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RECENT ADVANCES WHILE PREDICTIONS WITHIN THE PHARMACEUTICAL SCIENCES WITH REGARD TO BENZIMIDAZOLES

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ABSTRACT
A ring consisting of benzine in addition to an imidazole are fused to generate the heterocyclic molecule benzimidazole, which has two molecules of nitrogen. O-phenylenediamine can be condensed with carbonyl-based substances (also referred to aldehyde and ketones) or with aromatic acids and their derivatives to create benzimidazoles and its analogues. Another method for creating benzimidazole's is to rearrange other heterocyclic in shape substances like triazole-derived substances and quinoxaline analogues. This analysis focusses regarding a benzimidazoles medicine called along with its related compounds, the most significant methods employed for their diligence, and finally on the biological functions of the exacerbate in everyday situations. In the past few years, medicinal products have been manufactured through ecological techniques like microwaveable appliances and ultrasound procedures, the use of recyclable catalysts, approximately and reactions involving photosynthesis. These substitutes have drawn the attention of investigators and researchers due to their wonderful healthcare the effectiveness disregarding multiple medical conditions. The compounds derived from benzimidazole demonstrate several pharmaceutical effects, including cancer prevention. anti-inflammatory, anti-aging, anticoagulant medication, and antiviral in nature.

Keywords: *benzimidazole, Antiparasitic, heterocyclic, anthelminthic, B-12 vitamins.*

1. INTRODUCTION

Existence depends on heterocyclic in structure chemicals, which have been widely recognised in environment. Through every phase living cell's digestion has recently been significantly impacted through heterocyclic chemicals [1]. In recognition of humans, nitrogen-based compounds with heterocyclic nature are crucial. Benzimidazole, specifically more detail, represents nitrogen-based hydrocarbon molecule of great pharmacological and economic significance. Hobrecker created the initial benzimidazole analogue around 1872 [2]. Goodman and Nancy Hart disclosed groundbreaking research investigating the medical Features about benzimidazole around the year 1943. subsequently early 1944, the research of Woolley revealed that several benzimidazole compounds have antibacterial features. Around 1949, however, Norman's GB and Karl Folker identified 5, 6-dimethyl phosphate benzimidazole as a breakdown byproduct following the stomach acid decomposition throughout B-12 vitamins. DNA, amino acids, protein molecules, including micronutrients all include nitrogen-containing hetero bikes. The biological further exacerbate benzimidazole

comprises heterocyclic and smells fragrant. As translational antagonists binding cobalt, which throughout the form of vitamin B12, n-ribosyl the presence of dimethyl benzimidazole is probably the most abundant chemical-based found in environment that contains a benzimidazole framework [3]. Since imidazole's are have therapeutic qualities and could potentially utilised to make a variety of medications, these individuals are very significant combinatorial chemicals. Imidazole which a rectangular hetero-pentacyclic molecule having a fundamental structure of $C_3H_4N_2$, dissolves readily in highly polar liquids including water due to its predicted polarisation of 3.61. This amphoteric chemical has the ability to function as either an acidic or basic in nature substance. Two analogous tautomeric molecules of imidazole molecules are 1H-imidazole as well as 3H-imidazole, as the hydrogen atom can change from one of the nitrogen molecules to a different one as shown in Fig.1and Fig.2 and Various Marketed drug of benzimidazole as core moiety shown in Fig.3 [4].

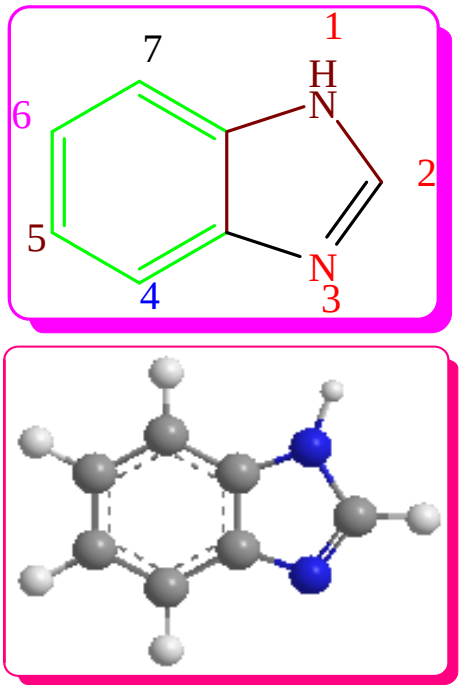


Fig.1 Structure of Benzimidazole Fig.2 3D Structure of Isatin Benzimidazole

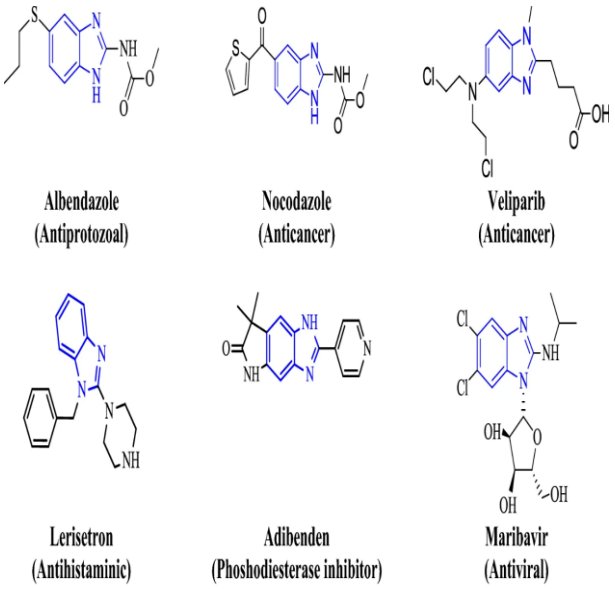


Fig. 3 Various marketed drug of benzimidazole as core moiety

Table .1 Details about benzimidazole with biological activity [5]

Sr. No.	Benzimidazole derivative	biological activity
1	Albendazole	Antiparasitic, anthelminthic
2	Mebendazole	Antiparasitic, anthelminthic
3	Metronidazole	Antibacterial, antiprotozoal
4	Omeprazole	Proton pump inhibitor
5	Lansoprazole	Proton pump inhibitor
6	Etofylline Bronchodilator	Bronchodilator
7	Levamisole	Immunomodulator, anthelmintic
8	Domperidone	Antiemetic
9	Meclizine	Antihistamine, antiemetic
10	Vardenafil	Erectile dysfunction treatment
11	Lansoprazole	sulphide Proton pump inhibitor
12	Astemizole oxide	Antihistamine, antiarrhythmic
13	Niclofolan	Anthelmintic
14	Clopidogrel	Antiplatelet
15	Rabeprazole sulphide	Proton pump inhibitor
16	Oxfendazole	Antiparasitic, anthelmintic
17	Thiabendazoles	Antiparasitic, anthelminthic
18	Itraconazole	Antifungal
19	Ketoconazole	Antifungal

20	Tinidazole	Antibacterial, antiprotozoal
21	Praziquantel	Anthelmintic
22	Tinidazole	Antibacterial, antiprotozoal
23	Nimorazole	Antibacterial, antiprotozoal
24	Mebendazole oxide	Antiparasitic, anthelminthic
25	Risperidone	Antipsychotic
26	Oxibendazole	Antiparasitic, anthelmintic
27	Carbendazim	Antifungal, antiparasitic
28	Albendazole sulfoxide	Antiparasitic, anthelminthic
29	Pantoprazole	Proton pump inhibitor
30	Niclosamide	Anthelmintic, antiparasitic

Recognised because of their merged benzene with imidazole molecules ring framework, benzimidazole's have several geometric nuances that make them crucial to their therapeutic properties. Examining the impact of radical modifications on the biological process and elucidating the relationship between structure and activity (SAR) concepts underlying govern how they collaborate with biologically relevant substances, the present chapter delves into the basic economic stability properties of benzimidazoles and various registered medications using a drug called benzimidazole as the main ingredient as shown in Fig. 4.as well as in Fig.5 [6-8]..

