Review Article

A Review on Imidazole Derivatives Having Appropriate Remedies for Extreme Diseases

Renjima K.M*[1], Resmy Menon[2], Divya Chacko[3]
[1]Student, Department of Pharmaceutical Chemistry, St.Joseph's College of Pharmacy, Kerala, India.
[2]Student, Department of Pharmaceutical Chemistry, St.Joseph's College of Pharmacy, Kerala, India.
[3]Assistant Professor, Department of Pharmaceutical Chemistry, St.Joseph's College of Pharmacy, Kerala, India.
***Corresponding author's E-mail: renjima99@gmail.com**

Received: 12-03-2020; **Revised:** 24-04-2020; **Accepted:** 29-04-2020.

ABSTRACT

Imidazoles have occupied a unique position in heterocyclic chemistry, and its derivatives have attracted considerable interests in recent years for their versatile properties in chemistry and pharmacology. This created interest in researchers to synthesize variety of imidazole derivatives. Imidazole is nitrogen-containing heterocyclic ring which possesses biological and pharmaceutical importance such as antibacterial, anti-inflammatory, anti-fungal, anticancer, anti-depressant, anti-viral and anti-tubercular. This paper aims to review the biological activities of imidazole during the past years.

Keywords: Imidazole, anti-fungal, anti-cancer, antibacterial, anti-inflammatory, anti-depressant, anti-viral.

INTRODUCTION

Imidazole is a five-member heterocyclic aromatic compound with two nitrogen atoms. Both Nitrogen atoms are sp^2 hybridized[1]. The natural products like histamine, histidine, and nucleic acid are the important constituent of imidazole ring[2]. Imidazole susceptible to nucleophilic and electrophilic attack. Imidazole generally colorless or pale yellow solid and it has amine like order. It is soluble in water and other polar solvents. Imidazole has melting point 88.9°C and it has boiling point 267.8°C. Imidazole has molecular formula $C_3H_4N_2$. The high beneficial properties of the imidazole containing drugs have encouraged the medicinal chemists to prepare a large number of new therapeutic molecules. Imidazole drugs have wide spectrum of applications in pharmaceutical field. Imidazole derivatives are pharmacologically and physiologically active and it is used in the treatment of various diseases. Imidazoles are important constituents and they are found in a large number of natural products and clinically active drug molecules. Synthetic imidazoles are present in many fungicides, anti-fungal, antiprotozoal and anti-hypertensive medications. Due to their significance, it has become a suitable target for the synthetic and clinical. There are different techniques that have been used for assembling and modifying the imidazole ring with different functional groups. The basic site in imidazole nucleus is N-3[1].

STRUCTURAL CHARACTERISTICS

The imidazole is a planar, five membered heteroaromatic compounds with 3C and 2N atom in 1 and 3 positions. It was present in two equivalent tautomeric forms because the hydrogen atom can be located on either of the two nitrogen atom (Figure :1).

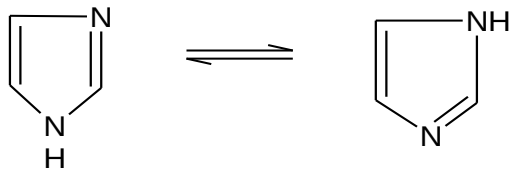


Figure : 1

Imidazole is a highly polar compound, as evidenced by a calculated dipole of 3.61D, and is completely soluble in water[3]. 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 (figure 2).

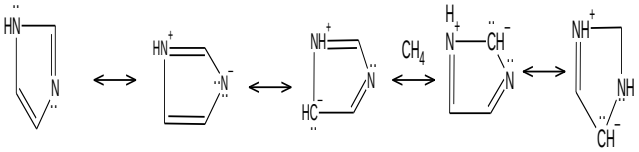


Figure : 2

Imidazole can function as both acid and base; hence it is amphoteric in nature (figure 3)[4]. As an acid, the pKa of imidazole is 14.5, making imidazole 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 pKa of the conjugated acid is approximately 7, making it is approximately sixty times more basic than pyridine. The resonance interactions help to explain these properties, which increase the basicity of the 3-nitrogen atom[3].

