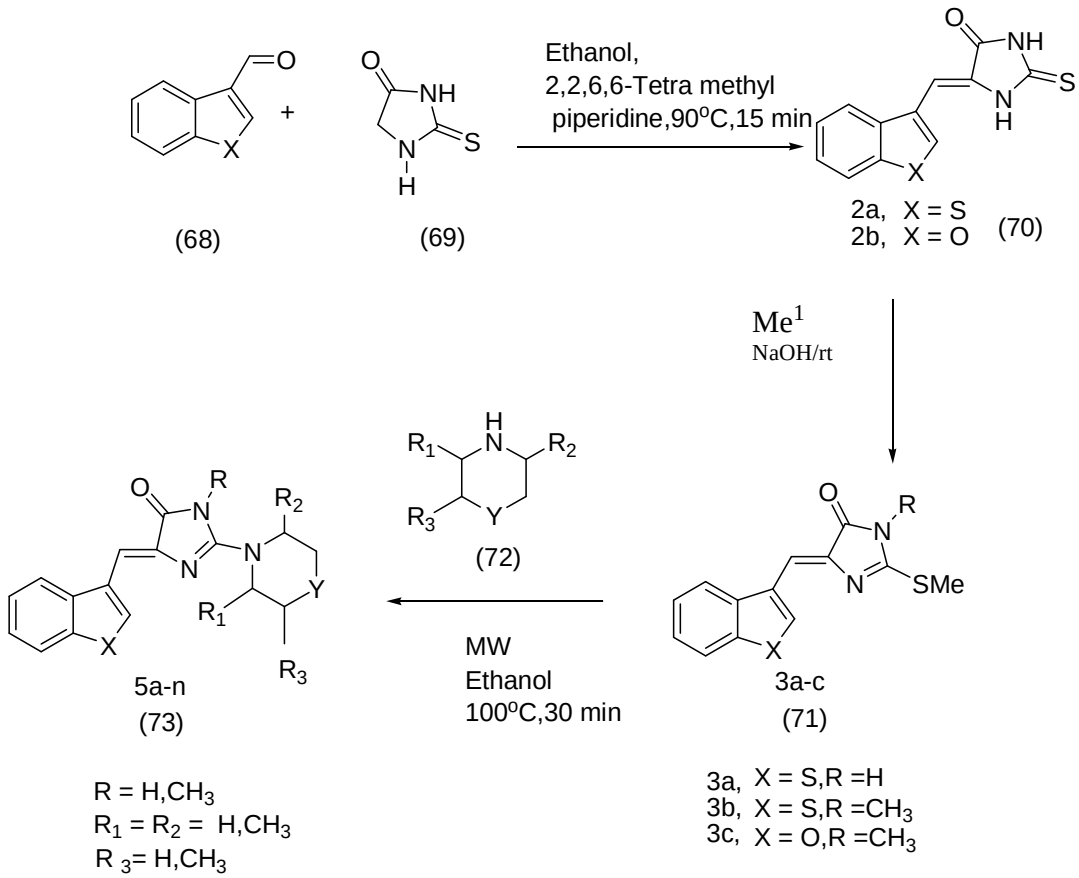

(63)

**Safari *et al* (2010)** $(NH_4)_6.Mo.7O_2.4H_2O$ was used as an efficient catalyst for an improved and rapid synthesis of 2,4,5-trisubstituted imidazoles (67) by a three-component, one-pot condensation of benzil (64), aryl aldehydes (66) and ammonium acetate (65) in good yields under solvent-free conditions using microwave irradiation. The reactions in conventional heating conditions were compared with the microwave-assisted reactions **[45]**.

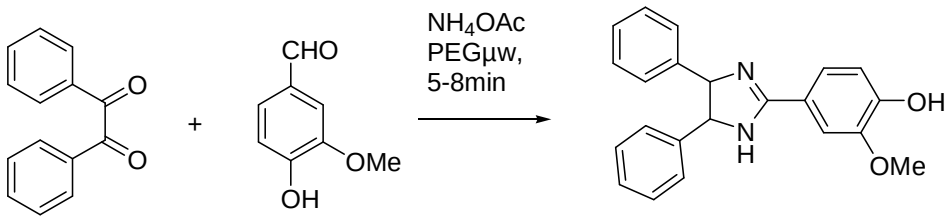



(64) (65) (66) (67)

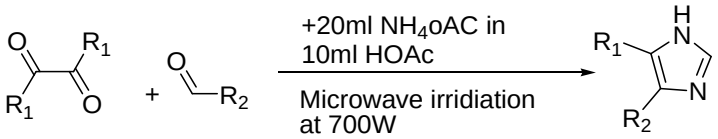
**Kamila *et al* (2011)** 2-(Alkyl-1-yl)-1H-imidazol-5(4H)-ones (73) were synthesized *via* nucleophilic substitution of the methylsulfanyl group of the corresponding 2-(methylthio)-1H-imidazol- 5(4H)-ones 3a–c (71) with suitably substituted secondary amines (72). The starting 2-thioxo- imidazolidin-4-ones 2a, 2b (70) were prepared by condensation of thiohydantoin (68) and benzo[b]- thiophene-3-carbaldehyde or benzofuran-3-carbaldehyde (69) under microwave irradiation (MW) conditions. 2-Methylthio derivatives 3a–c were prepared by treatment of 2a–b with methyl iodide in the presence of aqueous sodium hydroxide **[46]**.




**Nalage *et al* (2010)** described an efficient and green procedure for the synthesis of 2, 4, 6-triaryl-1H-imidazole (76) in polyethylene glycol by condensing benzil (74) and 3-methoxy- 4- hydroxy benzaldehyde (75) under microwave irradiation in excellent yield has been developed. Polyethylene glycol is non toxic, reusable, inexpensive and easily available **[47].**



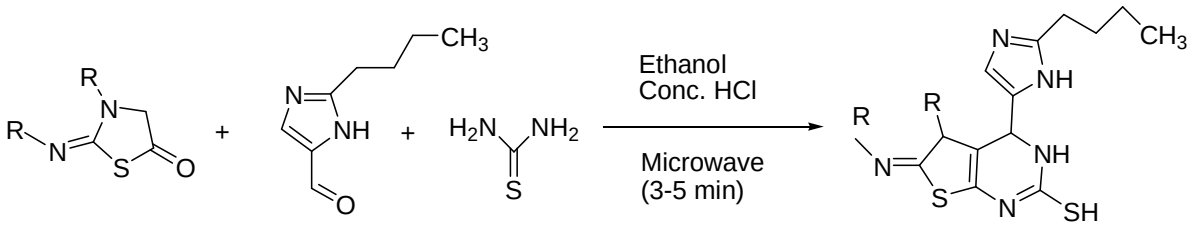

**#Wahyuningrum *et al* (2007)** Four 4,5-substituted imidazole derivatives (79) have been synthesized utilizing microwave assisted organic synthesis (MAOS) method, by reacting with suitable diketone (77) and some aldehyde or ketone (78), in order to investigate their corrosion inhibition mechanism on carbon steel surface **[48].**