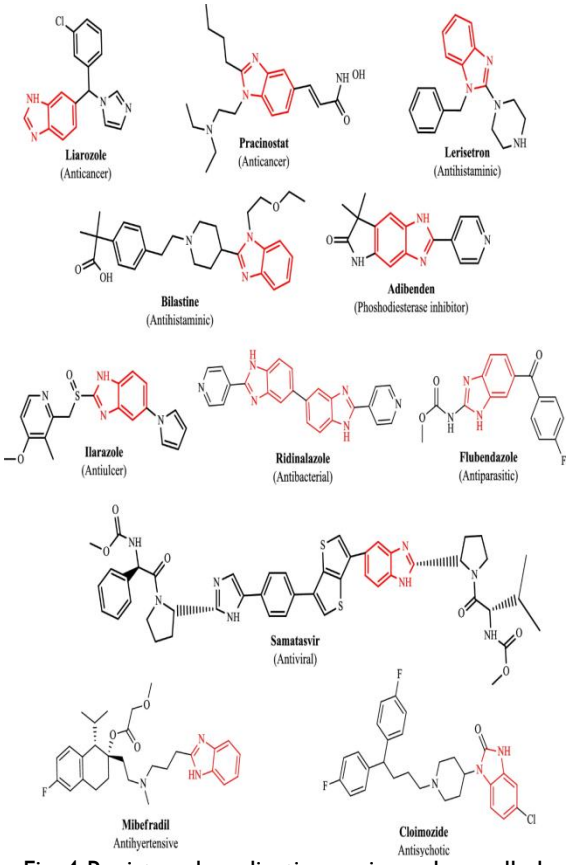


Fig. 4 Registered medications using a drug called benzimidazole as the main ingredient

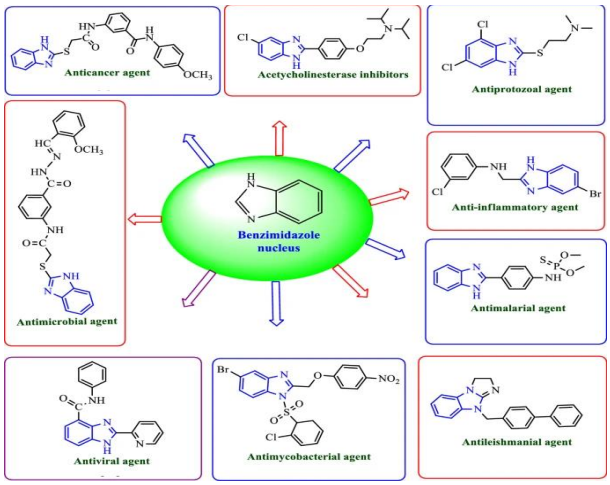


Fig.5 shows an objective approach inspired by a study of the published literature regarding benzimidazole analogues.

A hetero aromatic chemical having an amphoteric properties feature, benzimidazole is bicyclic and consists of a benzene merged together with an imidazole loop. antispasmodic, antibacterial, antioxidant, anticancer, antimicrobial, anti-inflammatory, antibacterial, anti-fungal, antiviral, antibacterial, antipsychotic, and antihistaminic properties are among the many properties displayed by this special architecture. Mebendazole as well as albendazole, the antibiotic thiabendazole, omeprazole,

lansoprazole, pantoprazole, astemizole, enviroxime, candesartan, cilexitil, telmisartan, and many other medications for the treatment of various illnesses are the products resulting from studies on the benzimidazole core [9-10].Benzimidazoles primarily decrease inflammation through associating with certain cytokines, including the 5-lipoxygenase stimulating proteins such as the enzyme cyclooxygenase (also known as COX), the cannabinoid receptors, bradykinin receptors, and momentary sensory physiological vanilloid-1, respectively [11-12].

1.1 Associations Between Benzimidazole Substitute' Structure and Effectiveness effective Anti-Inflammation Medications

Replacements within the N1 along with C2, C5, as well as C6 locations within the benzimidazole core significantly affect the anti-inflammatory action, according to the published SAR study. Benzimidazole's N1 heterocycle replacements provide different medicines their potent anti-inflammatory properties [13-15].

By combining the benzimidazole compound alongside anacardic acid, Paramashivappa and colleagues created analogue of benzimidazoles in 2003 as well as assessed their inhibitory of COX-2 efficacy in humans (Figure 6). Strong anti-inflammatory properties were demonstrated by a molecule having R = H and R1 = methoxy moiety, which inhibited COX-2 significantly 384-fold specificity over COX-1.The significance of benzimidazole's "NH" constituent in its anti-inflammatory action was further supported by the results of the investigation. nevertheless, benzimidazole's C5 displayed considerable reduction when –CH3 or –NO2 were substituted, whereas –OCHF2 did not exhibit a beneficial antagonistic effect as discuss in Fig 6 [16-18].

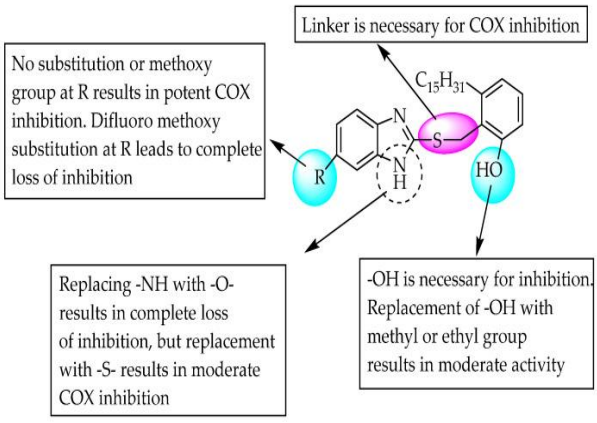


Fig. 6 (SARs) of derivatives of benzimidazoles coupled with analogous acid.

Bukhari et al. (2016) investigated the inhibition of COX and 5-lipoxygenase by a few 2-phenyl-substituted benzimidazoles, among other compounds. Figure 7 illustrates that while amine group substitution at R1 improved the inhibitory effects of each of the three enzymes, the group substituting at R2, R3, and R4 is favoured for COX-1 and 2, as well as 5-lipoxygenase inhibition. nevertheless, a hydrophilic group strengthens COX-2 inhibition, a methoxy alteration promotes 5-lipoxygenase limitation, while a lipophilic addition at R5 promotes COX-1 suppression [19-22].

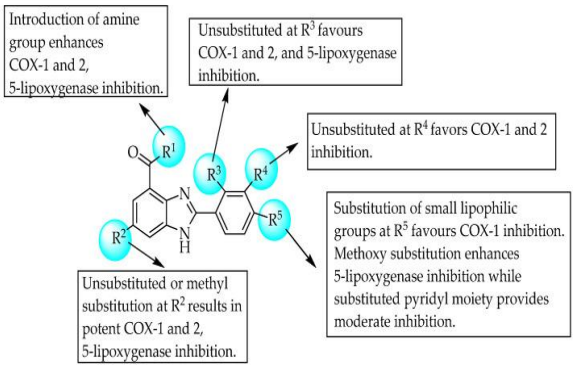


Fig. 7 Methyl-substituted benzimidazole. SARs

1.2 Characteristics about benzimidazoles' spectrum

1.2.1 Infrared (IR) spectroscopy

The main points aryl-based ring is present within the benzimidazole wavelengths of absorption close to the 2850A°, where the N-H stretching is present adjacent to the 3107A°, as well as the C-N stretching is present adjacent to about 1690A° [23].

1.2.2 Spectroscopic by mass

Conventional benzimidazole and imidazole molecules cleavage mechanisms are comparable.2 different hydrogen cyanide the molecules are sequentially lost to create the molecular ion, according to the benzimidazole spectrum. The first of these molecules is nonspecific, as shown by deuterium labelling techniques. Loss of carbon monoxide from the molecular ion is a hallmark of 2-acylthiophenes, 2-acyl group, along with 2-benzoylbenzimidazoles, whereas the removal of ethylene, which is from the polymeric ion is an identifiable feature of 2-npropylbenzimidazole cleavage [24-26].