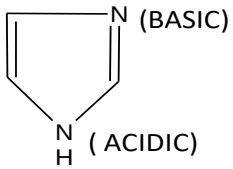


Figure : 3

PROPERTIES[5]

Physical Properties

- Imidazole generally colorless or pale yellow solid
- It has amine like order.
- It is soluble in water and other polar solvents.
- Imidazole has melting point 88.9°C
- It has high boiling point 267.8°C than all other 5-membered heterocyclic compounds due to the inter-molecular H-bonding (figure : 4), where there is linear association of molecule.

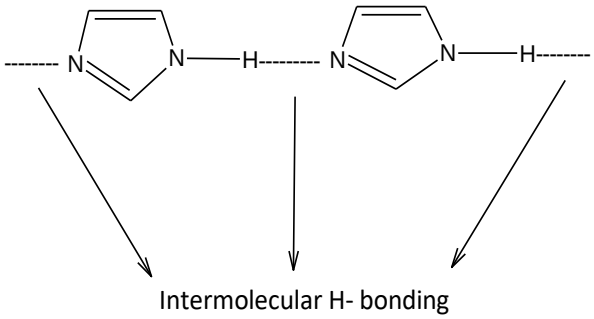


Figure : 4

- 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.

Chemical Properties

Reaction with acids: Imidazole is a mono acidic base. It reacts with acids to forms crystalline and also possesses weakly acidic property (figure 5).

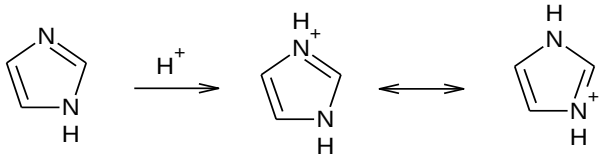


Figure : 5

Halogenation: Halogenation of imidazole is depending on the substrate, reagents and reaction conditions, direct chlorination gives undefined products. bromination yields 2, 4,5-tribromo derivative, iodination takes place in alkaline conditions to give 2, 4, 5-triiodoimidazole (figure 6).

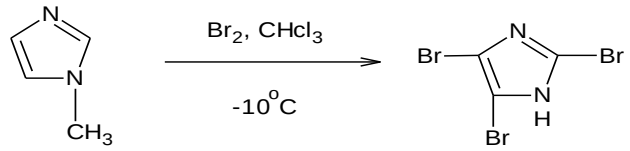


Figure : 6

Cycloaddition Reactions: Imidazoles gives addition across the carbon-carbon double bond. This kind of reaction performed under photochemical conditions. The reaction of imidazole with acrylonitrile is representative from the reaction given below (figure 7).

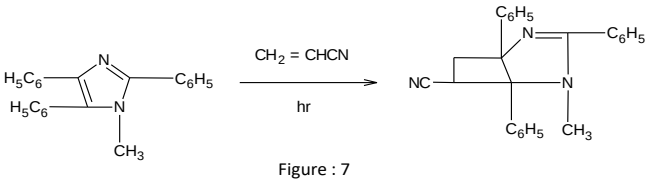


Figure : 7

SYNTHESIS OF IMIDAZOLE AND ITS DERIVATIVES

Imidazole was first synthesized by Heinrich Debus in 1858, but various imidazole derivatives had been discovered as early as the 1840s. The synthesis used glyoxal and formaldehyde in ammonia to form imidazole (Figure 8). Although various imidazole derivatives had been discovered earlier in the 1840s[2].

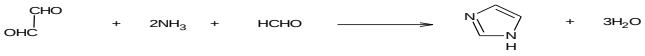


Figure : 8

Now-a-days several methods are available for the synthesis of imidazole and its derivatives, some of these are given below in Schemes 1-5 [5-8].

SCHEME-I

RE-Diszewski Synthesis

The synthesis denotes condensing a dicarbonyl compound such as glyoxal, a keto aldehyde or a diketones with an aldehyde in the presence of ammonia, with benzaldehyde and two molecules of ammonia react to yield 2,4,5-triphenyl-1H-imidazole (figure 9)[6,7].