(77) (78) (79)

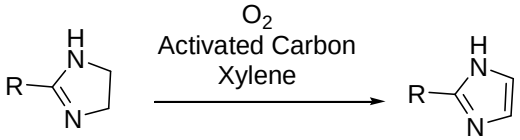
| $R_1$ | $R_2$ |
|---|---|
| -H | -H |
| $-C_6H_5$ | -H |
| $-C_6H_5$ | $-C_2H_5$ |
| $-C_6H_5$ | $-CH_3$ |

**Vaghasia *et al* (2007)** described the synthesis of thiazolo 5,4-dpyrimidines (83) can be achieved from different 5-thiazolidinones (80), 2-butyl-1H-imidazole-5-carbaldehyde (81) and thiourea (82) using microwave irradiation within 5 min. The structures of the products were supported by FTIR, PMR and MS data. The *in vitro* antimicrobial activity of the synthesized thiazolo 5,4-dpyrimidines 1a-j, having substituents at the 1- and 3-positions, were determined by the cup-plate method against several standard strains chosen to define the spectrum and potency of the new compounds. The antimicrobial activities of the thiazolo 5,4-dpyrimidines 1a-j are compared with those of known chosen standard drugs, viz. ampicillin, chloramphenicol, ciprofloxacin, norfloxacin and griseofulvin **[49]**.



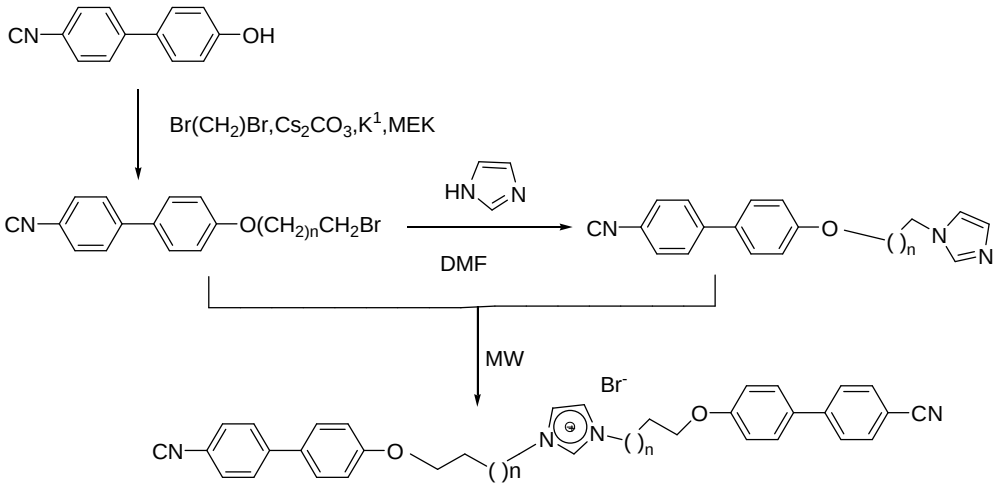

(80) (81) (82) 1a - j R = Aryl (83)

**Kawashita *et al* (2009),** a variety of heteroaromatic compounds, 2-substituted imidazoles (85) were synthesized by oxidative aromatization of 2-substituted imidazolines (84) using the activated carbon and molecular oxygen system **[50]**.



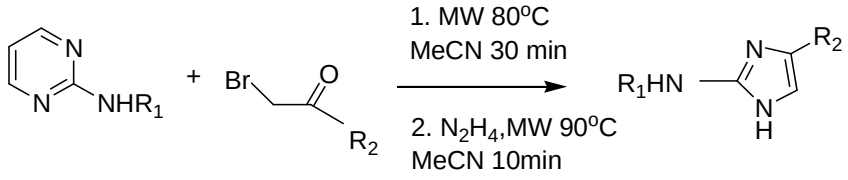

(84) (85)

**Kumar Pal *et al* (2006)** reported microwave promoted synthesis of novel imidazolium-based ionic liquid crystalline dimmers containing calamitic–calamitic (86), calamitic–discotic (87) and discotic–discotic (88) moieties. Classical reactions failed to produce these dimers. The thermotropic liquid crystalline properties of these salts were investigated by polarizing optical microscopy, differential scanning calorimetry and X- ray diffractometry. These salts except the one having calamitic–discotic units, with bromide as counter ion were found to be mesom **[51]**.



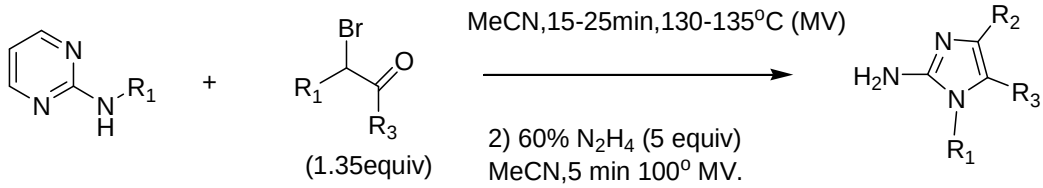

(86)

**Ermolat'ev *et al* (2010)** reported an efficient microwave-assisted one-pot two-step protocol was developed for the construction of disubstituted 2-amino-1H-imidazoles (91). This process involves the sequential formation of 2, 3-dihydro-2-hydroxyimidazo[1,2-*a*] pyrimidinium salts from readily available 2-aminopyrimidines (89) and α-bromoketones (90), followed by cleavage of the pyrimidine ring with hydrazine **[52]**.