1.2.3 Nuclear magnetic resonance (NMR) spectroscopy

An important feature of this work is that the protonation parameters derived from simple five and six membered heterocycles can be used to predict chemical shift changes resulting from nitrogen protonation and deprotonation in more complex molecules. δ7-9 values show multiples indicates the presence of benzimidazole aryl ring [27].

1.2.4 C13NMR

In contrast to TMS, which is the spectrum is shown to display distinct carbssson peaks in the 0-200 range. The range for benzimidazoles begins at δ115 and ends at 144.Through obtaining triplet and doublet peaks, overlapping may be easily verified. Proton-less carbon compounds are indicated by minimal intensity peaks. Thus, the location of the carbonyl cluster is identified. Techniques for Synthetic of Benzimidazole Trading derivatives: Characterizations of the Carbonyl compounds Identify Configuration [28-30].

1.2.5 Physical properties of benzimidazoles

The melting point of number of the benzimidazoles indicated that the introduction of a substituent into 1-position in general lowers the melting point. Benzimidazoles with the imide nitrogen are usually soluble in polar solvents and less soluble in organic solvents. With introduction of other non-polar substituents in various positions of the benzimidazole ring, the solubility in nonpolar solvents is increased. Conversely, the introduction of polar groupings into the molecule increases solubility in polar solvents. Benzimidazole distils unchanged above 300 C. Benzimidazoles are weakly basic, being somewhat less basic than the imidazole's and are in general soluble in dilute acids. Benzimidazoles are also sufficiently acidic to be generally soluble in aqueous alkali and form Unmetallic compounds. The acidic properties of the benzimidazoles, like those of the imidazole's, seem to be due to stabilization of ion by resonance. The more acidic benzimidazoles may be soluble in less basic solution, such as potassium carbonate solution [31-33].

1.2.6 Chemical properties of benzimidazoles

Benzimidazole has 2 nitrogen-containing atoms within its arrangement-one pyridine-type (fundamental) along with a resembles pyrrole (acidic)-it constitutes a fusion aromatically heterocyclic molecule with considerable chemistry plasticity. It may therefore form salts with strong acids and donate a proton from its NH group, exhibiting amphoteric behavior, serving as simultaneously a weak base and a weak acid [34]. The compound's responsiveness and spectrum characteristics are affected by tautomerism, a process in which a proton moves between the two nitrogen atoms.Because it is fragrant, the compound benzimidazole is chemically impermeable, although it is still explosive at certain locations. On the benzene ring, for instance, it easily undergoes electrophilic substitution reactions (like nitration and halogenation), while the C2 position is vulnerable to nucleophilic attack because of its electron-deficient nature. It can also go through acylation and N-alkylation processes at the nitrogen atom, creating several derivatives. Benzimidazole's involvement in living things and coordination chemistry is further enhanced by its participation in hydrogen bonding and metal coordination via its nitrogen atoms. Overall, it is a significant and versatile substance in chemical synthesis and pharmaceutical applications due to its distinct electrical configuration & responsiveness[35-38].

The framework of the compound benzimidazole, as depicted in Fig.8, shows that the benzimidazoles have a phenyl ring that is bonded together with an imidazole ring [39].

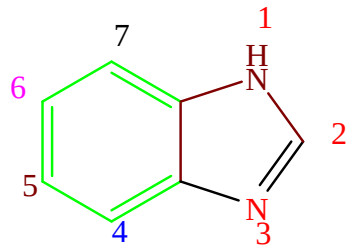
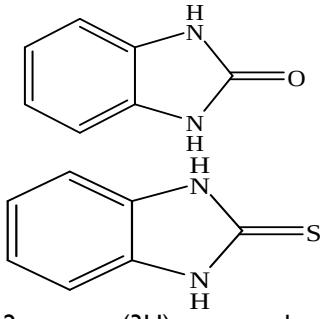


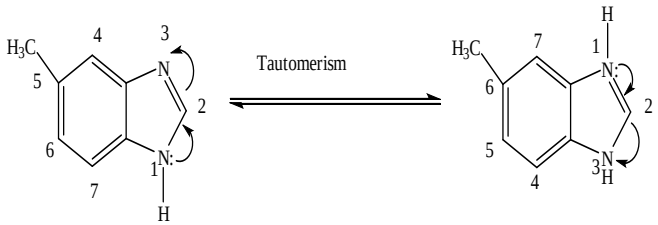
Fig.8 Benzimidazole Structure

Hoebrecker created the initial one benzimidazole chemical in 1872 by reducing 2-nitro-4-methylacetanilide to get 2,5- (also known as 2,6-) dimethyl benzimidazole. Throughout the literature, benzimidazoles have been referred to by a number of names, notably benzoglyoxalines. These have frequently been referred to as o-phenylenediamine counterparts in previous research; for example, benzimidazole was named methenyl-o-phenylenediamine, and 2-methylbenzimidazole was dubbed ethenyl-o-phenylenediamine. They are also regarded as derivatives of the imidazole moiety in the fused ring system under alternative nomenclature scheme. Benzimidazole medication called was additionssally found as o-phenylene formamidine, a compound under this technique. Similarly, o-phenyleneurea as well as o-phenylene thiourea both are alternate names for similar compounds like 2(3H)-benzimidazolone and 2(3H)-benzimidazolethione [40-42].



2 (3H)-benzimidazolone

2 (3H) benzimidazolethione



(Fig. 9) Tautomerism in benzimidazoles

Benzimidazole, with the molecular formula $C_7H_6N_2$, is a planar aromatic heterocycle characterized by extensive π-electron delocalization. Its structure contains two distinct nitrogen atoms: one behaves like a pyridine-type nitrogen with basic character, while the other resembles a pyrrole-type nitrogen bearing an acidic NH group [43]. This combination creates regions of both high and low electron density within the molecule, contributing to its diverse reactivity. Benzimidazole exhibits amphoteric behaviour, meaning it can function as both an acid and a base; it has a conjugate acid pKa

of around 5.6 and an NH proton pKa near 12.8. Consequently, it can form salts with strong acids such as hydrochloric acid and nitric acid, shows relatively weak basicity compared to imidazole, and can donate a proton through its NH group. Another important feature is its prototrophic tautomerism, in which a proton shifts between the two nitrogen atoms, resulting in equivalent forms in solution that influence both its chemical reactivity and spectroscopic properties. The reactivity of benzimidazole is largely governed by electron distribution: it readily undergoes electrophilic substitution reactions such as nitration, halogenation, and sulfonation at the electron-rich benzene ring positions (C4–C7), while the electron-deficient C2 position is more susceptible to nucleophilic attack. Additionally, it undergoes alkylation and acylation reactions primarily at the N1 position, forming derivatives like 1-alkylbenzimidazoles and, under stronger conditions, 1,3-dialkylbenzimidazolium salts. Its ability to form salts with acids further highlights its basic nature. Moreover, the nitrogen atoms in benzimidazole can coordinate with metal ions, and the NH group can participate in hydrogen bonding, both of which play significant roles in its biological activity and the stabilization of crystal structures [44-46].

1. Method of preparation

Regarding the preparation of benzimidazoles, numerous techniques have been successfully established and validated. One of these techniques is the method known as direct, which involves o-phenylenediamine mixed formic acid undergoing an immediate consolidation process to produce benzimidazole (Scheme 1). Benzimidazole derivative products can also be prepared in a variety of methods. As outlined in the procedures that follow, certain practices of these approaches have drawbacks, such as low yield, severe reaction circumstances, or lengthy reaction durations [47]. Other approaches are better suited for synthesis. The subsequent techniques summaries the physical attributes of medicinal products. The essential approaches to producing benzimidazole along with its byproducts, and additionally the naturally occurring implements about the ingredient in everyday activities, are the main topics presented in this review. The establishment manufacturing better processes that are less harmful to the environment, economical, and quick to operate have influenced recent technological advances. These processes selectively produce a combination of 1,2-disubstituted benzimidazoles with 2-supplanted benzimidazoles being the sole byproduct. For the production of 2-supplanted benzimidazoles, several accelerators have been documented. Hoe Brecker traditionally created the initial version of benzimidazole during 1872[48].