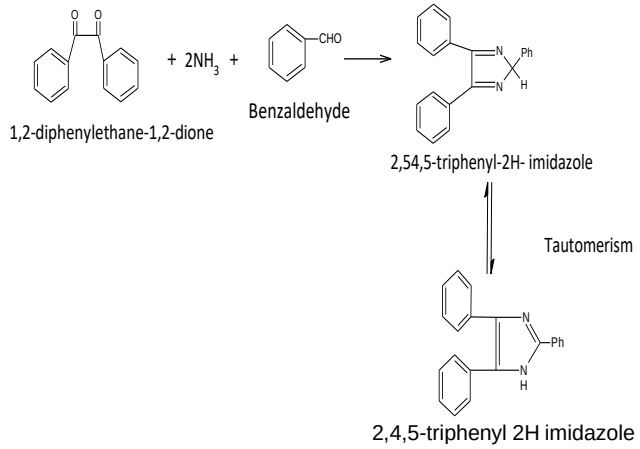
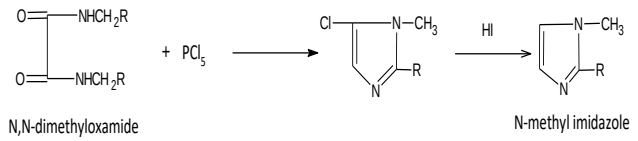


Figure 9: Re-diszewski synthesis

SCHEME-II

Wallach Synthesis

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 (figure 10) [5-8].

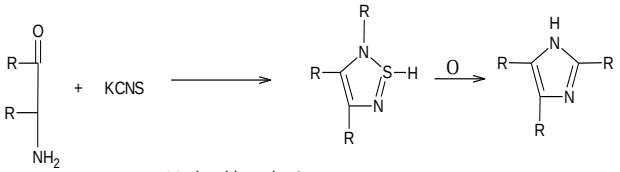


Wallach synthesis
Figure : 10

SCHEME-III

Markwald Synthesis

The preparation of 2- mercaptoimidazoles from an amino ketones or aldehyde and potassium thiocyanate or alkyl isothiocyanates is a common method for the synthesis of imidazoles. The sulfur is easily removed by oxidation (figure 11)[5].



Markwald synthesis
Figure : 11

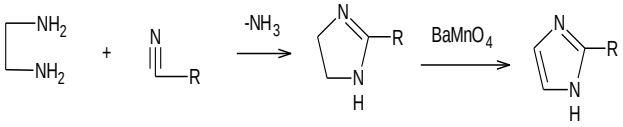
SCHEME - IV

Condensation of aldehyde and aminonitrile both under suitable reaction condition to give substituted imidazole (figure 12) [5].

From aminonitrile and aldehyde
Figure : 12

SCHEME - V

Knapp and coworkers have reported the conversion of imidazolines to imidazoles by using a milder reagent barium managanate and in the presence of sulphur to yield 2-substituted imidazoles. Imidazolines obtained from alkyl nitriles and 1, 2 ethanediamine on reaction with BaMnO4 (figure 13)[5].



Dehydrogenation of imidazoline
Figure : 13

PHARMACOLOGICAL ACTIVITIES

Imidazole has wide range of biological activities. The drugs which contain imidazole ring act on different receptors. For example, dopamine receptor, histaminic receptor, adreno-receptor etc [1]. On the basis of various literature surveys Imidazole derivatives shows various pharmacological activities.

1. Anti-fungal and anti-bacterial activity

Ramya v *et al* synthesized a series of novel 5-(nitro/bromo)-styryl-2-benzimidazole derivatives and tested for the antibacterial and anti-fungal activity. This was comparable with Ciprofloxacin.[9]

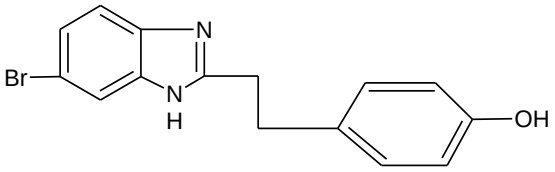
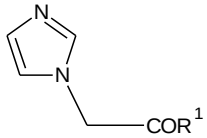


Figure : 14

Namita gupta *et al* synthesized N-substituted imidazole derivatives and the synthesized compounds are evaluated for in vitro antimicrobial activity against *Staphylococcus aureus, Bacillus subtilis* (Gram positive)*; Escherichia coli, Pseudomonas aeruginosa* (Gram negative) and *Candida albicans* and *Aspergillus niger.* All compounds showed moderate to good activity[10].



