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Green Synthesis Of Benzimidazole Analogues: An Overview

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ABSTRACT

Green chemistry gives importance to procedures of synthesis according to its well-known 12 principles, contributing to the sustainability, energy savings, lesser toxicity of reagents, intermediates and final products, lesser damage to the environment and human health, decreasing the risk of global warming, and more rational use of natural resources and agricultural wastes. In recent years, various heterocyclic compounds have synthesized owing to the extensive varieties of their pharmacological activities. Benzimidazole is an important Pharmacophore and privileged structure in medicinal chemistry which exhibits various therapeutic activities like antiulcer, antihypertensive, analgesic, antiviral, antifungal, antibacterial, anticancer, antihistaminic, anti-diabetic and anti-inflammatory. Because of its medicinal potential, the processes for their synthesis have become a focus of synthetic chemists. Therefore, this review focuses at compiling the chemistry of differently substituted benzimidazoles and greener methods.

Keywords: Benzimidazole, Green chemistry, Sustainable development, Bio-Active, Medicinal Chemistry, Pharmacophore and Biological agent.

Benzimidazole is considered as potential bioactive heterocyclic aromatic compound exhibiting remarkable pharmacological activities. It is an important pharmacophore and a privileged structure in medicinal chemistry.[1] This compound is bicyclic in nature which consists of the fusion of benzene and imidazole (Fig.1).[2] Historically, the first benzimidazole was prepared in 1872 by Hoebrecker, who obtained 2,5 (or 2,6)-dimethyl benzimidazole by carrying out reduction of 2-nitro-4-methylacetanilide.[2,]

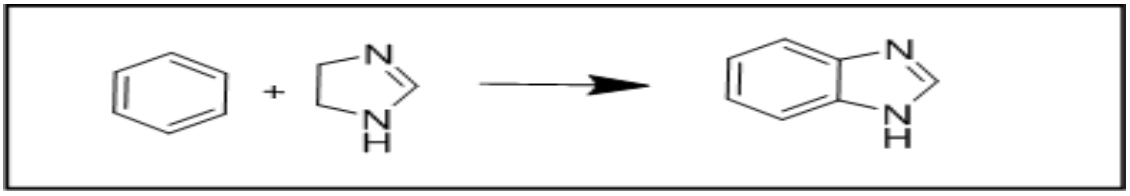

Fig. 1: Structure of Benzimidazole.

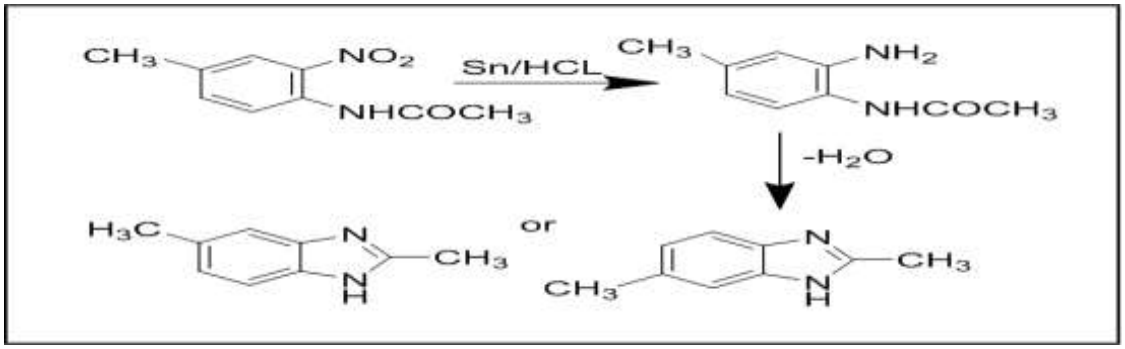

Fig. 2: Synthesis of first Benzimidazole in 1872 by Hoebrecker.

Benzimidazole plays a very important role in medical science having plenty of useful therapeutic activities such as: antiulcer,[4] anti-hypertensive,[5] analgesic,[6] antiinflammatory,[7] antiviral,[8] antifungals,[9] anticancer,[10] and anti-bacterial.[11]

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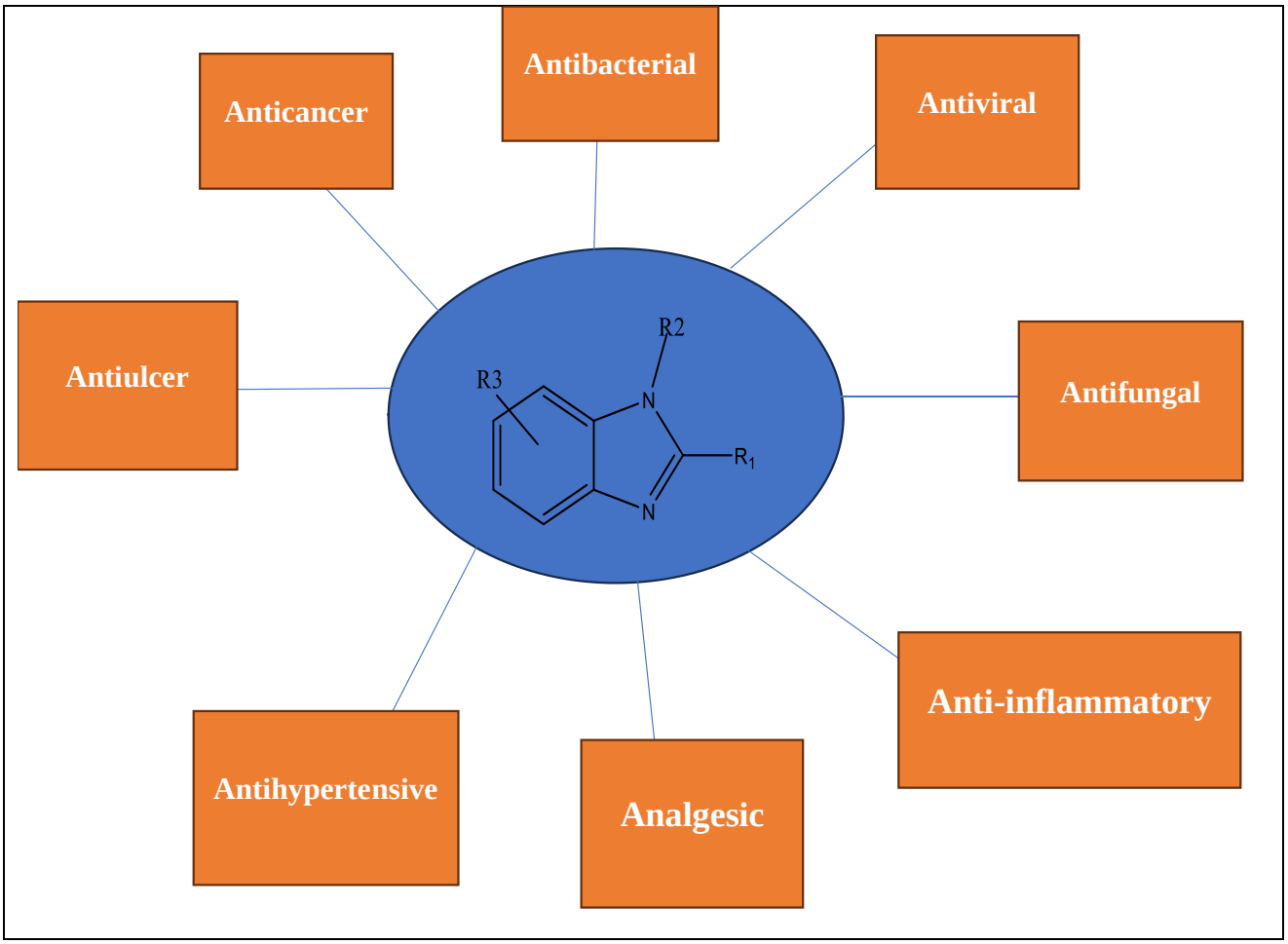
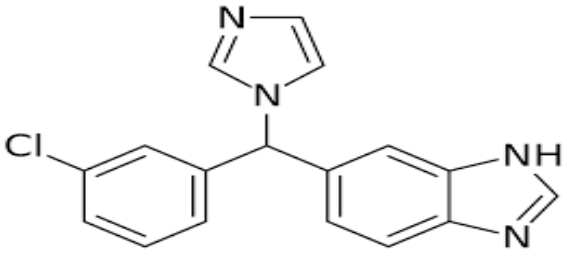
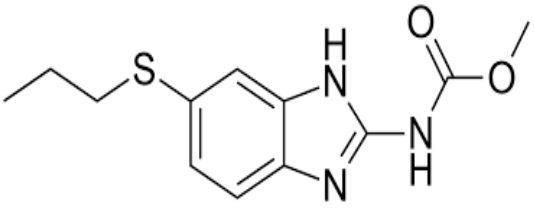