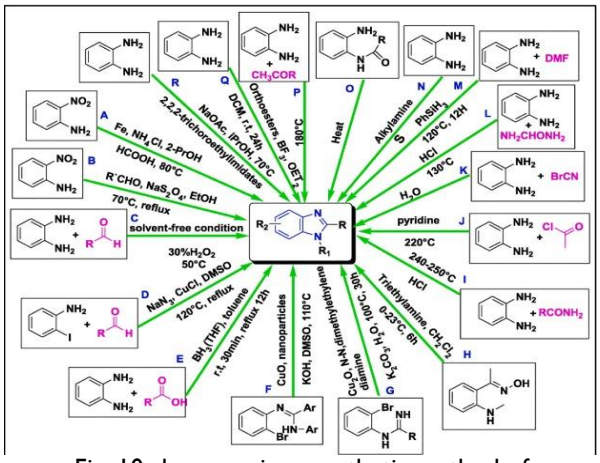


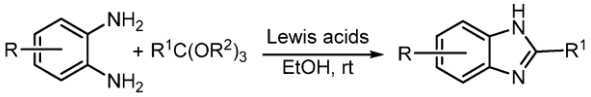
Fig .10 shows various synthetic method of benzimidazole

Hoebrecker and Associates performed the initial synthetic procedure for the benzimidazole compound via reduction of 4-methyl-2-nitroacetanilide, while Ladenburg and colleagues performed the subsequent synthetic procedure by distilling 3,4-diaminotoluene alongside acetic acid. Scheme 1 and Scheme 2 correspondingly show these. As knowledge grew and the needs of the period changed, several synthesis methods (as shown in Fig. 10) were created to create the adaptable pharmacological agent, benzimidazole framework. This paper examines the many synthetic techniques to benzimidazole frameworks and discusses their commercial and biological usages [49-52].

2.1Utilising Catalytic conversion to Facilitate the Production concerning Benzimidazole

Searching for additional appropriate and helpful synthesis methods to produce benzimidazoles is still a flourishing field of study as the creation of novel manufacturing procedures to get possible therapeutic compounds has grown to be a prominent scientific focus. Additionally, the application of accelerators has grown in significance [53-54].

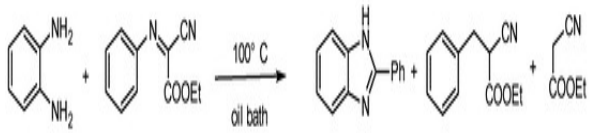
System 1. Extremely efficient catalysts have been discovered found for $ZrOCl_2$, $TiCl_4$, $SnCl_4$, 5H2O, and HfCl4. As a catalyst, however, various metal salts such Mg $(ClO_4)_2$, $CuCl_2$, Zn $(ClO_4)_2$, NiCl2.6H2O, LiCl, LiBr.H2O, CdCl2, 2.5H_2O, Ti $(SO_4)_2$, NH_4Ce $(NO_3)_2$, Bi $(NO_3)_5$, 5H2O, 6H_2O, $ZnCl_2$, 2H_2O, $CoCl_2$, $BF_3.Et_2O$, BCl_3, and Zr $(SO_4)_2.4H_2O$ were either less active or inert. Without a catalyst, no product was produced by the process. When ZrCl4 (10 mol%) and anhydrous EtOH were present, the reaction proceeded smoothly and produced adequate quantities at the ambient temperature [55].



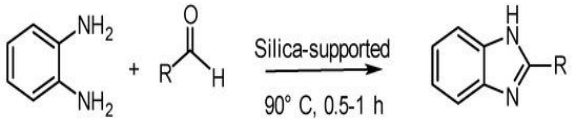
R = H, Me, Cl, NO_2
R_1 = H, Me, Et, $CH_3(CH_2)_3$
R_2 = Me, Et

System 2. Several catalysts, approximately including TFE/HFIP, 6 CuI / L- proline, TMS as well, amberlite -

ultraviolet (UV)-120, SiO2 / ZnCl2, Dowex-50 W, SDS micelles, which are silica sulphuric acid, FePO4, CAN, which stands Cu (NO3)2.3H2O, along with FeCl3 / Al2O3, are used in the manufacturing process of disubstituted benzimidazole. The chemical process frequently exhibits inadequate N-1, the number substitutions effectiveness, leading to creating comprising an assortment of 2-replaced it along with 1,2-disubstituted benzimidazoles. Additionally, the requirement of costly ingredients, lengthy turnaround times, and dangerous solvents made from organic matter are some of the main disadvantages of current methods. With reference concerning the afterwards, o-phenylenediamine along with diethyl a-cyan cinnamate were successfully converted into conjugated benzimidazoles using the transfer-hydrogenation procedure. Kappor et al. suggested alternative metal-free, extremely effective transfer-hydrogenation method for converting according situ-generated benzimidazole's into triggered oil-based compounds. Both catalysts and solvents were absent from the procedure in question. heating o-phenylenediamine and ethyl a-cyan cinnamate in equal amounts at 100 °C. Several additional components were discovered to appear, and the beginning material disappeared. The matching benzimidazole was obtained by purifying the residual compounds after the most polar compound was separated by dehydration (**System 2**) [56-57].



Benzimidazole is produced by electrically depleted olefins being hydrogenated by transfer.Benzimidazole analogues have been successfully synthesised without the inclusion concerning solvents as well catalysts by employing arylaldehydes or aryl methylene - malononitriles as base compounds, which are then absorbed by silicon dioxide gel. Either discontinuous pounding as well a microwave-assisted method was implemented to carry complete the process of reaction (**System 3)** [58].



Benzimidazole analogues are synthesised using silicon dioxide assistance.

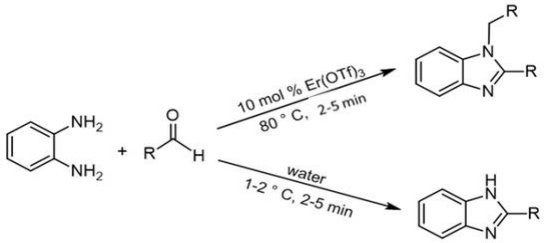


Fig. 11A variety of artificial strategies are currently effectively employed, as seen throughout

In order to produce benzimidazoleDuring 2012, *Bastug et al.* reported novel benzimidazole analogue made from ortho-substituted an aniline along with multipurpose o-esters. e approach employed through Hanan *et al.* (2010) involved the application about heterocyclic in nature aromatic substances including $H_2NC_6H_4NO_2$ with CH_2O_2, metallic elements powdered substances, along with ammonium chloride as precursors, subsequently performing a single vessel elimination of nitrogen dioxide (NO2) accompanied through imidazole treatment cyclisation producing bicyclic 2-H benzimidazole. Following decreasing the amount of o-nitroanilines, Yang et al. successfully synthesised benzimidazole by creating a novel a single-step process for the generation of 2-replaced -nitrogen hydrogen, -N-alkyl, as well as -N-aryl compounds containing benzimidazole within with the inclusion about aldehydes plus sodium dithionite, respectively [59].

In 2012, Cui *et al.* presented a different method for synthesising 2-substituted BnZ. This method involved creating triacyloxyborane precursors as well as 1,2-phenylenediamines through combining the actions of borane-THF with carboxylic acids, respectively for generating 2-replaced BnZ. Sluiter and Christoffers (2009)employed carbonitriles, sodium hydrate, as well as N-methyl-1,2-phenylenediamine among the initial components. In 2010, Wray produced 1H-indazoles utilising ordinary acylamino oximes that had multiple supports present; however, just a single base, triethylamine azole, enhanced the manufacturing of BnZ [60].