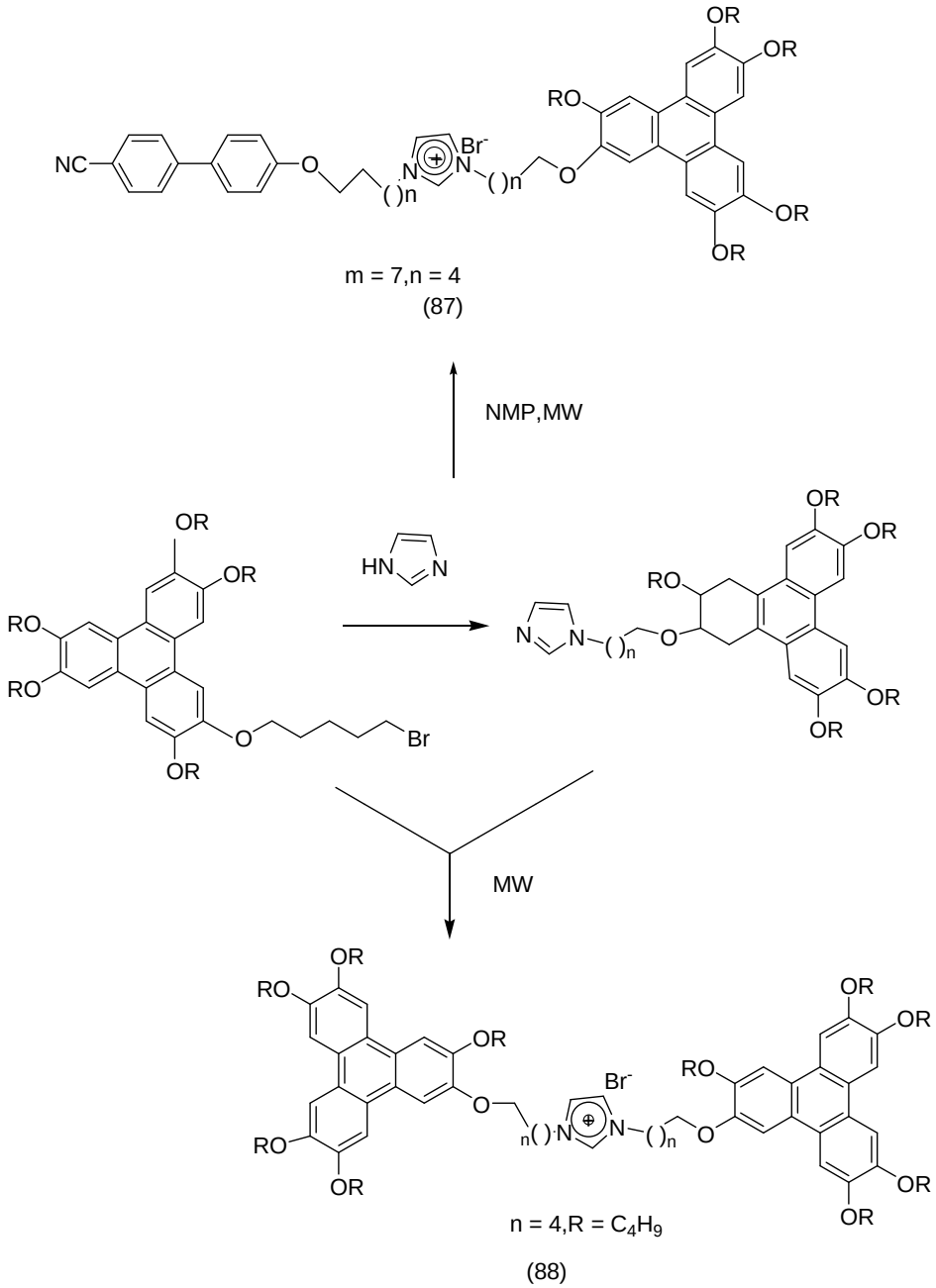



(89) (90) (91)

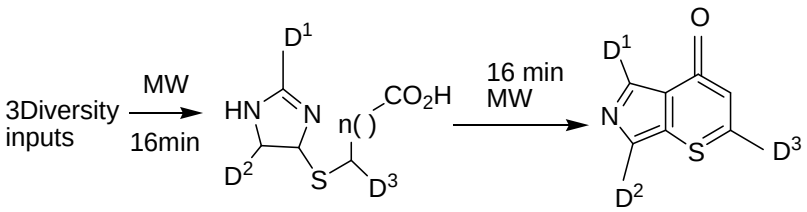
**Ermolat'ev *et al* (2006),** a microwave-assisted, one-pot, two-step protocol was developed for the construction of polysubstituted 2-aminoimidazoles (94). This process involves the sequential formation of imidazo [1,2-*a*] pyrimidinium salts from readily available 2-aminopyrimidines (92) and alpha-bromocarbonyl compounds (93), followed by opening of the pyrimidine ring with hydrazine [53].




(92) (1.35equiv) (93) (94)

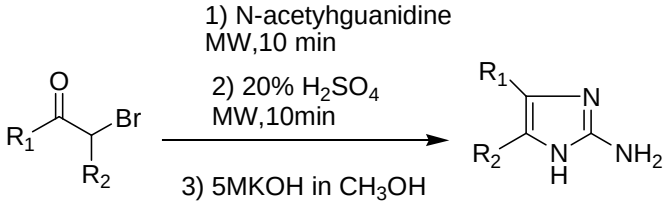



**Le Bas *et al* (2005)** A methodology for the generation of a microwave-assisted parallel library and its conversion into a second library is described. A 24-membered library of substituted 4(5)-sulfanyl-1H-imidazoles (97) was generated and subsequently converted into a second library of bicyclic imidazo[5,1-b] thiazol-3-ones (95) and imidazo [5,1-b]thiazin-4-ones (96). The first library was generated using a three-component reaction and transformed into a daughter library with a polymer-supported coupling agent. The procedure involved the use of an array of expandable reaction vessels, which can accommodate pressure buildup due to microwave heating without loss of volatile solvents or reagents. Library generation time for each library was 16 min [54]



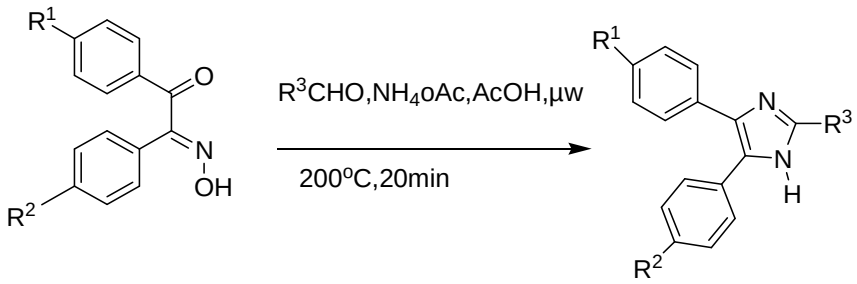

(95) (96) (97)

**Soh *et al* (2008)** developed a microwave-assisted protocol for the construction of di- and monosubstituted 2-aminoimidazoles. The two-step reaction involves the synthesis of N-(1H-imidazol-2-yl)acetamides (99) from readily available alpha-haloketones (98) and N-acetyl guanidine , followed by deacetylation. Significant rate enhancement was observed for both steps of the protocol, and the overall reaction time was shortened to 20 min compared to 48 h of the conventional procedures. A representative set of di- and monosubstituted 2-aminoimidazoles was prepared using commercially available parallel reactors **[55]**.