Fig. 3: Biological profile of heterocyclic benzimidazole derivatives.

In recent years, remarkable attention has been directed towards the advancement of benzimidazole heterocyclic molecules as antihistaminic 5-HT3 antagonist, e.g. lerisetron)[12], antimicrobial (antibiotic, e.g. ridinilazole)[13] antiulcer (proton pump inhibitor (PPI), e.g. ilaprazole)[14], antihypertensive (calcium channel blocker, e.g. mibefradil)[15], antiviral (non-structural protein inhibitor (NS5A), e.g. samatasvir)[16], antiparasitic (specifcally anthelmintic, e.g. Albendazole[17], antipsychotic (D2 receptor antagonist, e.g. clopimozide)[18], analgesic (opioid analgesic, e.g. clonitazene)[19], phosphodiesterase inhibitor (PDE3 inhibitor e.g. adibendan) and anticancer (aromatase inhibitor, e.g. liarozole, histone deacetylase inhibitor (HDAC), e.g. pracinostat) agents.[20]



Liarozole (Anti-Cancer)



Albendazole (Anthelmintic)

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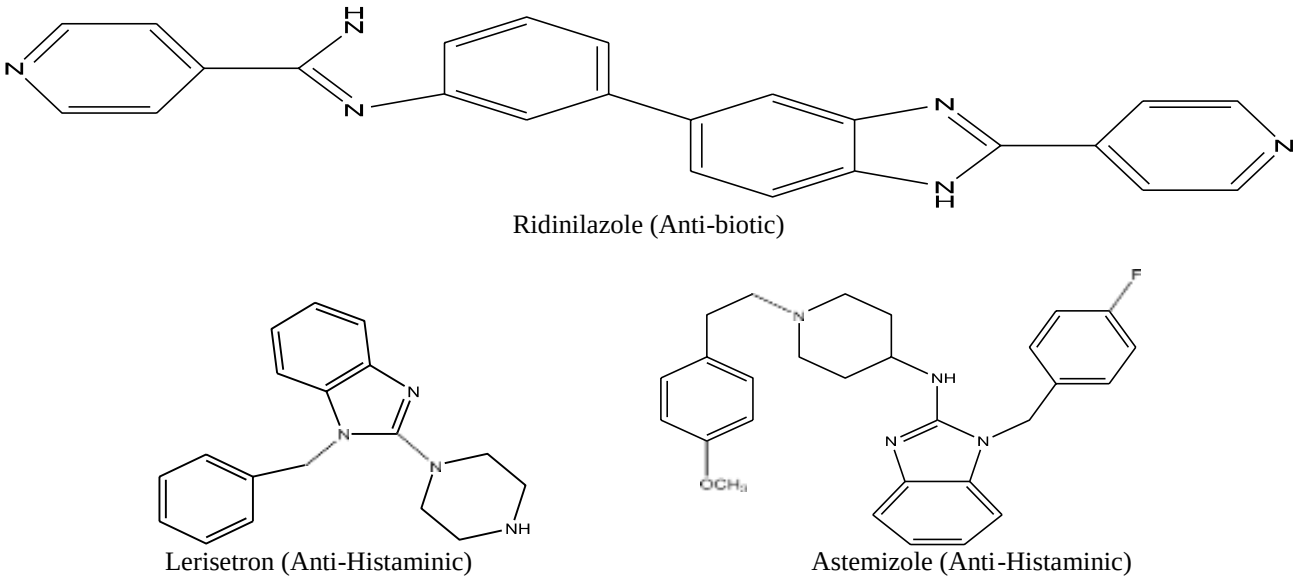


Fig. 4: Drugs Containing Benzimidazole Core Moiety.

In 1990, Paul Anastas and John Warner defined Green Chemistry: "The design of chemical products and processes that reduce or eliminate the use and generation of hazardous substances".
There are twelve principles of Green Chemistry. Paul T. Anastas and John C. Warner first published their 12 principles of Green Chemistry in their book, Green Chemistry: Theory and Practice, in 1998.[21]
In summary, the 12 principles are:
1.Prevent waste rather than treating it or cleaning it up.
2.Incorporate all materials used in the manufacturing process in the final product.
3.Use synthetic methods that generate substances with little or no toxicity to people or the environment.
4.Design chemical products to be effective, but reduce toxicity.
5.Phase-out solvents and auxiliary substances when possible.
6.Use energy efficient processes, at ambient temperature and pressure, to reduce costs and environmental impacts.
7.Use renewable raw materials for feed stocks.
8.Reuse chemical intermediates and blocking agents to reduce or eliminate waste.
9.Select catalysts that carry out a single reaction many times instead of less efficient reagents
10.Use chemicals that readily break down into innocuous substances in the environment.
11.Develop better analytical techniques for real-time monitoring to reduce hazardous substances.
12.Use chemicals with low risk for accidents, explosions, and fires.