Peng et al. synthesised economical and eco-friendly BnZ using cuprous oxide, potassium carbonate, $(CH_3NH)_2C_2H_4$, and water. Cuprous nanoparticles made of oxide function as an initiator and cyclize ortho-bromoaryl molecules intramolecularly. Saha et al. successfully synthesised 2-aminobenzimidazole as well as conjugated BnZ. Additionally, this technique may repair the catalyst without changing its activity. By using warmth in an environment that was acidic, Diao et al. used CuI/l-proline as a catalyst to condense 2-iodoacetanilides and aqueous ammonia for cyclisation, resulting in modified 1H-BnZ [61].

BnZ analogues were created via Kim et al. by both evaporation and C-N bond generation. RCHO, sodium azide (NSA), and 2-haloanilines are effective starting materials for one-pot biosynthesis. In a combination of 20 mL PPA (polyphosphoric acid) along with 10 mL H3PO4, Tao Zhang initially demonstrated an experiment describing the chemical reaction of BnZ with(10 mmol) and benzonitrile (NC-R) during the effects of microwave radiation (MC 275 W, 15 min), yielding a 92% yield [62-64].

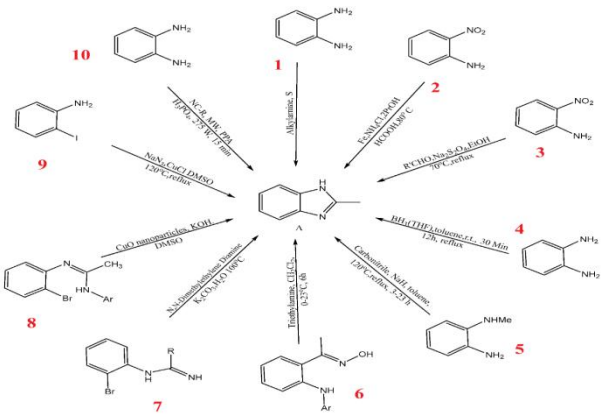
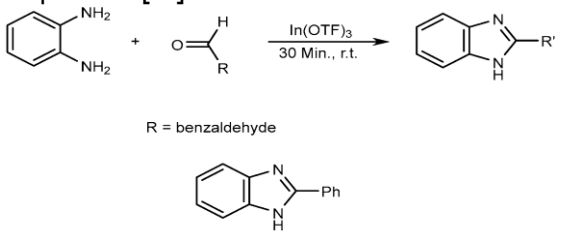


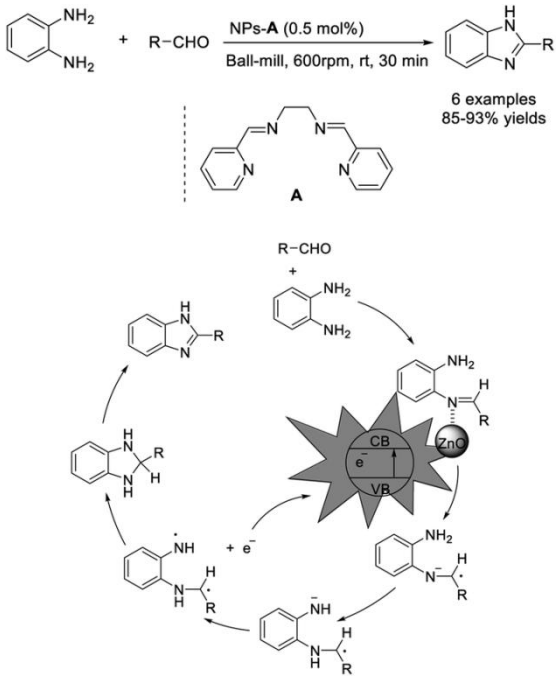
Fig. 12 various roots for synthesis of Benzimidazole

2.2 Alternatives to Benzimidazole Catalysed by Metals Benzamide Derivatives Catalysed by Metals One of the characteristics of metal catalysts is their recoverability. The surface effectiveness of catalysts allows them to catalyse processes and raise the total reaction rate. In their 2006 report, De et al. disclosed the synthesis of MSBs (IX-a) with good yields using indium [III]triflate as a reusable catalyst. Using a catalytic amount of in (OTf)3, o-phenylenediamine (VII) is fused with aldehydes [where R = benzaldehyde (VIII)] to produce 2-substituted BnZ without the need for a solvent. To conduct the reactions, VII and VIII were mixed in a 1:1.1 molar ratio and heated for 30 minutes to room temperature [65].



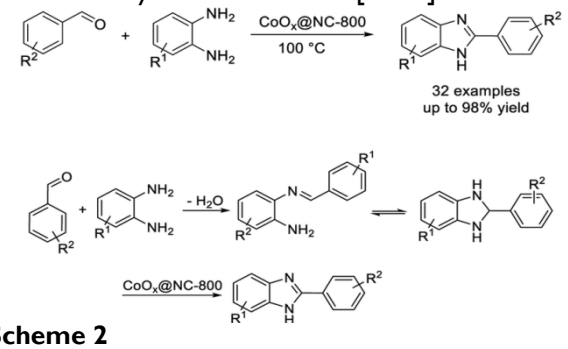
2.3 Manufacturing associated with benzimidazole's through hydrolysis of 1,2-benzenediamines alongside aldehydes (Utilising catalysts made of nanomaterials)

Sharma et al. exploited a ZnO-NP reagent along with a ball-milling approach to generate benzimidazole from 1,2-benzenediamine and several aldehydes. Using a sol-gel technique, the catalyst was created by decorating the ZnO surface in situ with organic ligand A. The synthesis has a number of benefits, including quick reaction times, easy product purification, high efficiency, solvent-free conditions, ZnO-NP catalyst recyclability, and scalability.70 According to a mechanistic research, the catalyst's function is to activate the imine intermediate so that it may take up a single electron [66-68].



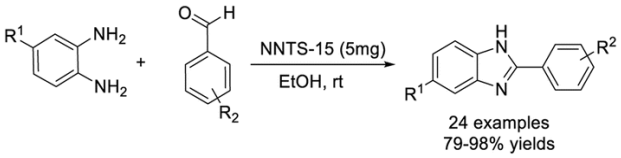
Scheme 1

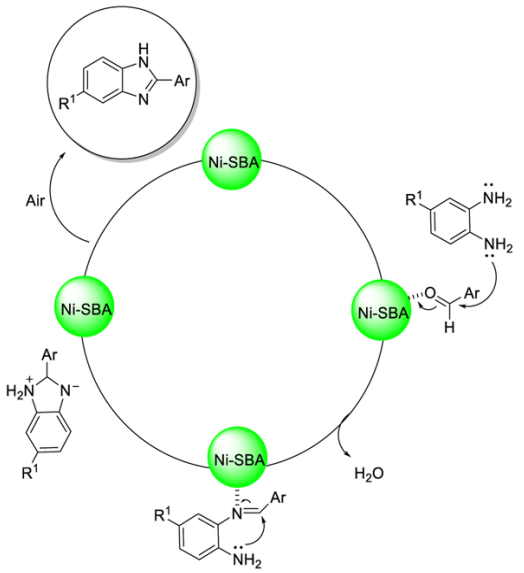
Employing via cobalt nanotechnology catalyst utilised, Wang et al. showed how to synthesise an inventory of benzimidazoles in a single pot by a coupling reaction between phenylenediamines and aldehydes. Scalability, excellent functional grouping, high product yields, and a wide range of substrates are the synthesis's appealing attributes. Moreover, the catalyst may be recycled using a straightforward process and utilised five times without causing a noticeable drop in reaction yields.71. In order to create the required benzimidazole with the release of hydrogen molecules, the catalyst known as CoOx@NC-800 catalyses the dehydrogenation process of dihydrobenzimidazole [69-70].



