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Review Paper Synthesis of Imidazole Derivatives: Methods and Biological Activities

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Abstract: *Imidazole and its derivatives constitute a significant class of heterocyclic compounds with diverse biological activities, making them attractive targets in medicinal chemistry. This research paper provides an in-depth analysis of the synthesis methods employed for the preparation of imidazole and its derivatives, along with an exploration of their biological activities. Various synthetic routes, including traditional and modern methodologies, are discussed in detail, highlighting their advantages and limitations. Furthermore, the biological activities exhibited by imidazole derivatives, such as antimicrobial, anticancer, and anti-inflammatory properties, are thoroughly examined, providing insights into their potential applications in drug discovery and development.*

Keywords: Imidazole, heterocyclic compounds, biological activities, antimicrobial, anticancer, anti-inflammatory,drug discovery

I. INTRODUCTION

A five-membered imidazole ring is a structural unit found in many biologically active compounds. The strong therapeutic properties of imidazole containing drugs have encouraged medicinal chemists to synthesize a large number of novel chemotherapeutic agents comprising this entity. Amongst others, imidazole core care structures are found in different carboxypeptidase, hemeoxygenase and lactamase inhibitors, as well as among antiinflammatory, anticancer, antibacterial, antifungal, antitubercular, antidiabetic and antiviral products(Saudi, Zmurko et al. 2014) The Imidazole compounds exhibited different cytostatic and cytotoxic activities for further developing potential application as anticancer drugs(Chen,Yu et al. 2013, Hossain, Świtalska et al. 2013) the compounds of benzofuran and imidazole moieties and their potential antitumor activities (Liu, Wang et al. 2013, Martins, Jesus et al. 2015) benzimidazole derivatives exhibited moderate tuberculostatic activity (Gobis, Foks et al. 2015) Imidazole is a 5-membered planar ring, which is soluble in water and other polar solvents(Bhatnagar, Sharma et al. 2011). It exists in two equivalent tautomeric forms (Fig.1) because the hydrogen atom can be located on either of the two nitrogen atoms. Imidazole is a highly polar compound. Imidazole behave as amphoteric compound as it can function as both an acid and a base(Chawla, Sharma et al. 2012). The compound is classified as aromatic due to the presence of a sextet of - electrons, consisting of a pair of electrons from the protonated nitrogen atom and one from each of the remaining four atoms of the ring(Shalini, Sharma et al. 2010). The imidazole and derivatives have so many Pharmacological Activities like antitubercular ,antifungal ,analgesic ,anti-HIV , anticancer and antibacterial (Verma, Joshi et al. 2013).

Figure.1

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II. 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 2). Although various imidazole derivatives had been discovered earlier in the 1840[1].

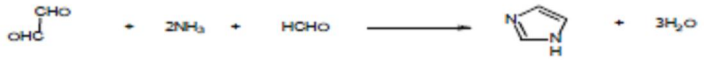

Figure.2

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 3)[6,7].

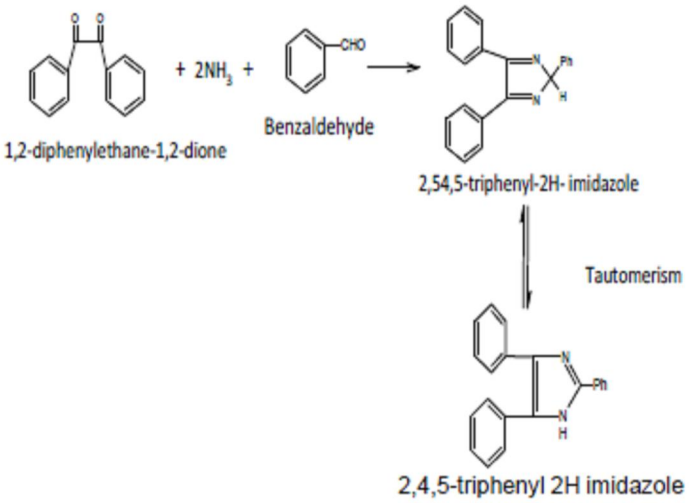

Figure.3

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 4) [5-8].

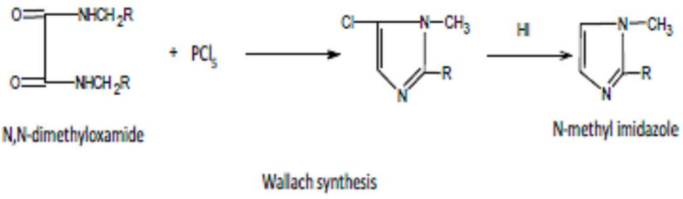

Figure.4

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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 5)[5].

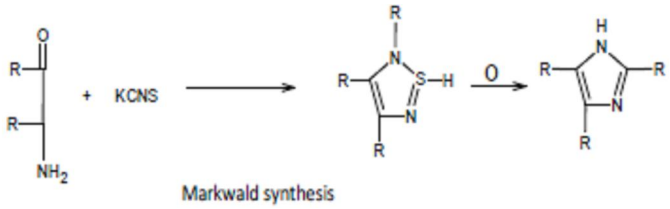

Figure.5

SCHEME - IV

Condensation of aldehyde and aminonitrile both under suitable reaction condition to give substituted imidazole (figure 6)[5].