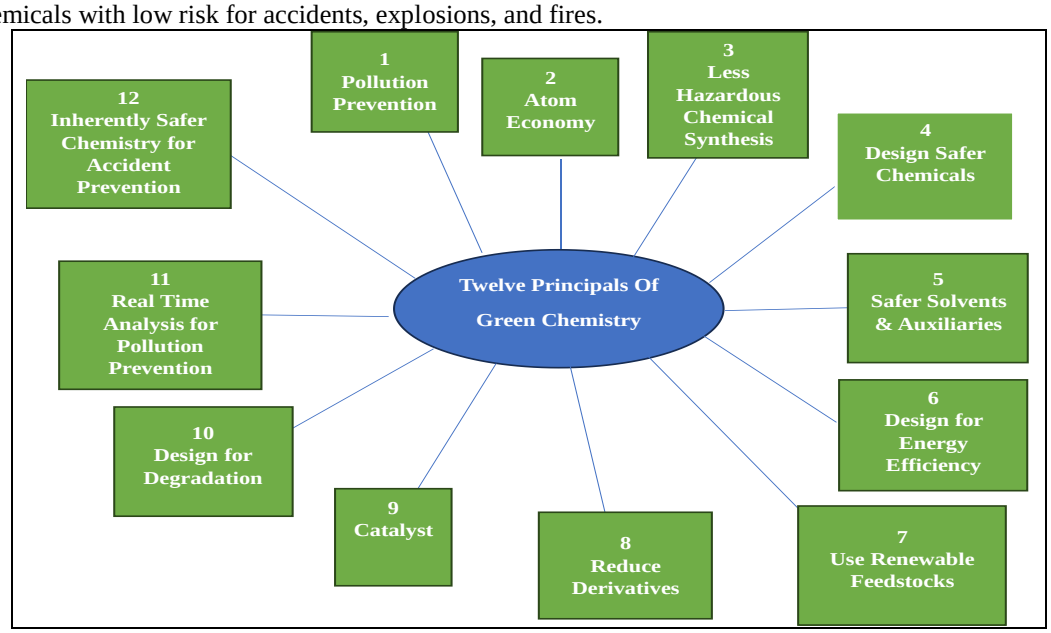
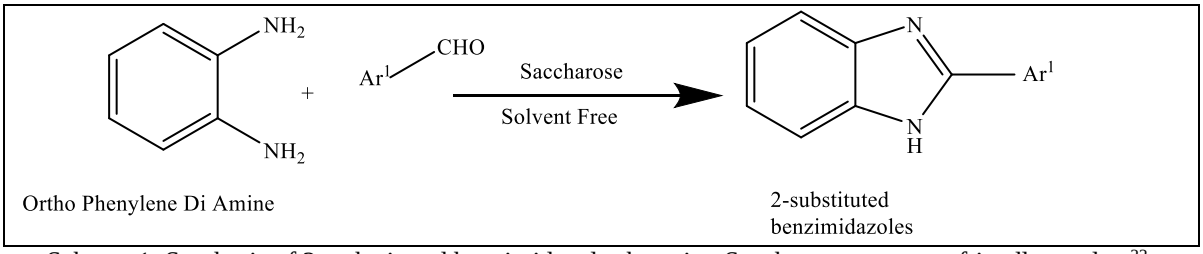


Fig. 5: Principals of Green Chemistry.

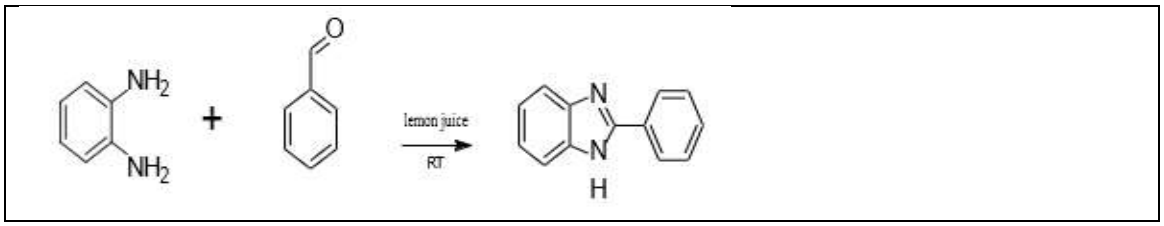
The present research paper is classified into two Green categories: 1. Synthesis of benzimidazole analogues by using plant-based catalysts. 2. Synthesis of benzimidazole analogues by using Micro-Wave Irradiation.

1. **Synthesis of benzimidazole analogues by using plant-based catalysts:**
In 2015, M. T. Maghsoodlou[22] and co-workers synthesized 2-substituted benzimidazoles by using saccharose as an eco-friendly catalyst. This method shows many advantages, such as using aqueous or solvent-free media, recyclable catalyst, low temperature, good yield, and bio-based nontoxic-catalyst.

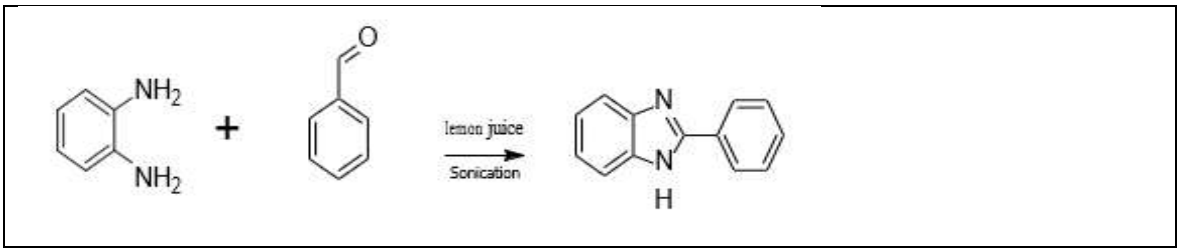


Scheme 1: Synthesis of 2- substituted benzimidazoles by using Saccharose as an eco-friendly catalyst[22].

In 2016, Gurumeet Wadhwa[23] et al synthesized substituted benzimidazoles through the one-pot reaction of phenylenediamine with various aldehydes in the presence of lemon juice as catalyst without any solvent. The reactions proceed smoothly in excellent yield, high chemo selectivity and with an easy work-up.

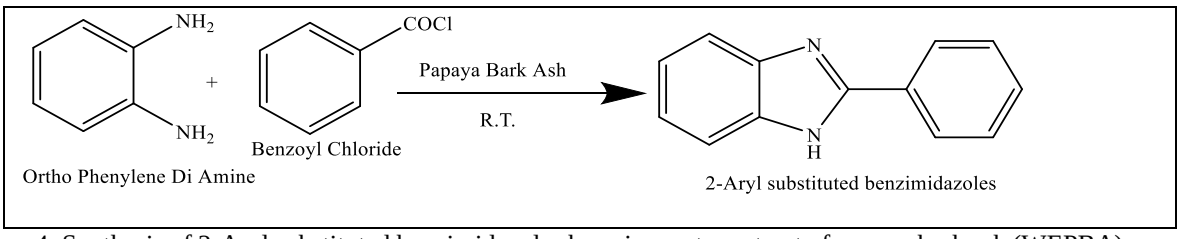


Scheme 2: Reaction of phenylene diamine with benzaldehyde at room temperature in the presence of Lemon Juice as Catalyst[23].