Scheme 2

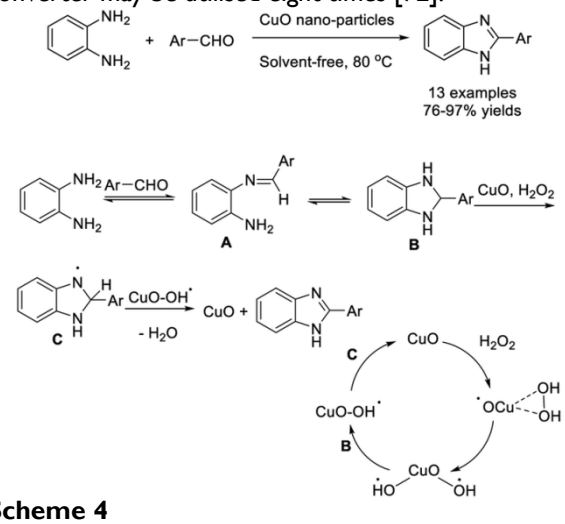
To create 2-aryl-substituted benzimidazoles, Kalhor et al. synthesised a nickel-decorated SBA-15 nanocomposite (Ni/TCH@SBA-15) and used it as a catalyst for the reaction. Moderate circumstances for reaction, a simple initial evaluation process, strong functional category acceptance, substantial product productivity, excellent reagent versatility are some of the synthesis's advantages.72 Both the intermediate and the aldehyde were intended to be activated by the Ni/TCH@SBA-15 [71].





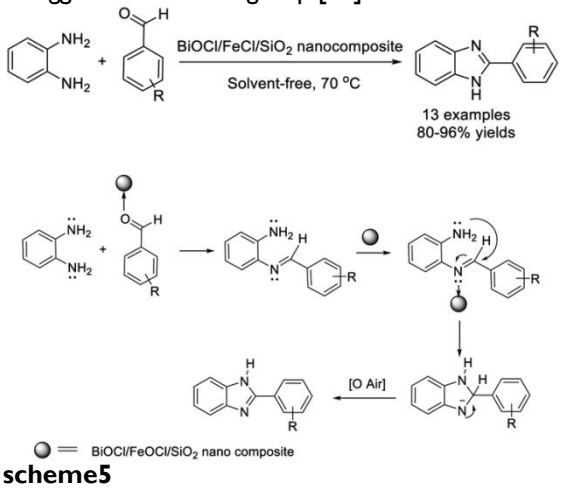
Scheme 3

With the goal to assemble 2-arylbenzimidazoles through a vaporisation interaction involving 1,2-benzenediamine colleagues' hydrocarbons, Fazlinia and Sheikh synthesised nanoparticles made of copper oxide. Under void of solvents Under certain circumstances, a variety of 2-arylbenzimidazoles are generated quickly and in high quantities.73 With no appreciable decrease in catalytic efficiency, the catalytic converter may be utilised eight times [72].



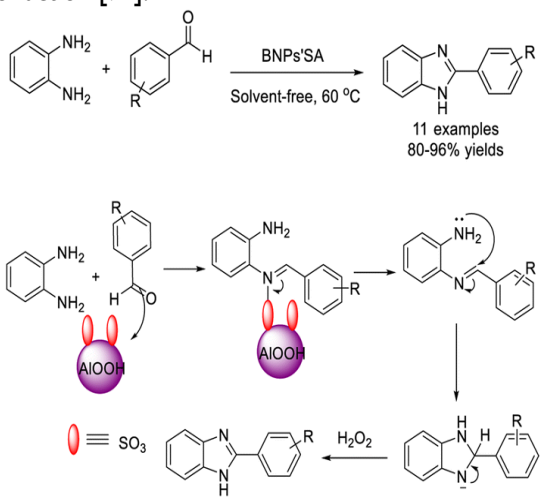
Scheme 4

The development of BiOCl/FeOCl microscopic rods co nstructed using cylindrical nanoparticles of silicon dioxi de plus the application aforementioned nanocatalyst to wards the manufacture of 2-arylbenzimidazoles were demonstrated by Mohammadi et al.Numerous benefits of the procedure were demo nstrated, including quick reaction times, high efficiency, moderate reaction circumstances, ease of use and setup, and catalyst recyclability.74By forming a coordinating bond with the Lewis acid site of BiOCl/FeOCl over th e surface of SiO2 as a mediation agent and the imine as the intermediate concentrations. for the ring sealing re sponse reactive BiOCl/FeOCl/SiO2 nanotechnology ca n trigger the aromatic group [73].



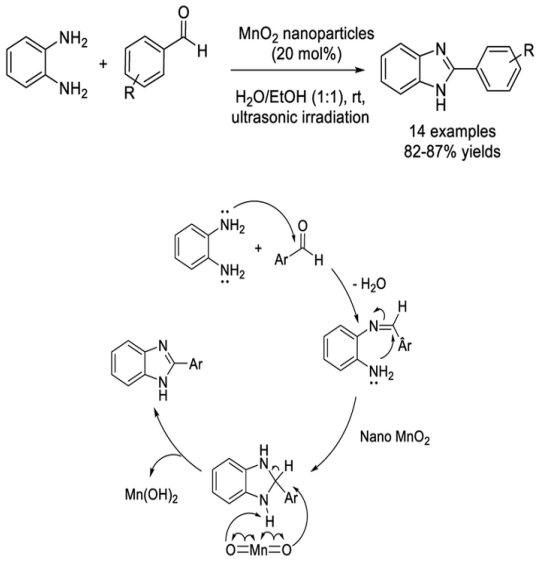
scheme5

synthesised (AlOOH) – SO_3 nanoscale (BNPs' SA) and used them as a reusable accelerator. Void of solvents circumstances were used to accomplish the chemical reaction amongst aromatic compounds along with o-phenylenediamines (Figure 6). The procedure also has the added advantages of rapid response a period of time easy investigation, and substantial intermediate production [74].



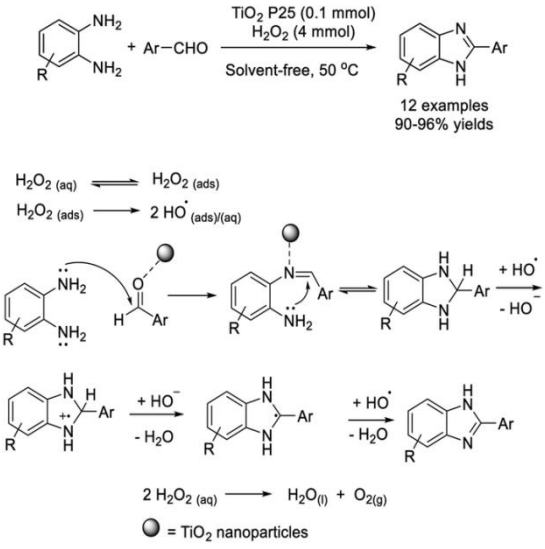
Scheme 6

According per Naeimi along with Babaei, MnO2 nanomaterials can readily prepared along with used as highly effective oxidative ingredient towards the manufacture variety benzimidazoles.76 During ultrasonography electromagnetic radiation, a variety benzimidazoles can readily produce quickly and economically [75].



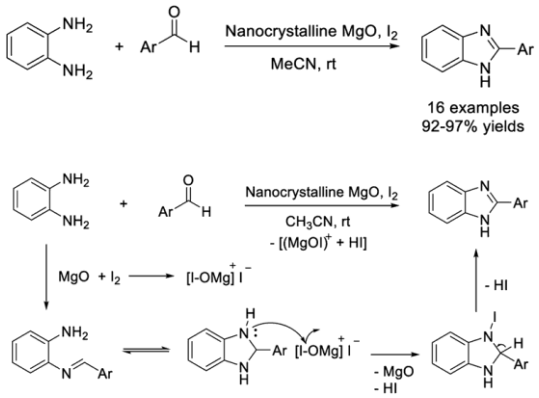
Scheme 7

An assortment synthetic 2-replaced benzimidazoles were assembled using the H2O2/TiO2 P25 nanoscale technology for an accelerator in a work published by Bahrami et al. High concentrations of a variety of molecules have been achieved from 1,2-phenylenediamines as well as aldehydes with aromatic compounds without the use of solvents.77. The catalyst's function in the suggested reaction process is to trigger both the aromatic compounds along with the imine that is the intermediary, as described beneath [76].