R^1=$C_{12}H_{13}N_3O$,$C_{11}H_{17}N_3O$, $C_{16}H_{15}N_3O$,$C_{11}H_{11}N_3O$, $C_{10}N_{15}N_3O$
Figure : 15

2. Anti-inflammatory and analgesic activities

Kavitha C.S *et al* synthesized a series of 2-methylaminibenzimidazole derivatives and the synthesized compounds were screened for analgesic and anti-inflammatory activities. This compound (compound : shows analgesic and anti-inflammatory activity, Nimesulide used as standard drug [11].

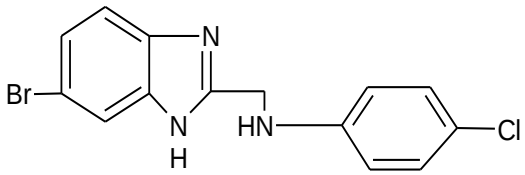


Figure : 16

3. Anti-cancer activity

Yusuf Ozkay *et al* synthesized many novel imidazole-(Benz) azole and imidazole epiperazine derivatives and synthesized compounds are tested for anticancer activity. All compounds showed good activity. Cisplatin was used as reference drug[12].

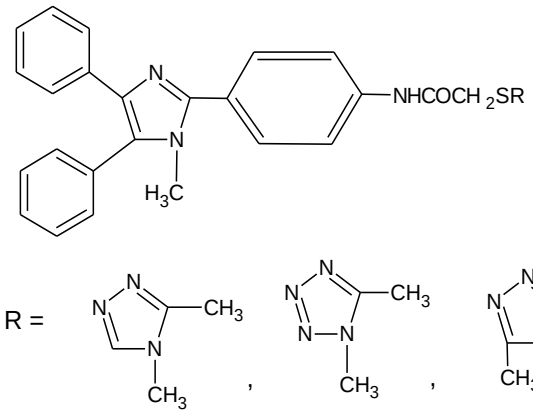
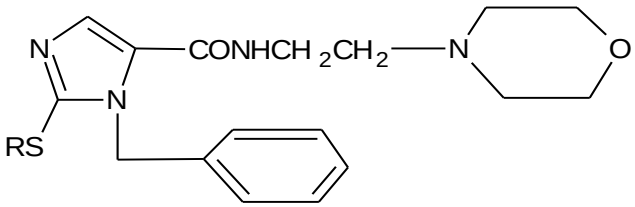


Figure : 17

4. Anti-depressant activities

Farzin Hadizadeh *et al* synthesized moclobemide analogues by replacing moclobemide phenyl ring with substituted imidazole and studied for the antidepressant activity using forced swimming test. All the analogues showed moderate to good activity[13].

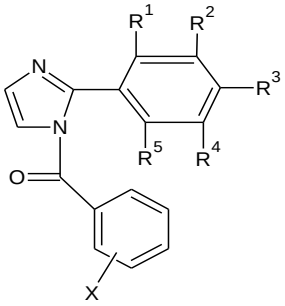


$R = CH_3, C_2H_5, CH_2C_6H_5$

Figure : 18

5. Antiviral activity

Deepika Sharma *et al* synthesized imidazole derivatives and tested for their antiviral activity. All the compounds showed good activity against viral strains. Ribavirin was used as standard drug[14].



$R^1, R^2 = H$

$R^3 = Cl, NO_2$

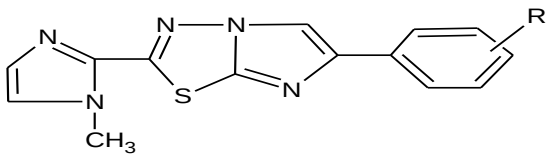
$R^4, R^5 = H$

$X = 4\text{-}NO_2$

Figure : 19

6. Anti-tubercular

Harun M. Patel *et.al* synthesized imidazole [2, 1-b] [1, 2, 3] thiadiazole derivatives and evaluated for *in-vitro* anti-tubercular against *M. tuberculosis* strain H37Rv by using the MABA method. All the synthesized compounds (A-J) exhibited an interesting activity profile against the tested mycobacterial strain[15].