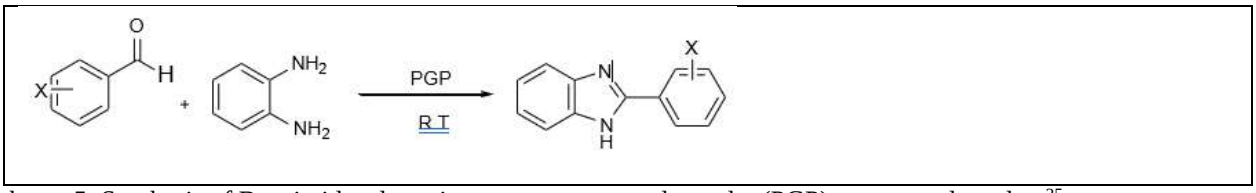
Scheme 3: Reaction of phenylene diamine with benzaldehyde (Sonication) in the presence of Lemon Juice as Catalyst[23].

In 2018, K. Kantharaju and Prashant Hiremath[24] developed a green route for the synthesis of 2-substituted benzimidazoles by the reaction of substituted
o-phenylenediamine with different substituted benzoyl chloride using water extract of papaya bark ash (WEPBA) as a green catalyst at room temperature. This method provides several added advantages of being completely green, economic, giving high yields and minimizing use of hazardous solvents.



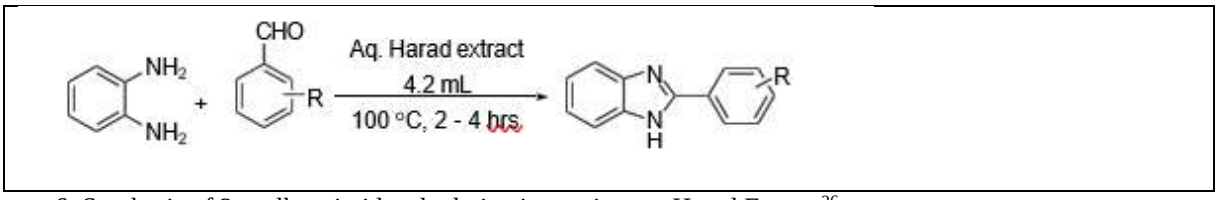
Scheme 4: Synthesis of 2-Aryl substituted benzimidazoles by using water extract of papaya bark ash (WEPBA) as a green catalyst at room temperature[24].

In 2021, Swati Ghodke[25] et al reported an efficient route for the synthesis of benzimidazole derivatives by the reaction of aromatic aldehydes and o-phenylenediamine at room temperature by using pomegranate peel powder (PGP) as a natural catalyst.



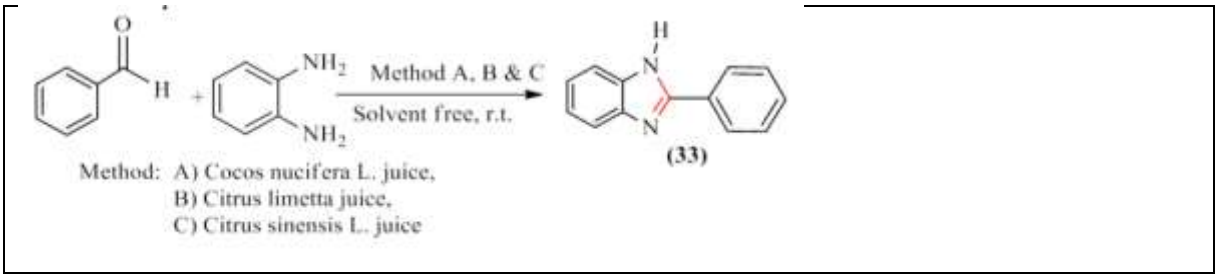
Scheme 5: Synthesis of Benzimidazoles using pomegranate peel powder (PGP) as a natural catalyst[25].

In 2021, Babita Veer[26] et al synthesized benzimidazoles by using Harad plant extract. Their research showed several advantages like mild reaction conditions, short reaction time, high yield, and reduced environmental impact.



Scheme 6: Synthesis of 2-arylbenzimidazole derivatives using aq. Harad Extract[26].

In 2021, Susheel Gulati[27] and co-workers reported a novel benzimidazole derivatives, synthesized from the condensation of substituted aldehydes and o-phenylenediamine using Cocos nucifera L.,
Citrus limetta, and Citrus sinensis L. fruit juice under the solvent-free condition at room temperature.

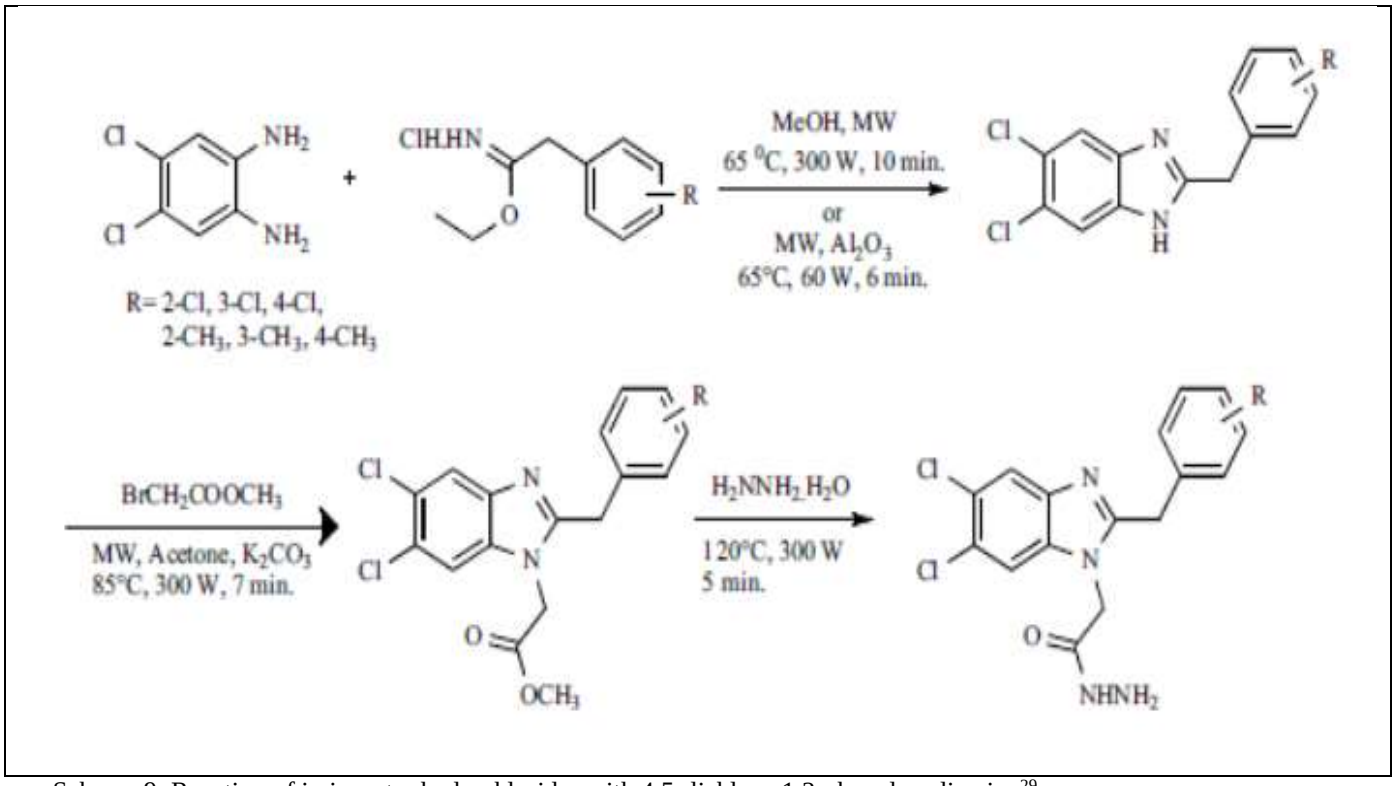


Scheme 7: Synthesis of 2-arylbenzimidazole derivatives using Method A, B & C(i.e. Cocos nucifera L., Citrus limetta, and Citrus sinensis L. fruit juice) [27].