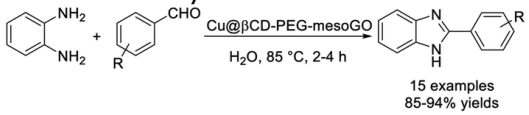
Scheme 8

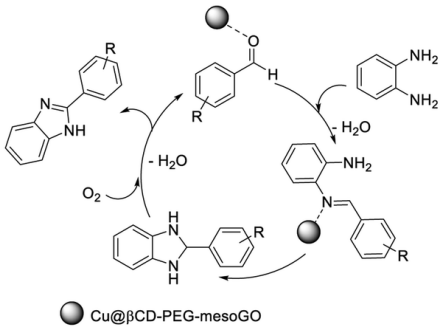
A successful strategy was developed by Naeimi alongside Alishahi for manufacturing 2-supplanted benzimidazole employing nanocrystalline material magnesium oxide as a solid base catalyst. The protocol had several benefits, including mild reaction conditions, short reaction times, scalability, and high product yields.78 Additionally, the catalyst could be recovered and reused for five more cycles without experiencing a significant drop in reaction yield [77].



Scheme 9

Bahadorikhalili *et al.* investigated the synthesis of benzimidazoles from *o*-phenylenediamines and benzaldehydes using a β-cyclodextrin functionalized PEGylated mesoporous silica nanoparticle-graphene oxide hybrid (Cu@βCD-PEG-mesoGO) as a catalyst. The catalyst was prepared from a mesoporous silica nanoparticle-graphene oxide hybrid by functionalization with PEG-600 ended β-cyclodextrin followed by immobilization with Cu. Attractive features of the benzimidazole synthesis include high yield of products, simple work-up procedure, mild reaction conditions, and recyclability of catalyst. The tentative reaction mechanism suggested that the role of the catalyst is to activate the aldehyde and the imine intermediate [78].





Scheme 10

2. Benzimidazole Derivatives' Pharmacological Significance and SAR

The key core in many compounds that operate at many sites to elicit a variety of pharmacological effects is the benzimidazole nucleus, which is known as the "Master Key." Although a variety of chemical compounds can be inserted into any one of the benzimidazole nucleus' seven places, the majority of physiologically active benzimidazole-based compounds have functional groups at positions 1, 2, and/or 5(or 6). Derivatives of the nucleus that are mono-, di-, or tri-substituted can therefore be found in the compounds. Antihypertensive, anti-inflammatory, antibacterial, antifungal, anthelmintic, antiviral, antioxidant, antiulcer, antitumor, pyschoactivity, etc. are only a few of the

main activities. Benzimidazole is available in a variety of productises shown in Fig.13 [79].

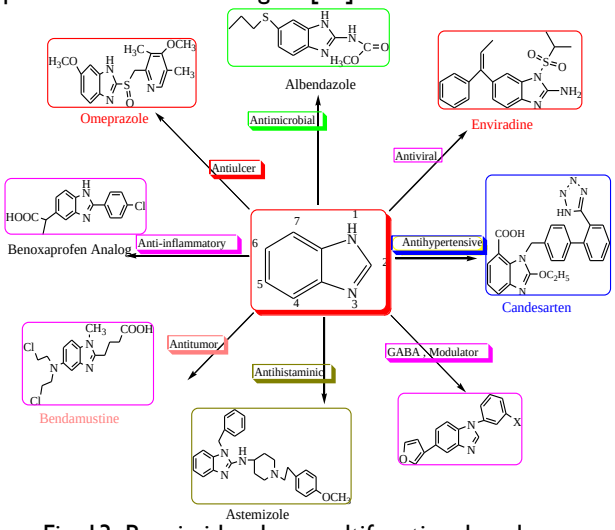


Fig. 13. Benzimidazole, a multifunctional nucleus.

The butyrylcholinesterase along with acetylcholinesterase inhibitory effects of a class of N-2-[4-(1H-benzimidazole substituted amines was assessed by Alpan et al. Employing tacrine to serve as a reference medication, it was discovered that molecules 1a along with 1b were the most effective towards both eeAChE as well as hAChE respectively among all synthesised analogues [80-83].

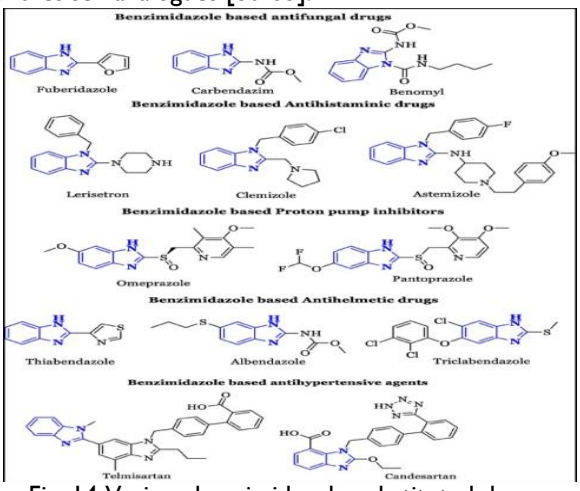


Fig. 14 Various benzimidazole substituted drugs

According to Shaldamet *al.* 2023, novel isatin-derived sulphonamides that are synthesized in this investigation as potential dual enzyme inhibitors of VEGFR-2 and carbonic anhydrase respectively with cancer fighting properties are depicted in Fig. 15 and 16. Initially, the NCI-USA panel of 58 tumor cell lines was used to assess each target isatin's in vitro anticancer efficacy. The most potent substances were then evaluated for their capacity to inhibit both VEGFR-2 and the physiologically significant hCA transcripts I and II as well as the tumor-linked hCA IX isoform. The steric effect of the surrounding methoxy group may be the reason why the target sulphonamides exhibited strong VEGFR-2 inhibitory efficacy but failed to inhibit the CA isoforms [86-90].

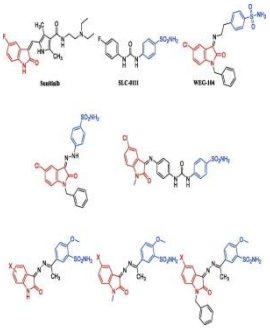


Fig. 15

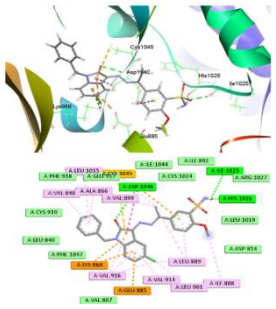


Fig. 16

Benzimidazole-related molecules are in a desirable geographical region for the development of new therapeutic chemicals, according to Pham et al. (2023). Although it resembles pure bases and permits attachment to enzymes as well as receptors using bonds of hydrogen, especially at the nitrogen one location, the SAR of compounds made from benzimidazole demonstrates that the benzimidazole nucleus is crucial for biological functioning. The essential modification when assessing activity occurs at the C-2 location, where groups including alkyl ether, aryl, along with carbamate greatly affect the drug's effectiveness. For instance, carbamate substitution is frequently linked to strong antibacterial effectiveness, as observed in medications including the antibiotic mebendazole and albendazole.he N-1 position may remain unsubstituted to allow hydrogen bonding, although alkylation can increase lipophilicity and membrane permeability but sometimes reduces activity. Substitutions on the benzene ring, particularly at C-5, play an important role in modulating activity, where electron-withdrawing groups such as halogens or nitro groups generally enhance antimicrobial and antiparasitic effects. Additionally, structural modifications linking benzimidazole to other heterocycles can diversify activity, as seen in Omeprazole, where it contributes to proton pump inhibition. Overall, activity depends on the nature and position of substitutions, with C-2 being the key determinant, N-1 influencing binding, and benzene ring substitutions modifying potency and selectivity [91-94].