Compound A R = 3-Nitro
B R = 4-Bromo
C R = 4-Chloro
D R = 4-Fluoro
E R = H
F R = 4-Nitro
G R = 4-Methyl
H R = 3-Methyl
I R = 2,4-Dichloro
J R = 2,4-Dihydro

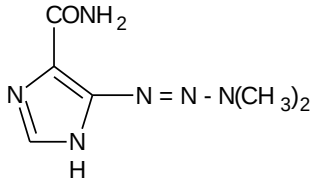
Figure : 20

MARKETTED FORMULATIONS

The list of imidazole containing clinically used drugs or drug candidates includes Dacarbazine, Ketoconazole, Clotrimazole, Econazole, Miconazole, Tioconazole, Butoconazole, Sulconazole, Metronidazol and Tinidazole.

1) Dacarbazine

- It is a monocarboxylic acid amide that is 1H- imidazole-4- carboxamide.
- The trade name of dacarbazine is DTIC-Dome. DTIC, DIC or imidazole carboxamide are other names for dacarbazine.
- It is used for the treatment of metastatic malignant melanoma, and in combination with other drugs for treatment of hodgkins disease and soft-tissue sarcoma.



Dacarbazine
Figure : 21

- Mechanism of action: DTIC is metabolically bio-activated by CYP450. Initial demethylation to mono methyl triazenyl imidazole carboxamide (MTIC) is followed by the formation of diazomethane, a potent methylating agent. It methylates the N-7 position of guanine (figure 22).

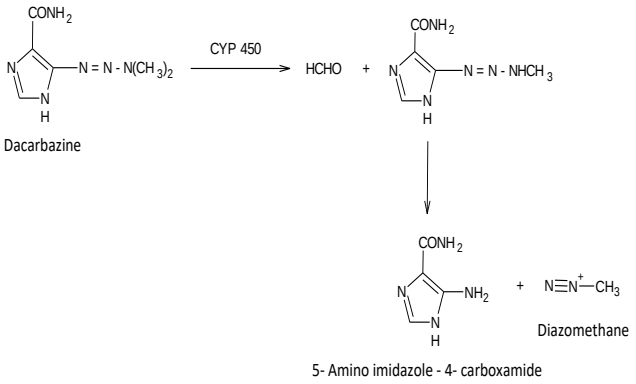
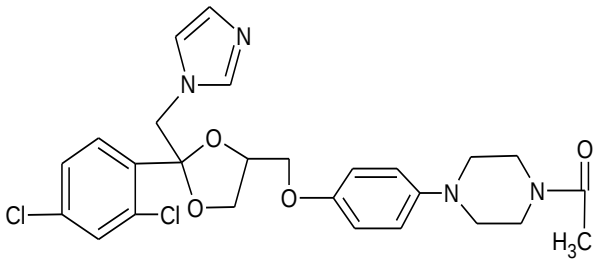


Figure : 22

2) Ketoconazole

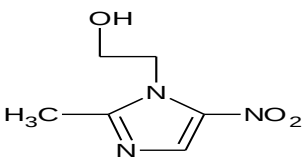
- Ketoconazole, sold under the brand name Nizoral, It is an antifungal medication used to treat a number of fungal infections.
- It is used for fungal skin infections such as tinea, cutaneous candidiasis, pityriasis versicolor, dandruff, and seborrhoeic dermatitis.
- Mechanism of action: Ketoconazole interacts with 14-α-sterol demethylase, a cytochrome P-450 enzyme necessary for the conversion of lanosterol to ergosterol. This results in inhibition of ergosterol synthesis and increased fungal cellular permeability due to reduced amounts of ergosterol present in the fungal cell membrane.



Ketoconazole
Figure : 23

3) **Metronidazole**

- It is an antibiotic and antiprotozoal medication
- It marketed under the brand name Flagyl.
- It is an effective amoebicide and the drug of choice for the treatment of all symptomatic forms of amoebiasis.
- Mechanism of action: It inhibits nucleic acid synthesis by disrupting the DNA of microbial cells.