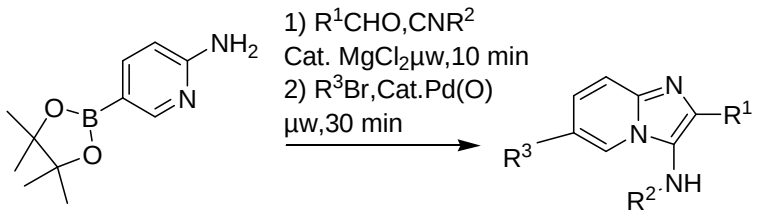

(98) (99)

**Sparks *et al* (2004)** were synthesized 2,4,5-Triaryl-imidazoles (101) directly from the keto-oxime in moderate to good yields via cyclization to the N-hydroxyimidazole (100) and an unprecedented in situ thermal reduction of the N-O bond upon microwave irradiation at 200 degrees C for 20 min **[56]**.



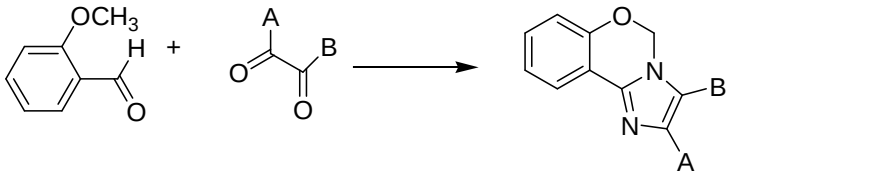

(100) (101)

**Dimauro *et al* (2007)** observed the rapid and efficient synthesis of various 2, 6-disubstituted-3-amino-imidazopyridines (102) using a microwave-assisted one-pot cyclization/Suzuki coupling approach is described. The utility of a 2-aminopyridine-5-boronic acid pinacol ester as a robust and versatile building block for the synthesis of diverse compound libraries is emphasized. The boronate functional group is remarkably tolerant to the Lewis acid catalyzed cyclizations, and the subsequent Pd(0)-catalyzed Suzuki coupling reactions proceed cleanly in the presence of magnesium salts. This work highlights the vast potential of microwave-assisted, metal-catalyzed, multicomponent reactions **[58]**.




(102)

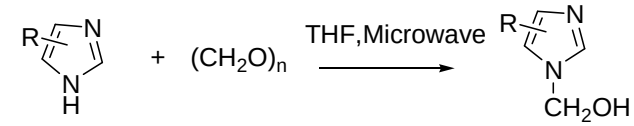
**Fantini *et al* (2010)** observed a simple and efficient microwave assisted synthesis of imidazo benzoxazines (103) with broad chemistry scope is described. The molecules were prepared both under conventional as well as microwave heating conditions, to provide in high yields with clean and scalable reactions a small library of imidazole-based privileged structures for drug discovery **[59]**.




A,B = H,$CH_3$,-$CH_2CH_2CH_3$,Ph

(103)

**Lupsori *et al* (1956)** a series of 1-hydroxymethylazoles (104) were synthesised by condensation reaction of azoles (105) (pyrazole, imidazole, 3,5-dimethylpyrazole, 2-methylimidazole and benzimidazole) with paraformaldehyde (106). The reactions were carried out under microwave irradiation conditions using tetrahydrofurane (THF) or dimethyl sulfoxide (DMSO) as solvents. Microwaves assisted procedure has noticeable advantages compared to classical methods: yield increase, substantial reduction of reaction time, solvents consumption and waste minimization **[60].**




R= 2-methyl

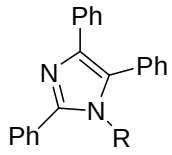
(105) (106) (104)

**Pharmacological activity**

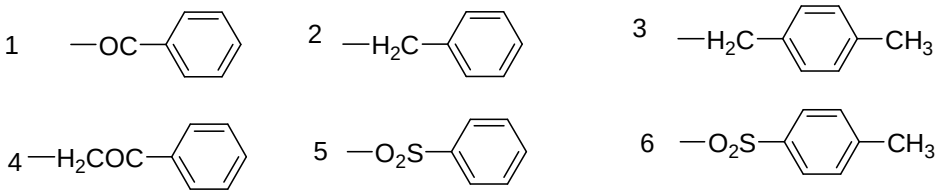
The high therapeutic properties of the imidazole related drugs have encouraged the medicinal chemists to synthesize a large number of novel chemotherapeutic agents. Imidazole drugs have broadened scope in remedying various dispositions in clinical medicines. Numerous methods for the synthesis of imidazole and also their various structure reactions offer enormous scope in the field of medicinal chemistry. literature survey revealed that imidazole and its derivative are reported to have, antianthelmintic activity [61], cardiovascular activity [62, 63], analgesic and anti-inflammatory activity [64-67], anti-neoplastic activity [68], anti- fungal

activity [68-69], enzyme inhibition activity, anti-filarial agent, anti-viral activity and anti- ulcer activity [70-72].

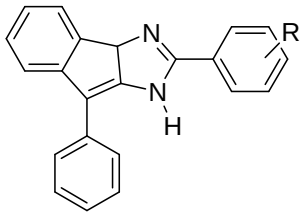
**Yashoda et al,(2009)** synthesized a series of 1-substituted 2, 4, 5 triphenyl imidazoles (107) by the reaction equimolar mixture of 2, 4, 5 triphenyl imidazole with chloro compound in the presence of anhydrous potassium carbonate. Antiinflammatory activity was screened by carageenan induced rat paw oedema method. Compounds 4 & 5 showed highly significant activity. Antimicrobial activity was screened by disc-plate method. All the compounds showed mild to moderate activities [73].




(107)



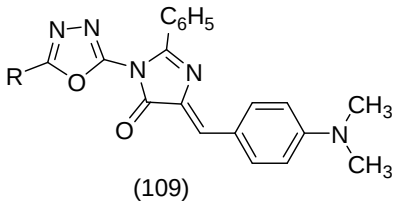

**Bhragual et al, 2010** evaluated the **a**nticonvulsant activity by Maximal Electroshock Method (MES). Substitution of chloro and nitro group at 2nd position in the substituted ring (108) showed significant anticonvulsant activity without neurotoxicity while hydrogen and 4-nitro substitution does not showed the anticonvulsant activity [74].