The antibacterial activity of benzimidazoles is influenced by various structural modifications. Metal complexation, particularly with nickel (Ni), enhances DNA intercalation and improves antibacterial activity, especially when substitution occurs at position-2. Substituents on the 2-phenyl ring also play a crucial role, where meta-substituents like 3-$NHSO_2CH_3$ increase potency, while para-substituents tend to reduce activity. The presence of an unsubstituted amidino group at the 5-position contributes to broad-spectrum antibacterial action, and addition of lipophilic groups such as isopropyl enhances selectivity towards Gram-positive bacteria like MRSA. Electron-withdrawing groups such as Cl and CF_3 at position-5 significantly boost antibacterial activity, whereas electron-donating groups like methyl decrease it. Molecular hybridization with other heterocycles, such

as quinazoline or triazole at position-2, further enhances antibacterial effects. The nature of substituents on triazole also affects activity; aliphatic ester chains promote broad-spectrum action, while bulky or aromatic groups tend to restrict activity mainly to Gram-positive bacteria. Incorporation of hydrophilic groups like carboxylic acid improves antibacterial potency compared to lipophilic substitutions. However, the presence of bulky groups, such as a methoxy group at position-1, negatively impacts antibacterial activity. The occurrence of substituted molecules that transfer charges, including Cl, F, nitro compounds along with trifluoromethyl positions on the phenyl Ring, which is connected to the C-5 position of the pyrazole nucleus, is determined by the microbiological research. Amino, hydroxyl, methyl compounds and methoxy groups in proteins have reduced antibacterial activity in vitro. SAR studies revealed that, while the activity of unsubstituted derivatives remained mild, the activity of molecules with a group that withdraws electrons was greater than that of molecules with a group that donates electrons (Fig.17) [95-98].

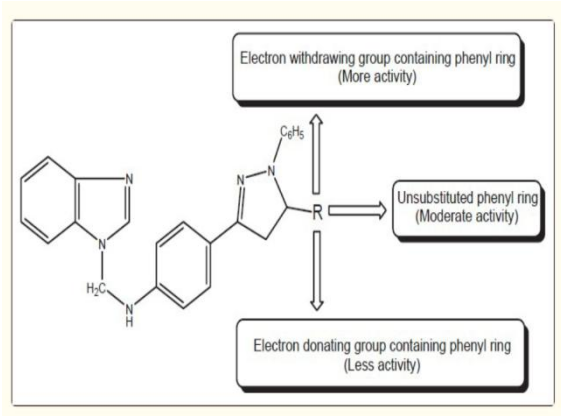


Fig.17

Antiviral activity of benzimidazoles is strongly influenced by specific structural features. Molecular hybridization with a thiosemicarbazone moiety at position-5, along with an unsubstituted phenyl ring at position-2, is crucial for enhanced activity against Influenza A and coronavirus, as seen in compound. The incorporation of a benzotriazole moiety at position-2 improves selectivity toward respiratory syncytial virus (RSV), as observed in Fig.18. For anti-Zika virus activity, the presence of a free $–NH_2$ group at position-2 is essential for optimal efficacy, as demonstrated by compounds 95a and 95b, whereas substituted analogues as shown in Fig. reduced activity. Additionally, a cyano group at position-5 further enhances antiviral potency, and substitution at the N1 position with aliphatic chains is more favourable than phenyl substitutions. In the case of Coxsackie virus, introducing a pyrimidine moiety at position-1 together with an unsubstituted phenyl ring at position-2, as in compound, is important for activity. For HIV, antiviral potency is improved by para-substitution of the phenyl ring with a bulky atom such as chlorine, as seen in compound [99-104].

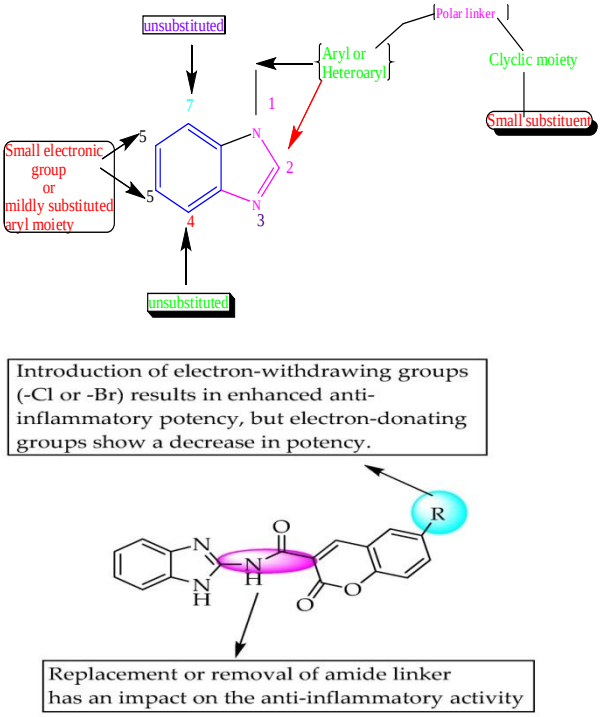


Fig. 18 benzimidazole medication's architectural needs for its ability to reduce inflammation.

Inflammation is a complex biochemical response initiated when tissues are injured or infected, leading to activation of immune cells such as macrophages and mast cells, which release cytokines like interleukins (IL), tumour necrosis factor (TNF), and interferon-γ (IFN-γ). These mediators activate intracellular signalling pathways including nuclear factor-κB (NF-κB), mitogen-activated protein kinase (MAPK), and Janus kinase (JAK), which regulate the expression of inflammatory genes. Cell membrane phospholipids are converted into arachidonic acid, which is metabolized by cyclooxygenase (COX) to produce prostaglandins (PG) and thromboxane's (Tx), and by lipoxygenase (LOX) to produce leukotrienes (LT). Prostaglandins cause pain, fever, and vasodilation, thromboxane's promote platelet aggregation, and leukotrienes increase vascular permeability and attract leukocytes. Nitric oxide (NO) further contributes to vasodilation and enhances blood flow. These mediators collectively lead to redness, swelling, heat, and pain at the site of injury, while recruiting immune cells to eliminate the cause of damage. The process is amplified through feedback mechanisms involving NF-κB and MAPK pathways, and eventually resolves through anti-inflammatory signals, although failure to resolve may result in chronic inflammation [105-110].

3. CONCLUSION

In accordance with the available research assessment, an object's functional cluster has a significant impact on the physical attributes the particle exhibits. Investigators should comprehend the proportional

involvement of every functional category in order to develop improved pharmaceutical agents. The benzimidazole molecular structure, a pharmacological and based on structure straightforward heterocyclics chemical, has performed an essential function in therapeutic chemistry. It could possibly be used in the creation and exploration of novel medications containing possible physiological consequences. Numerous compounds containing benzimidazole with potential biological effects have been identified found by the investigators throughout the previous ten years of attempts to synthesise for health purposes significant benzimidazole analogues.The current research investigation aims to deliver an overview about the manufacturing process of multiple compounds made from benzimidazole and their effects on life. Potential investigators within the discipline of benzimidazole-based medication discovery are expected to find this overview useful.Between 2015 and 2026, significant progress has been made in the synthesis and antimicrobial evaluation of benzimidazole derivatives, reinforcing their importance in medicinal chemistry. The adoption of modern synthetic approaches, especially those based on green chemistry, has enabled more efficient and environmentally friendly production. Various structural modifications and the design of hybrid molecules have shown notable antimicrobial effects, including activity against multidrug-resistant pathogens. Structure–activity relationship (SAR) studies have contributed to a deeper understanding of how chemical features influence biological activity, supporting the rational development of more potent compounds. However, certain limitations persist, including the need to enhance selectivity, minimize toxicity, and improve pharmacokinetic properties for clinical use. Future research should emphasize the development of benzimidazole-based nanomaterials and advanced drug delivery systems, which may improve therapeutic performance and help overcome resistance. Continued interdisciplinary research and collaboration will be essential to fully realize the potential of benzimidazoles as next-generation antimicrobial agents in combating antimicrobial resistance.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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