In 2021, Prashant Hiremath and K. Kantharaju[28] synthesized 2-aryl benzimidazoles through the reaction of a substituted o-phenylene diamine with substituted benzoyl chloride catalyzed by Banana Peel Ash Extract (BPAE) under ultrasound waves at room temperature. They established an eco-friendly, sustainable and novel method for the synthesis of 2-aryl benzimidazoles using natural feedstock BPAE. The major merits of BPAE include its use as an agro waste derived catalyst. It is also highly abundant, inexpensive, yields faster reactions, has a simple workup, and this method does not require the use of column chromatography.

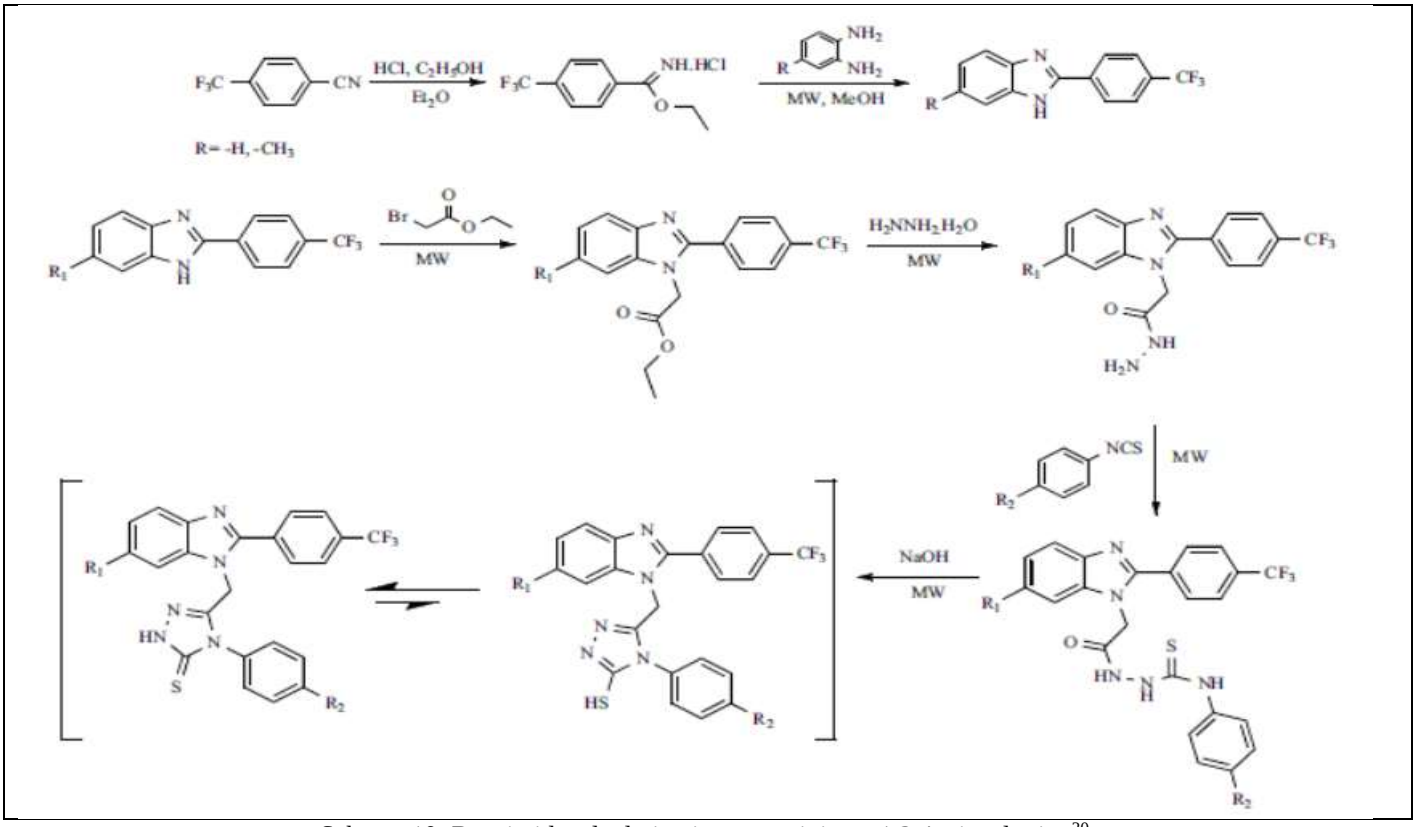
Scheme 8: Synthesis of 2-arylbenzimidazole derivatives using Banana Peel Ash Extract (BPAE) under-ultrasound-waves-at-room-temperature[28]

2. Synthesis of benzimidazole analogues by using Micro-Wave Irradiation:
In 2013, Kahveci[29] and co-workers developed a method for the synthesis of benzimidazole derivatives. This method uses imino ester hydrochloride with 4,5-dichloro-1,2-phenylenediamine under microwave irradiation. Require less reaction time.



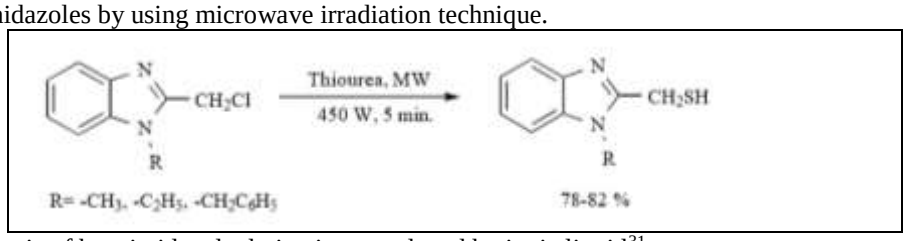
Scheme 9: Reaction of iminoester hydrochlorides with 4,5-dichloro-1,2-phenylenediamine[29].

In 2013, Menteşe[30] and co-workers reported microwave- assisted synthesis and biological evaluation of some benzimidazole derivatives containing a 1,2,4-triazole ring. This method is very effective and provide pure products in few minutes.