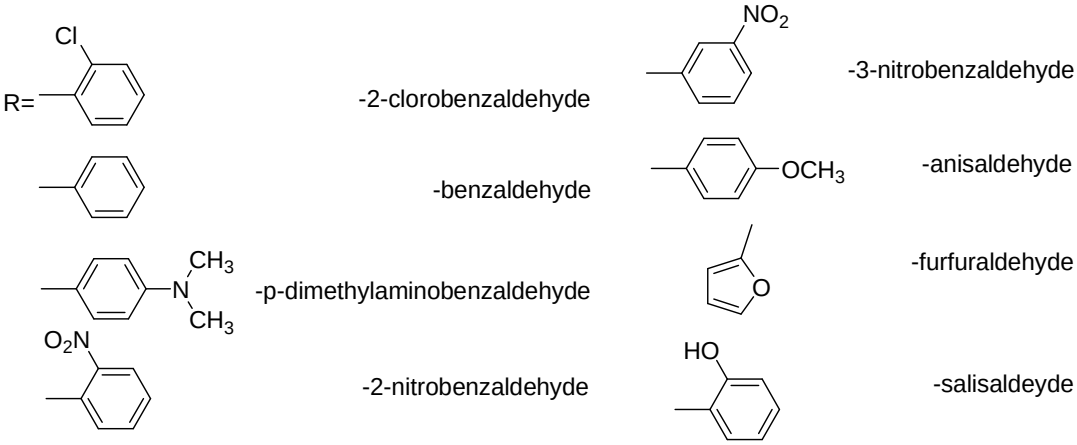

R= H, 2-Cl, 2-$NO_2$, 4-$NO_2$

(108)

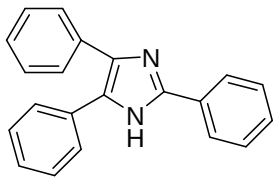
**Patel et al, 2010** The screened compounds (109) were tested for anthelmintic activity. After all, the synthesized compounds in overall estimation confirms the better activity against peritum posthuma [75].



(109)

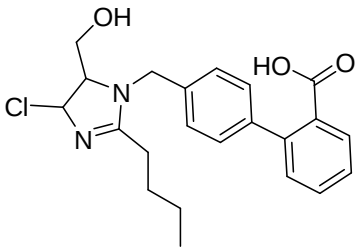



**Satyajit *et al* (2010)** A series of 2-substituted-4,5-diphenyl imidazoles (110) were synthesized by refluxing benzil with different sub-stituted aldehydes in the presence of ammonium acetate and glacial acetic acid. Compounds were screened for an-thelmintic activity. Test results revealed that compounds showed paralysis time of 0.24 to 1.54 min and death time of 0.39 to 4.40 min while the standard drugs albendazole and piperazine citrate showed paralysis time of 0.54 and 0.58 min and death time of 2.16 and 2.47 min, respectively, at the same concentration of1%(m/V ) [82].



(110)

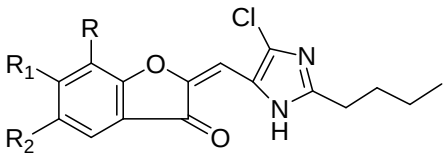
**Shreenivas et al, (2011)** Compounds (111) were screened for their in-vitro antibacterial activity against *S.aureus* and *B. subtilis* employing cup-plate method at the concentration of 100µg/ml in nutrient agar media and also for in-vitro antifungal activity against C. *albicans and A. Niger* by cup plate method at 100µg/ml**.** concentration using sabouraud-dextrose agar. DMSO was used as solvent control for antimicrobial activity. Streptomycin was used as standard for antimicrobial. The area of inhibition of zone measured in cm [76].




(111)

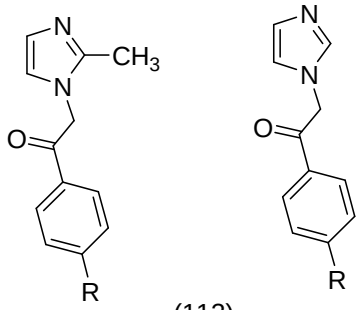
R= H, o-Cl, p-F, p-Me, p-OMe, 2,4-$(OMe)_2$, 2,4-$(OEt)_2$

**Bhaskar *et al* (2010)** In the present study, the oxidation of 3-(4-chloro-1H-imidazol-5-yl)-1-(2-hydroxyphenyl) prop-2-en-1-ones with mercuric (II) acetate in in polyethylene glycol (PEG-400) gave the corresponding 2-((4-chloro-1H-imidazol-5-yl)methylene)benzofuran-3(2H)-ones. Newly synthesized compounds (112) were tested for their in vitro antimicrobial activity [81].




(112)

**Lakshmanan et al (2011)** of all prototypes (113) were tested in this bioassay at various concentrations of 10, 50 and 100 µg/ml, and Concentration-response curves were plotted to check their ability to reverse the activity of Histamine on prior (5 min) contact with the atria. When evaluated against Histamine all the compounds at 100µg/ml significantly ($P<0.05$) antagonized the contraction of guinea pig atria, in a competitive and concentration dependent manner [77]

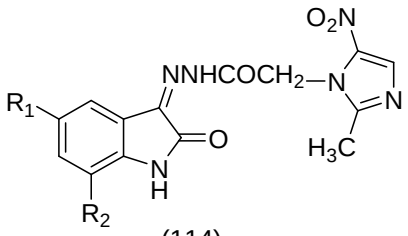



(113)

R= Cl, Br, Phenyl, $NO_2$

.

**Jays et al (2011)** The antibacterial activity of newly synthesized Isatin derivatives was carried out by agar diffusion method against *Staphylococcus aureus and Bacillus Subtilis (*gram-positive) and *Klebsiella and Proteus Vulgaris (gram-negative)* using **:** Amoxicillin and Ciprofloxacin as standard reference drugs. All compounds (114) have shown antibacterial activity against the gram-positive and gram-negative bacteria tested. The order of the antibacterial activity for the synthesized compounds is as follows [78].

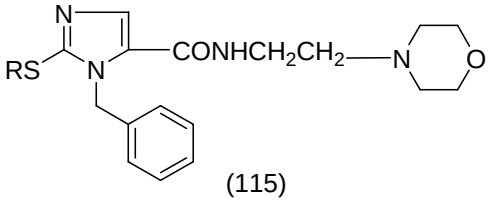


(114)

$R_1$ = H, $NO_2$, Cl, I, $CH_3$, F, Br

$R_2$ = H, F

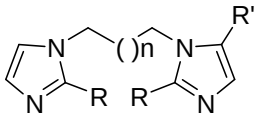
**Hadizadeh *et al*(2008)** Moclobemide is a selective and reversible monoamine oxidase-A inhibitor, which is used as an antidepressant. Three moclobemide analogues were synthesized by replacing moclobemide phenyl ring with substituted imidazoles and studied for the antidepressant activity using forced swimming test in mice. Analogues (115) were found to be more potent than moclobemide [79].