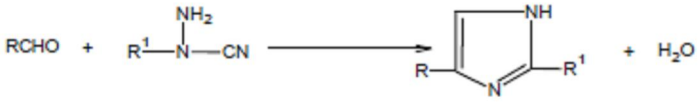

Figure.6

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 7)[5].

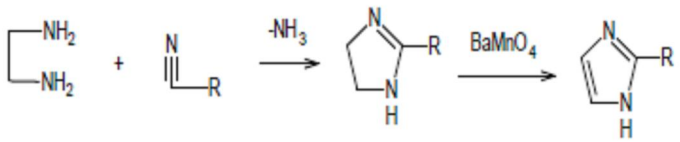

Figure.7

BIOLOGICAL ACTIVITIES

Imidazole has wide range of biological activities. 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]

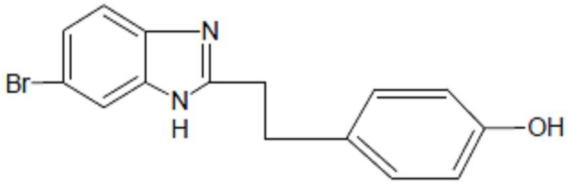

Figure.8

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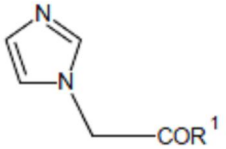
The scientists Namita Gupta *et al* synthesized N-substituted imidazole derivatives and the synthesized compounds are tested for in vitro antimicrobial activity against *Staphylococcus aureus, Bacillus subtilis* (Gram positive)*; Pseudomonas aeruginosa* (Gram negative), *Escherichia coli,* and *Candida 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.9

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].

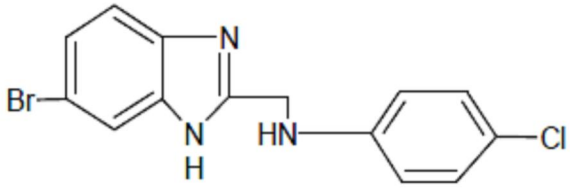


Figure.10

3. Anti-cancer activity

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

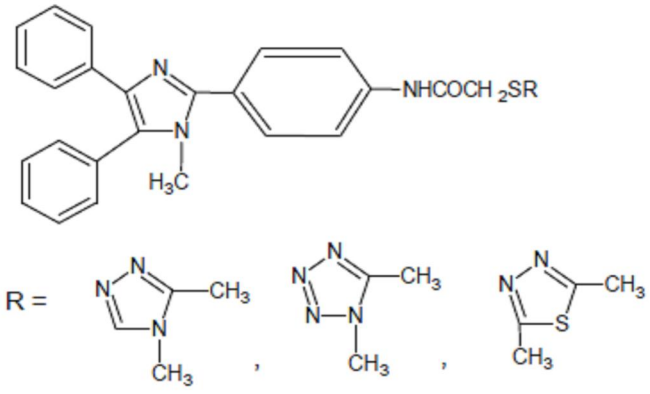


Figure.11

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].

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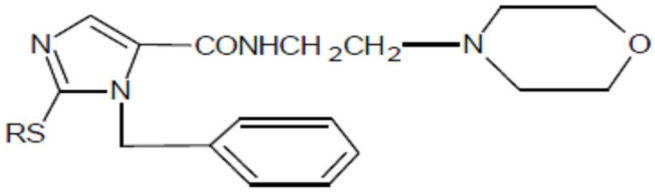
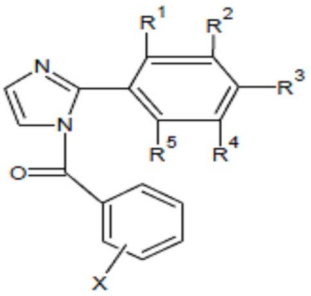


$R = CH_3, C_2H_5, CH_2C_6H_5$

Figure.12

Antiviral activity

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

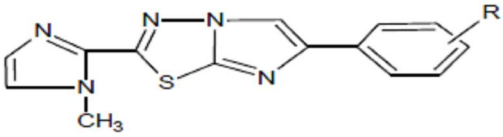


$R^1, R^2 = H$
$R^3 = Cl, NO_2$
$R^4, R^5 = H$
$X = 4\text{-}NO_2$

Figure.13

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.14

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III. CONCLUSION

Imidazole-based drugs have many uses in medicine and chemistry. They are active in treating different diseases. Studies have found that imidazole derivatives can work as anti-fungal, antibacterial, anti-inflammatory, analgesic, anti-cancer, antidepressant, anti-viral and anti-tubercular. By making small changes to the imidazole structure, scientists can make these drugs even more effective. Recent developments in imidazole drugs have shown improved results with fewer side effects. So, scientists are paying a lot of attention to researching imidazole derivatives because they have great potential for medical use.

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