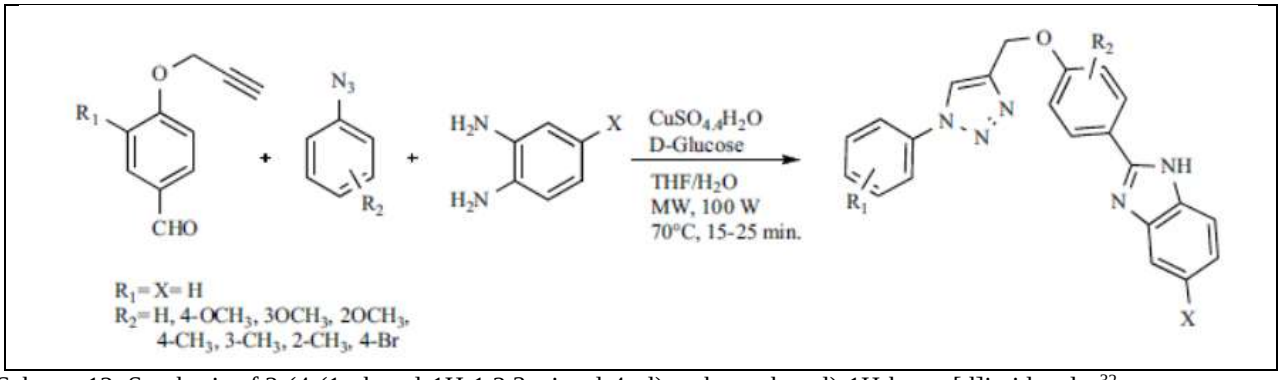
Scheme 10: Benzimidazole derivatives containing a 1,2,4-triazole ring[30].

In 2014, S. Srinivas Rao[31] and co-workers reported a green approach for the synthesis of N-alkyl-2-thiomethylbenzimidazoles by using microwave irradiation technique.



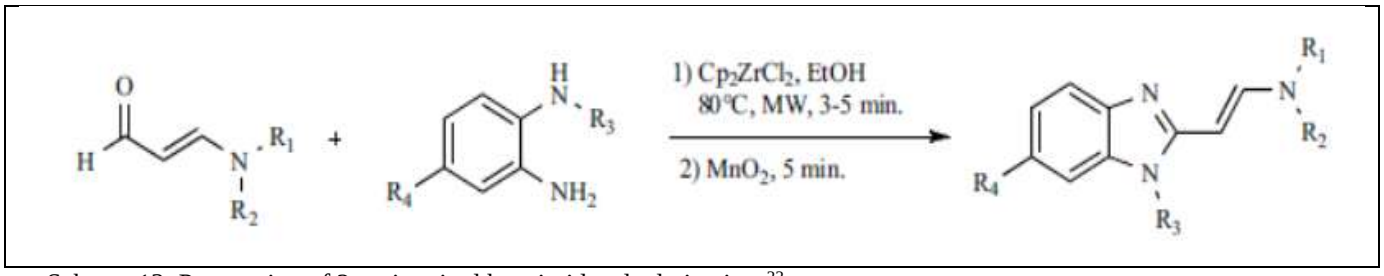
Scheme 11: Synthesis of benzimidazole derivatives catalyzed by ionic liquid[31].

Yagesh Kumar[32] et al. (2014) improved a novel micro- wave-assisted CuI-catalyzed one-pot reaction for the synthesis of 2-(4-(1-phenyl-1H-1,2,3-triazol-4-yl)methoxyphenyl)-1H-benzo[d]imidazoles.



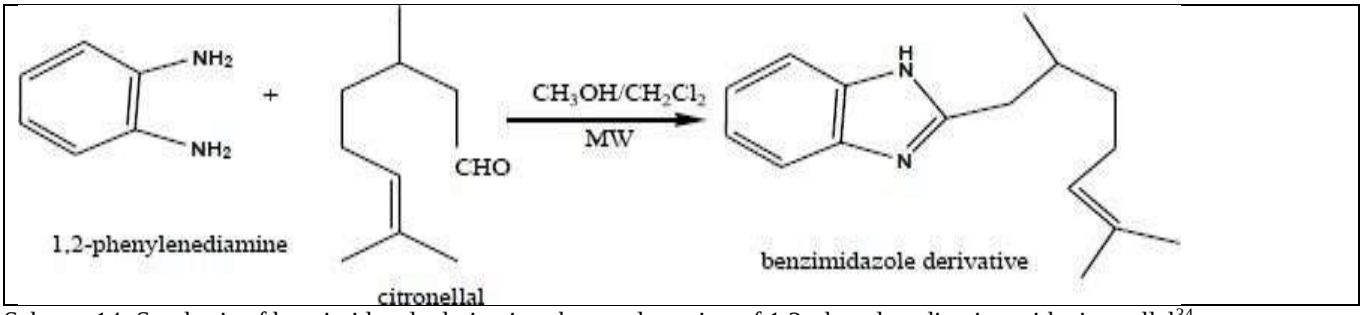
Scheme 12: Synthesis of 2-(4-(1-phenyl-1H-1,2,3-triazol-4-yl)methoxyphenyl)-1H-benzo[d]imidazoles[32].

In 2015 Sun Q[33] and co-workers Synthesized a series of 2-aminovinyl benzimidazole derivatives were synthesized by the reaction of 1,2-Phenylenediamines and-N-arylated/N,N-dialkylated-3-amino acroleins-with bis(cyclopentadienyl)zirconium(IV) dichloride (Cp2ZrCl2) as the catalyst under microwave irradiation, which resulted in good-yield.



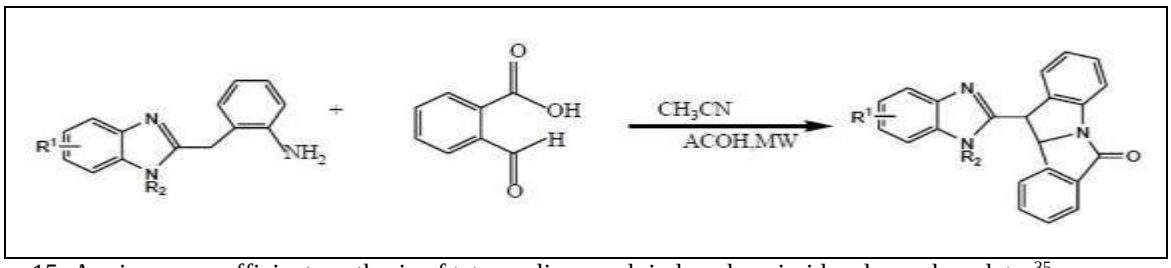
Scheme 13: Preparation of 2-aminovinyl benzimidazole derivatives[33].

Dwi Sapri Ramadhan[34] et al in 2018 reported in their paper about development of an efficient protocol for the condensation process of 1,2-phenylenediamine with citronellal in polar media (by using Microwave irradiation) describing the synthesis of benzimidazole derivatives.