(115)

R = $CH_3$ , $C_2H_5$ , $CH_2C_6H_5$

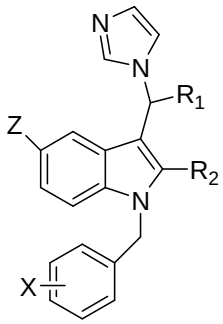
**Pandey *et al*(2009)**A series of imidazole based compounds (116) were synthesized by reacting simple imidazoles either with alkyl halides in presence of tetrabutylammonium bromide (TBAB) or by conjugate addition of imidazoles to ethyl acrylate or glycosyl olefinic ester. The synthesized compounds were screened against M. tuberculosis where compound (116) exhibited good in vitro antitubercular activity that may serve as a lead for further optimization [80].



n = 1;R = Propyl,R' = H

(116)

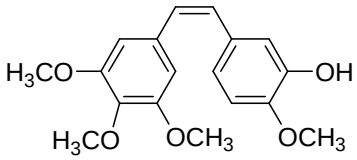
**Min Na *et al* (2003) a** series of 1-benzyl-3-(imidazol-1-ylmethyl) indole derivatives were prepared under mild reaction conditions and tested for their antifungal activity. All of the compounds were evaluated in vitro against two human fungal pathogens, Candida albicans (CA980001) and Aspergillus fumigatus (AF980003); amphotericin B, fluconazole and itraconazole were used as references. Seven out of 27 compounds exerted significant antifungal activity against C. albicans [83].



(117)

| Z | $R_2$ | X | $R_1$ | Z | $R_2$ | X | $R_1$ |
|---|---|---|---|---|---|---|---|
| H | H | 4-Cl | H | H | H | 4-F | Methyl |
| H | H | 4-Cl | Methyl | H | H | 2,4-diF | H |
| H | H | 4-Cl | Ethyl | H | H | 2,4-diF | Methyl |
| H | H | 4-Cl | n-Propyl | H | H | 2,4-diCl | H |
| H | H | 4-Cl | i-Propyl | H | H | 2,4-diCl | Methyl |
| H | H | 4-Cl | Propenyl | H | $CH_3$ | 4-F | H |
| H | H | 4-Cl | n-Butyl | H | $CH_3$ | 4-F | Methyl |
| H | H | 4-Cl | t-Butyl | H | $CH_3$ | 4-Cl | H |
| H | H | 4-F | H | Br | H | 2-Cl | H |

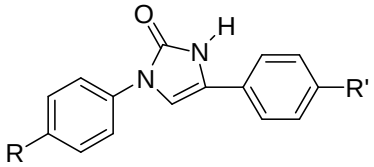
**Batnagar *et al* (2011)** Imidazole is an entity which is being synthesized in many of its derivative form from past few years; the entity is major source of interest for many of medicinal chemist to explore its various pharmacological potentials. In present article we review the chemistry of imidazole and its pharmacological actions as antihelmintics, anticancer, antifungal , anti-inflammatory agent by studying its various new synthesized derivatives like antimitotic activity. [83]



(118)

**Baroniya *et al* (2010)** Cancer is the second leading cause of death world wide after heart disease. A number of noble drugs are discovered for the treatment of cancer. In the present time imidazole plays an important part in the development of new drug for treatment of cancer. Imidazole is a nitrogen containing heterocyclic ring which possesses biological and pharmaceutical importance. Imidazole ring consists of variety of important natural product like histidine and purine. Imidazole derivatives have an important application in cancer treatment and an important agent used in medicinal chemistry. Despite these progresses the

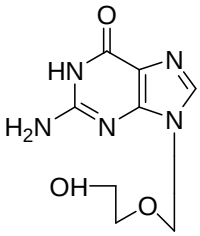
majority of patient diagnosed with their major malignancies will die of their disease and therefore, there is a need for few new agents with novel mechanism of action. Though much effect has been focused on the development of novel tyrosine-kinase inhibitors and antibiotics directed at signal transduction, exploration of new compound directly against traditional target of DNA and tubulin continues to be important [84].




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

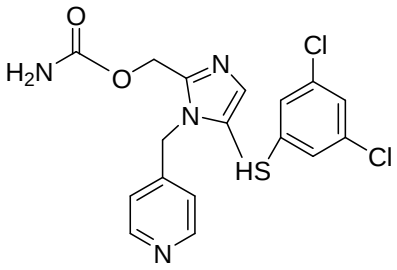
(119)

**Sadek *et al*(2011)** reported an update for the relationship between type of chemical substitution (aliphatic or aromatic) of imdazole-containig drugs and their tendency to affect hepatic metabolizing enzyme cytochrome P450 (CYP). In the present review, examples of different therapeutically used imidazole-containing drugs are highlighted to support the first evidence regarding the relationship between CYP-inhibition and chemistry of imidazole ring system [85].




(120)

**Y. Al-soud *et al* (2007)** Compounds were tested for their in vitro anti-HIV-1 (strain IIIB) and HIV-2 (strain ROD) activity in human T-lymphocyte (MT-4) cells using the MT-4/MTT assay . The results are summarized in Table III, in which the data for efavirenz and capravirine (121) were included for comparison. [86].




(121)

**Acknowledgement**
We wish to thanks Dr. Anil Kumar Sharma, Director CTIPS, Jalandhar, for providing the appropriate guidance and motivation for writing the above review.

## CONCLUSION

Microwave reactions are extremely attractive to synthetic organic chemists owing to their ability to improve regio and/or chemoselectivity and for ecofriendly & lesser reaction times. In case of imidazole derivatives which are proved to be having great potential for the different pharmacological activities, therefore synthesis of these by using microwave techniques are found to be further advantageous.