Metronidazole
Figure : 24

CONCLUSION

Drugs containing imidazole nucleus have wide spectrum of applications in heterocyclic as well as in pharmaceutical field which are pharmacologically and physiologically active and it is used in the treatment of various diseases. On the basis of various literature surveys imidazole derivatives show various activities like anti-fungal, anti-bacterial, anti-inflammatory, analgesic, anti-cancer, anti-depressant, anti-viral and anti-tubercular. The possible improvements in the activity can be further achieved by slight modifications in the substituents on the basic imidazole nucleus. Various recent new drugs developments in imidazole derivatives show better effect and less toxicity. Thus, pyrazole has been long focused for research interest in the field of medicine, due to excellent activities exhibited by its derivatives.

REFERENCES

1) Munish K, Deepak K and Vinit R, Studies on imidazole and its derivatives with particular emphasis on their chemical/biological applications as bioactive molecules/intermediated to bioactive molecule, Current synthetic and systems biology, 5, 2017, 1-10.

2) Amita v, Sunil J and Deepika S, Imidazole: Having versatile biological activities, Journal of chemistry, 2013, 2013, 1-12.

3) Delia H R, Victor E. T H, Oscar G B *et al*, Synthesis of imidazole derivatives and their biological activities, Journal of chemistry and biochemistry, 2, 2014, 45-83.

4) Kumari S, Pramod K S, Nitin K, Imidazole and its biological activities: A review. Der chemica sinica, 1, 2010, 36-47.

5) Deepak C, Janmajoy B, Niraj S, Nomi S, Routes of synthesis and biological significances of imidazole derivatives: Review, World journal of pharmaceutical sciences, 3, 2015, 1668-1681.

6) Anushul C, Ashu S and Anil K S, Review: A convenient approach for the synthesis of Imidazole derivatives using microwaves, Der pharma chemica, 4, 2012, 116-140.

7) Bhatnagar A, Sharma P. K, Kumar N, AReview on "imidazole": Their chemistry and pharmacological potentials, International Journal of Pharma Tech Research, 3, 2011, 268-282.

8) Purnima M, Dr. Wakode S R, Avneet K, A Review: imidazole synthesis and its biological activities, International journal of pharmaceutical science and research, 1, 2016, 12-16.

9) Shingalapur R. V, Hosamani K. M, Keri R. S, Synthesis and evaluation of *in-vitro* anti-microbial and anti-tubercular activities of 2-styryl benzimidazoles, European journal of medicinal chemistry, 44, 2009, 4244-4248.

10) Namita G and Pathak D. P, Synthesis and evaluation of N-substituted imidazole derivatives for antimicrobial

activity, Indian journal of pharmaceutical sciences, 73, 2011, 674-678.

11) Kavitha C.S. Achar, Kallappa M. Hosamani, Harisha R. Seetharamareddy, *In-vivo* analgesic and anti-inflammatory activities of newly synthesized benzimidazole derivatives, European journal of medicinal chemistry, 45, 2010, 2048-2054.

12) Ozkay Y, Isikdag I, Incesuz and Akalin G, synthesis of 2-substituted-N-[4-(1- methyl-4, 5-diphenyl-1H-imidazole-2-yl) phenyl] acetamide derivatives and evaluation of their anticancer activity, European journal of medicinal chemistry, 45, 2010, 3320-3328.

13) Hadizadeh F, Hosseinzadeh H, Motamed-Shariaty V S *et al,* Synthesis and antidepressant activity of N-substituted imidazole-5-carboxamides in forced swimming test model, Iranian journal of pharmaceutical research, 7, 2008, 29-33.

14) Deepika S, Balasubramanian N, Pradeep K *et al,* Synthesis, antimicrobial and antiviral evaluation of substituted imidazole derivatives, European journal of medicinal chemistry, 44, 2009, 2347-2353.

15) Harun M. P, Malleshappa N. N, Navdeep S S *et al,* Synthesis and antitubercular evaluation of imidazo [2,1-b] [1,2,3] thiadiazole derivatives, Arabian journal of chemistry, 10, 2017, 990-1002.

Source of Support: Nil, **Conflict of Interest:** None.