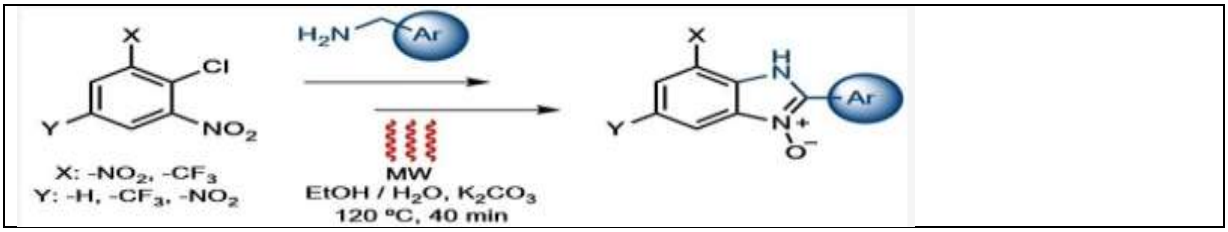
Scheme 14: Synthesis of benzimidazole derivatives by condensation of 1,2-phenylenediamine with citronellal[34].

A microwave efficient synthetic pathway for tetracyclic pyrroloindone benzimidazole-carboxylates via 2-subsituted carboxaldehydes reported by Yun-ta Lee[35] et al in 2019.



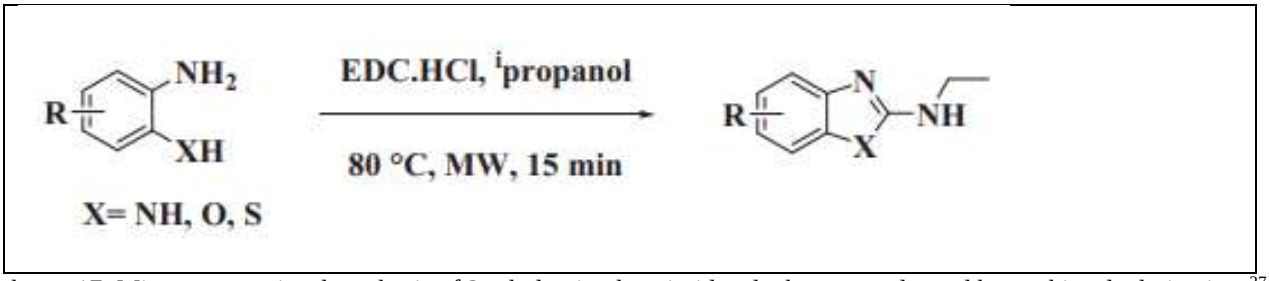
Scheme 15: A microwave efficient synthesis of tetracyclic pyrroloindone benzimidazole- carboxylates[35].

In 2019, Nicholas E. Leadbeater[36] and coworkers reported in Molecules the preparation of 2-aryl-benzimidazole-3-oxide derivatives via a one-pot two-step protocol, and prepared 42 new compounds.



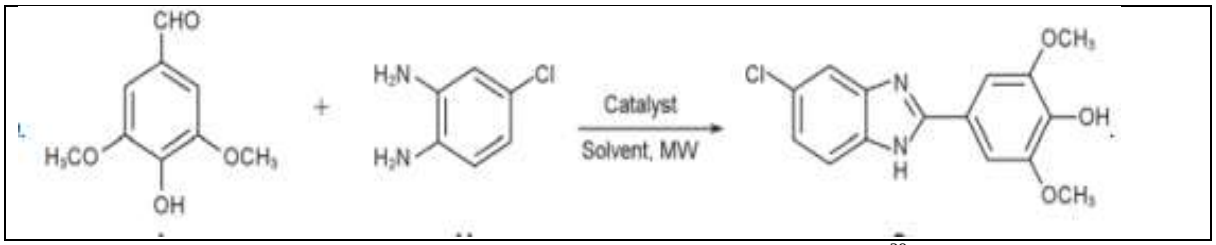
Scheme 16: Synthesis of 2-aryl-benzimidazole-3-oxide derivatives[36].

A rapid and efficient one-pot method for the synthesis of 2-ethylamino benzimidazole, benzoxazole, and benzothiazole derivatives has been described by Thirupati Rapolu[37] and co-workers in 2019.



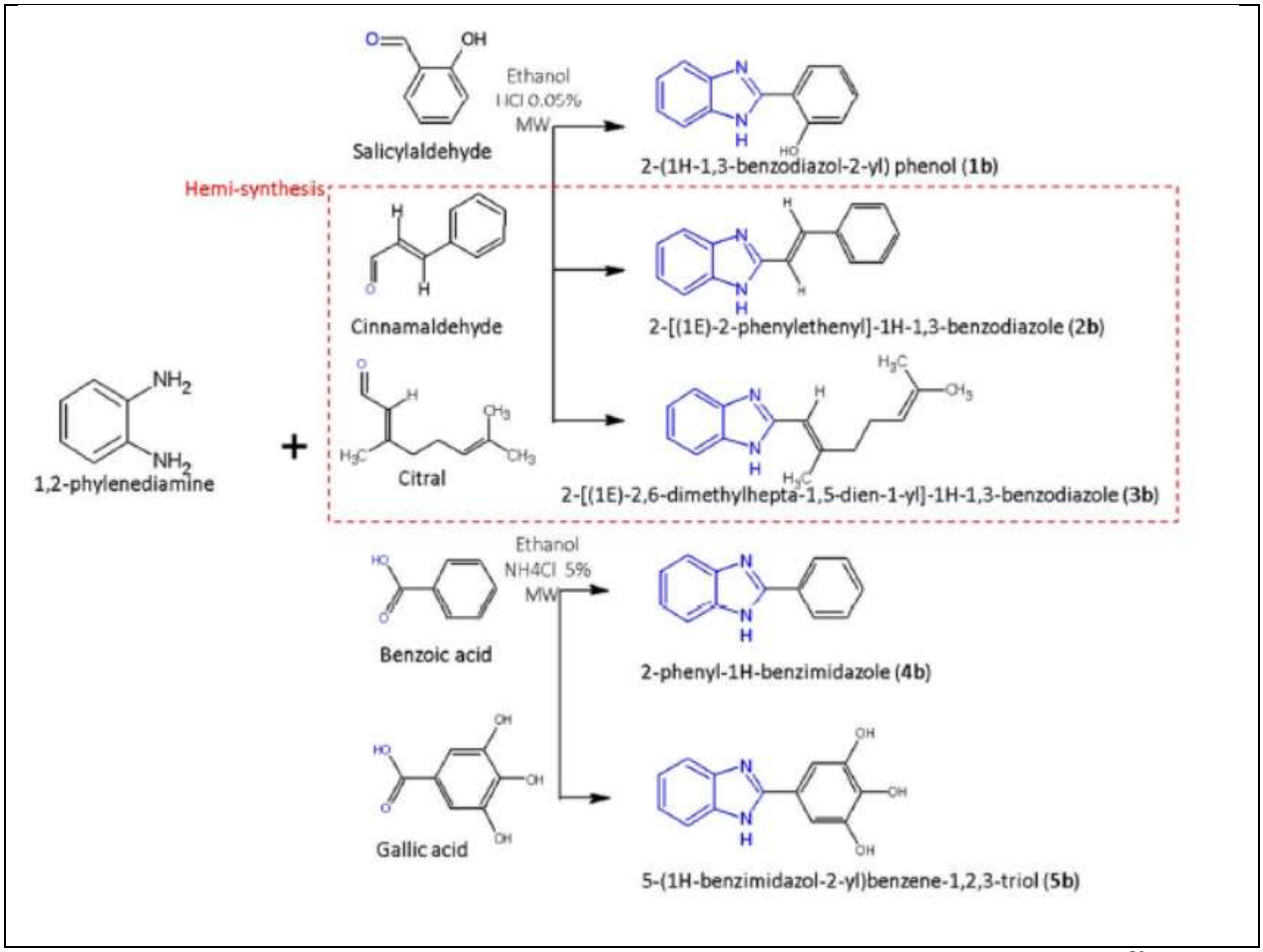
Scheme 17: Microwave assisted synthesis of 2-ethylamino benzimidazole, benzoxazole, and benzothiazole derivatives[37].