## REFERENCES

[1] A.R. Katritzky, Rees. *Comprehensive Heterocyclic Chemistry.*,**1984,** 5, 469-498.
[2] M.R. Grimmett. *Imidazole and Benzimidazole Synthesis.*,**1997,** Academic Press.
[3] E.G. Brown, *Ring Nitrogen and Key Biomolecules.*, **1998,** Kluwer Academic Press,.
[4] A.F. Pozharskii, *Heterocycles in Life and Society.*,**1997**, John Wiley & Sons,
[5] TL Gilchrist, Heterocyclic Chemistry The Bath press **1985.**
[6] H. Debus , *Annalen der Chemie und Pharmacie* .,**1858**, 107, (2), 199 – 208.
[7] F. Rondu, G. Le Bihan, X. Wang, A. Lamouri, E. Touboul, G.Dive, T.Bellahsene, B.Pfeiffer, P.Renard, B. Guardiola-Lemaitre, D. Manechez, L. Penicaud, A.Ktorza, J.J. Godfroid, *J. Med. Chem*., **1997**, 40, 3793.
[8] P.Bousquet, Feldman, *J. Drugs*., **1999**, 58, 799.
[9] M.Ueno, K. Imaizumi, T. Sugita, I.Takata, M. Takeshita, *Inter. J. Immunopharmac*., **1995**, 17, 597.
[10] (a)T. Hayashi, E. Kishi, V.A.Soloshonok, Y. Uozumi, *Tetrahedron Lett*., **1996**, 37, 4969. (b)M.E. Jung, A. Huang, *Org. Lett*., **2000**, 2, 2659.
[11] (a) E.J.Corey, M.J. Grogan, *Org. Lett*., **1999**, 1, 157. (b) T. Isobe, K. Fukuda, Y. Araki, T. Ishikawa, *Chem. Commun*., **2001**, 243.
[12] H. Fujioka, K. Murai, Y. Ohba, A.Hiramastu, Y. Kita, *Tetrahedron Lett*., **2005**, 46, 2197.
[13] (a)E.E. Korshin, L.I. Sabirova, A.G. Akhadullin, Y.A. Levin , *Russian Chem. Bull*., **1994**, 43, 431. (b) G.Levesque, J.C. Gressier, Proust, M. Synthesis, **1981**, 963.
[14] H. Vorbriiggen, K. Krolikiewicz, *Tetrahedron, Lett*., **1981**, 22, 4471.
[15] G. Neef, U. Eder, G.J.Sauer, *Org. Chem*., **1981**, 46, 2824.
[16] A.J. Hill, J.V. Johnston, *J. Am. Chem. Soc*., **1954**, 76, 922.
[17] N.A. Boland, M. Casey, S.J.Hynes, J.W.Matthews, M.P. Smyth, *J. Org. Chem*., **2002**, 67, 3919.
[18] G.I.Shin, J.I. Lee, J.H. Kim, *Bull. Korean Chem. Soc*., **1996**, 17, 29.
[19] A. Davood, E. Alipour2, A. Shafiee,*Turk J Chem* ., **2008**,32, 389 – 395.
[20] F. Harvey, Microwave Engineering, Academic Press, New York, **1963**.
[21] A. G. Horeis, S. Pichler, A. Stadler, W. Gössler, C. O. Kappe, Fifth Inter. Electronic Conference on Synthetic Organic Chemistry (ECSOC-5).,**2001**, 1–30.
[22] Lidstrom Pelle, Jason Tierney, BernardWathey and Jacob Westman, *Tetrahedron*.,**2001,** 57.
[23] The Chemistry of Heterocyclic Compounds, Imidazole and Its Derivatives, Volume 6, By Klaus Hofmann ,13, John Wiley and Sons.
[24] A. Bhatnagar ,P.K. Sharma ,N. Kumar . *Inter. J. Pharm Tech Res*., **2011**, 3( 1), 268-282.
[25] S. Baroniya, Z. Anwer, P. K. Sharma, R. Dudhe, N. Kumar. *Der Pharmacia Sinica*., **2010**, 1 (3), 172-182.
[26] E. Lunt ,C.G. Newton ,C. Smith,G.P. Stevens ,M.F.Stevens ,C.G. Straw,R.J. Walsh, P.J.Warren ,C. Fizames , F. Lavelle , *J. Med. Chem*., Feb., **1987**, 30 (2), 357- 66.

[27] K. Hoffman , *Interscience* ,**1953**, 143-145.
[28] H.Bredereck, R. Gompper ,D. Hayer , *Chem. Ber*.,**1959**, 92, 338.
[29] C.Robert, Elderfield**, 1957**, V-5, 744.
[30] Wallach & Schuelze, *Ber*., **1881,** 14,420-423.
[31] Wallach , *Ber*., **1876** , 184,33-35.
[32] Wallach , *Ber* .**1881**, 14,735, Wallach 7 Stricker , Ber., **1880**,13**,**51, Wallach & Schulze , Ber ., **1880**, 13,1514 .
[33] Sarasin & Weymann, Helv. *Chim, Acta*, **1924**, **7**,720.
[34] I.L.Finar, stereochemistry and chemistry of natural products, Organic chemistry**,**vol 2, V thedition,622, 629.
[35] Syed Sultan Qasim, Syed Shahed Ali, *Der Pharma Chem*, **2011**, 3(1): 518-522.
[36] Na Zhao , Yu-Lu Wang , Jin-Ye Wang ,*J*. of the *Chinese Chem*. *Soci* , **2005**, 52 , 535-538.
[37] M.Y. Pathan, V.V. Paike, P.R. Pachmase, S.P. More, S.S. Ardhapure, R.P. Pawar, *ARKIVOC*., **2006** , (xv)205-210.
[38] D.S. Ermolat'ev , E.P. Svidritsky, E.V. Babaev , E.V. Eycken , *sci dir Tetrahedron Lett* .,**2009,** 5218–5220.
[39] S. Bharadwaj, D.K. Rathore, B. Parashar, V.K.Sharma ,*J. Chem. Pharm*. Res., **2010**, 2(5), 392-398
[40] K.Bhanat, N. Parashar, K. Jain, V.K.Sharma , *Asian J. of Biochem. and Pharm Res*., **2011,** 1 (1),22,2231-2560**.**
[41] H.Höpfl, B.Gómez, R.M. Palou ,*J. Mex. Chem. Soc.* **2005**, 49(4), 307-311.
[42] P. Raghavendra, G. Veena ,G.A. Kumar, G.R.Kumar, N. Sangeetha ,*Rasyan .J.chem.***2011,** 4, (1), 91-102.
[43] A.Marek, J.Kulhanek, M.Ludwig F.Bures, B.Sirivennela, S.Smarani, H.P.Kumar, R. Suthakaran, *Molecules*., **2007**, 12, 1183-1190.
[44] P.V.Frank, K.S. Girish, B. kalluraya.,*J. Chem. Sci*., **2007**, 119, 1, 41–46.
[45] J. Safari, S.D. Khalili, S.H. Banitaba., *J. Chem. Sci*.,**2010,** 122, 3, 437–441.
[46] S. Kamila, H.Ankati, E.R. Biehl., *Molecules* .,**2011**, 16, 5527-5537.
[47] S.V. Nalage, M.B. Kalyankar, V.S. Patil, S.V. Bhosale, S.U. Deshmukh, R.P. Pawar., *The Open Catalysis J*., **2010**, 3, 58-61.
[48] D. Wahyuningrum, S. Achmad, Y.M. Syah, Buchari and Bambang Ariwahjoedi., *Inter. Conference On Chem Sci*.,**2007**, 24-26. MAT/42-6.
[49] S.J. Vaghasia, V.H. Shah .,*J. Serb. Chem. Soc*.,**2007**, 72 (2) 109–117.
[50] Y. Kawashita, M. Hayashi, *Molecules* **2009**, 14, 3073-3093.
[51] S.K. Pal, S. Kumar, *Sci dir Tetrahedron Letters* ., **2006,** 47**,** 8993–8997
[52] D.S. Ermolat'ev , B. Savaliya , A. Shah, E. Van der Eycken , *Mol Divers.*, **2011**,15(2),491-6.
[53] D.S.Ermolat'ev , E.V. Babaev, E.V. Van der Eycken, *Org Lett.*,**2006**,7,8(25),5781-4.
[54] D.S. Ermolat'ev, V.N Giménez, E.V. Babaev, E. Van der Eycken, *J Comb Chem.*,**2006** ,8(5),659-63.
[55] M.D.Le Bas, D.F. O'Shea, *J Comb Chem.*, **2005** ,7(6),947-51.
[56] C.H. Soh, W.K. Chui , Y. Lam, *J Comb Chem.*, **2008** ,10(1),118-22.
[57] R.B. Sparks, A.P. Combs,*Org Lett.*, **2004** ,8- 6(14),2473-5.
[58] E.F. Dimauro, J.M. Kennedy, *J Org Chem.* **2007** , 2-72(3),1013-6.
[59] M.Fantini , V. Zuliani , M.A. Spotti, M. Rivara, *J Comb Chem*., **2010** ,12(1),181-5.
[60] S. lupsor,S., I. Tarcomnicu, F. Aonofriesei, M. Iovu, N.putochin ,*J. Ber*., **1922**, 55, 2749.