YAN Liuqing[38] and co-workers reported microwave assisted an efficient and facile method of synthesis of benzimidazoles bearing phenolic hydroxyl in 2020. This paper concluded that microwave heating has shortened the reaction time as compared to conventional-heating.



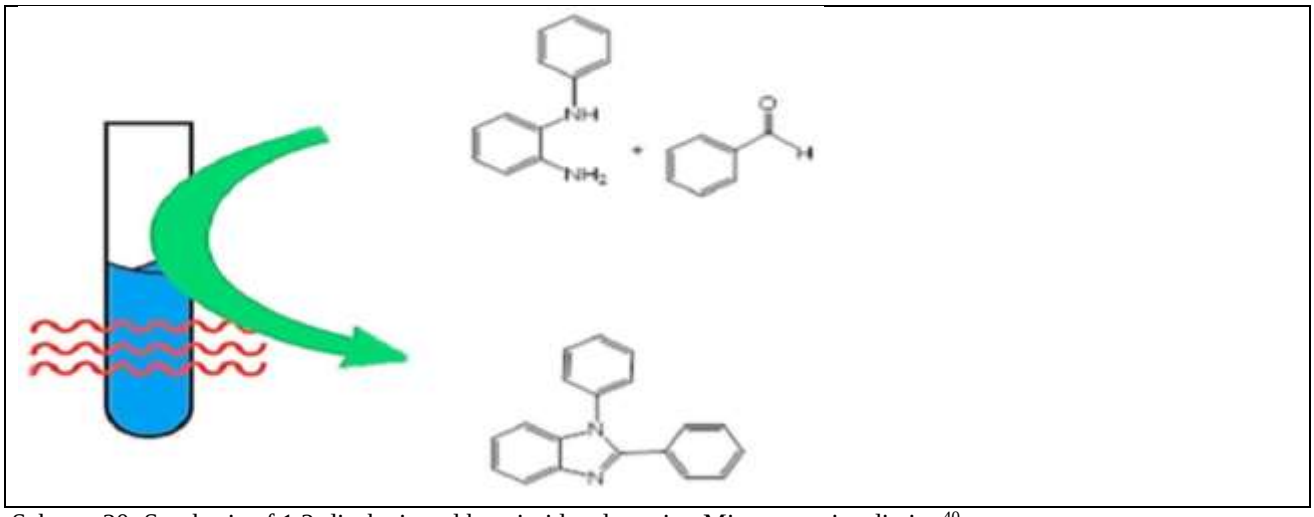
Scheme 18: Microwave assisted synthesis of benzimidazole bearing phenolic hydroxyl[38].

In 2021, Asmaa Sameut[39] and co-workers reported a method of microwave assisted chemical synthesis and hemi-synthesis of novel benzimidazole derivatives. In this method five new benzimidazole derivatives were prepared by reacting o-phenylenediamine with several aldehydes and phenolic acids through chemical synthesis and hemi-synthesis using a quick microwave-assisted-processes



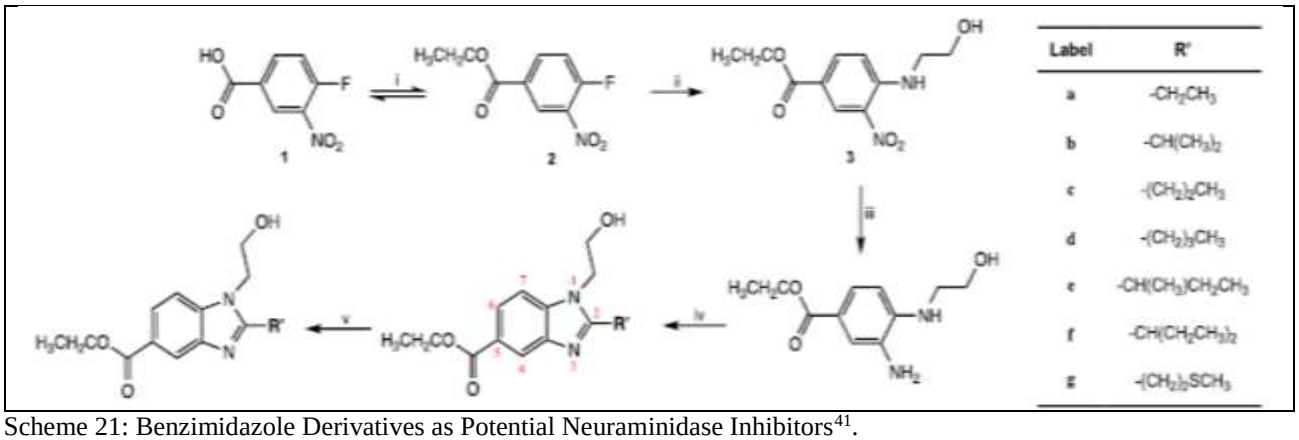
Scheme 19: Microwave assisted chemical synthesis and hemi-synthesis of novel benzimidazole derivatives[39].

In 2022, Monica Nardi[40] and co-workers reported highly efficient synthesis of 1,2-disubstituted benzimidazoles using Microwave irradiation. The combination of the molar ratio of N-phenyl-o-phenylene diamine: benzaldehyde (1:1) using microwave irradiation and only 1% mol of Erbium(III)trifluoromethanesulfonate [$Er(OTf)_3$] provides an efficient and environmental mild access to a diversity of benzimidazoles under solvent-free-conditions.



Scheme 20: Synthesis of 1,2-disubstituted benzimidazoles using Microwave irradiation[40].

Nurasyikin Hamzah[41] and co-workers recently in 2023 reported microwave assisted synthesis of benzimidazole derivatives as potential neuraminidase inhibitors. In their present study they have synthesized two series of benzimidazole analogues and they have concluded that microwave reactions were more effective than conventional methods.



Scheme 21: Benzimidazole Derivatives as Potential Neuraminidase Inhibitors[41].

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The author sincerely thanks Department of Chemistry, N. G. Acharya and D. K. Marathe College of Arts, Science and Commerce, Chembur, Mumbai; as well as Department of Chemistry, University of Mumbai, Kalina for the constant support and valuable suggestions for completing this manuscript.

Conflict of Interest
The author declares no conflict of interest.

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