[61] E. Lunt , C.G. Newton, C. Smith, G.P. Stevens, M.F. Stevens, C.G. Straw, R.J. Walsh , P.J.Warren , C. Fizames , F.Lavelle. *J. Med. Chem*.,**1987**, 30(2),357- 66.
[62] D.W. Robertson , E.E. Beedle , J.H. Krushinski ,G.D. Pollock ,H.Willson ,J.S. Wyssvl , Hayes, *J. Med. Chem*.,**1985**, 28(6),717-27.
[63] P.W. Erhardt , A.A. Hagdon , D.Davey ,C.A. Pease, Venepalli, C.W.Griffin ,R.P. Gomez ,J.R. Wiggins, W.R. Ingebretsen , D.Pang . *J.Med. Chem*., **1989**, 32 (6),1173-6.
[64] M. Suzuki, S. Maeda , K.Matsumoto . *Boll chem farm*., l, **1986**, 34(8), 3111-3120.
[65] F.Suzuki, T. Kuroda,T. Tamura. *J. Med. Chem*., **1992**, 35(15), 2863-2870.
[66] S.A. El – Feky , Z.K. Abdel – Samii. *Pharmazie*., **1995**, 50 (5), 341-343.
[67] L. Isikdag , A. Meric , *Boll chem Farm*., **1999**, 138(1), 24-29.
[68] R.A. Johnson , S.M. Huong , E.S. Huang, *Anti viral research.*, **1999**, 41 (3), 101-111.
[69] M.D. Brewer, R.J. Dorgan ,B.R. Manger, P. Mamalis, R.A.Webster , *J. Med. Chem*., **1987**, (10),1848- 53.
[70] J.A. Nathanson , *Mol. Pharmacol*., **1985**, 28(3), 254-68.
[71] L.I. Kruse , C. Kaiser, J.S.Frazee, E. Garvey, E.L. Hilbert, W.A. Faulkner, K.E.Flaim ,J.L.Sawyer , B.W. Berkowitz , *J. Med. Chem*., **1986**, 29(12) ,2465-72.
[72] H.S. Liyk Hsu, H. Kiyota , M. Segawa, *J. Bio chem***., 1998**, 23(3), 416-422.
[73] A. Yasodha , A.Sivakumar, G. Arunachalam, A. Puratchikody , *J. of Pharma. Sci. Res.* ,**2009,** 1 (4), 127-130.
[74] *D.D.* Bhragual, N. Kumar, S. Drabu , *J. Chem. Pharm. Res*., **2010**, 2(2), 345-349.
[75] *K.* Patel, E. Jayachandran, V. Shah, V. Javali ,G.M. Sreenivasa, *Inter. J. Pharma and Bio Sci* .**2010**. 1(3),ISSN-0975-6299.
[76] M.T. Shreenivas, B.E. Kumara Swamy,G.R. Srinivasa,B.S. Sherigara , *Der Pharma Chemica*., **2011**, 3(2),156-161.
[77] *B.* Lakshmanan , P.M. Mazumder , D.Sasmal , S. Ganguly , *J. pharm. Sci. and Res.*,**2011**, 3(1), 961-965.
[78] J. Jays, A. Kumar, C .H. S .Venketaramana, B .V. Sumaa, V. Madhavan , *Inter. J. Chem. Tech. Res.*,**2011**,3, 2, 772-777.
[79] F.Hadizadeh , H. Hosseinzadeh, Vahideh-Sadat Motamed-Shariaty M. Seifib, S. Kazemi , .*Iranian J. of Pharm. Res.*, **2008,** 7 (1) 29-33.
[80] J.Pandey, V.K. Tiwari, S.S.Verma , V. Chaturvedi, S. Bhatnagar ,A.N.Sinha, A. N. Gaikwadb ,R.P.Tripathi, *European J. Medicinal Chemistry*., **2009,** 44, 3350–3355.
[81] B.S.Dawane, S.G. Konda, N.T.Khandare, S.S.Chobe, B.M.Shaikh, R.G. Bodade, V.D. Joshi, *Org. Commun..*, **2010**, 3,2 22-29.
[82] S. Dutta, *Acta Pharm..*, **2010**, 60, 229–235.
[83] A.Bhatnagar, P.K.Sharma,N.Kumar, *Int.J. PharmTech Res*.**,2011**,3(1) 276.
[84] S. Baroniya, Z. Anwer, P. K. Sharma, R. Dudhe, N. Kumar ,*Der Pharmacia Sinica..*, **2010**, 1 (3), 172-182.
[85] B. Sadek , *Der Pharma Chemica*., 2011, 3(1), 410-419.
[86] Y. Al-soud,N. al-masoudi,H. G. hassan, E. D. clercq, C. Pannecouque, *Acta Pharm*.,**2007**, 57, 379–393.