इन सब में बड़ी बात यह की वह खुद को भी नहीं बखस्ते यदि वह स्वयं उसके गिरफ़्त में हों। 'तीसरे दर्जे के श्रद्धेय' व्यंग्य में वो लिखते हैं- "श्रद्धेय के भी दर्जे होते हैं। तीसरे दर्जे का श्रद्धेय प्रेरणा नहीं देता। वह शर्म देता है। गांधीजी की बात अलग थी। वे तीसरे को भी पहले दर्जे की महिमा दे देते थे। हम तो पहले दर्जे में बैठकर भी तीसरे की हीनता अनुभव करते हैं। संत और बुद्धिजीवी में यही फर्क है। मुझे विशेष सावधान रहना पड़ता है। पाठ्यक्रम में आ गया हूँ। कोर्स का लेखक हो गया हूँ। कोर्स का लेखक वह पक्षी है, जिसके पाँवों में घुँघरू बाँध दिये गए हैं। उसे ठुमककर चलना पड़ता है। ये आभूषण भी हैं और बेड़ियाँ भी। रायल्टी मिलने लगती है तो जी होता है कि 'सत्साहित्य' ही लिखो, जिससे लड़के-लड़कियों का चरित्र बने। उसे आचार्यगण तुरंत गले लगा लेंगे। परेशानी यही है कि 'सत्साहित्य' कुल आठ-दस वाक्यों में आ जाता है, जैसे – सत्य बोलो, किसी को कष्ट मत दो, ब्रह्मचर्य से रहो, परायी स्त्री को माता समझो, आदि।"

व्यंग्यकार की बड़ी खूबी यही है कि वह अपनी कमियों पर पर्दा डालने के बजाय उसमें व्यंग्य का जायका डालने की कोशिश करता है और इस कार्य में परसाई जी से बेहतर कोई नहीं। परसाई जी समाज के उन फर्जी चारित्रवादियों को भी आड़े हाथों लेते हैं जो किसी स्त्री और पुरुष को साथ देख लें तो तुरत व्यभिचारी घोषित कर देते हैं। इस तरह के लोगों पर परसाई जी लिखते हैं- "किसी स्त्री और पुरुष के संबंध में जो बात अखरती है, वह अनैतिकता नहीं है, बल्कि यह है कि हाय! उसकी जगह हम नहीं हुए। ऐसे लोग मुझे चुंगी के दरोगा मालूम होते हैं। जो हर आते-जाते ठेले को रोककर झांककर पूछते हैं- तेरे भीतर क्या छिपा है?"
इसी में वे लिखते हैं, "कितने लोग हैं जो 'चरित्रहीन' होने की इच्छा मन में पाले रहते हैं, मगर हो नहीं सकते और निरे 'चरित्रवान' होकर मर जाते हैं। आत्मा को परलोक में भी चैन नहीं मिलता होगा और वह पृथ्वी पर लोगों के घरों में झांककर देखती होगी कि किसका संबंध किससे चल रहा है।" परसाई जी समाज की नब्ज को जिस तरह पकड़ते थे उससे साफ समझ में आ जाता है कि समाज किस बीमारी से जूझ रहा था। आज भी ये बीमारियाँ समाज में बुरी तरह फैली हुई हैं बस फर्क सिर्फ़ इतना है कि आज परसाई जी जैसा वैद्य इन बीमारियों के इलाज के लिए खड़ा नहीं दिखता और जो दिखता भी है तो उसे बीमारी का ठीक-ठीक अंदाजा नहीं। इसलिए इन रोगों की नब्ज पकड़ने से पहले साहसिक और बौद्धिक तौर पर मजबूत होना होगा जो इस दौर की पारसाईता को परसाई की तरह जिंदा रख सके।

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संदर्भ:-

I. परसाई रचनावली- भाग३, विकलांग श्रद्धा का दौर , राजकमल प्रकाशन, नई दिल्ली, पृष्ठ सं.३७
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X. परसाई रचनावली- भाग२, वह जो आदमी है न, राजकमल प्रकाशन, नयी दिल्ली, पृष्ठ सं.५२

A Complete Investigation Of The Chemistry and Molecular Pharmacology of Benzimidazole

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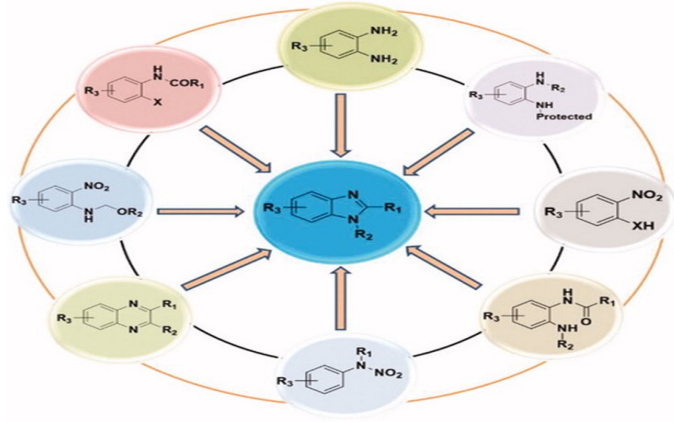
Abstract: The benzimidazole category of chemical compounds, which includes anthelmintic, analgesic, and antiulcer medications, is extremely important in medicine. chemical chemistry research is heavily focused on the chemical synthesis of benzimidazoles and their derivatives to produce active pharmaceutical molecules. Concerns about the synthesis of these crucial pharmaceuticals and the pharmaceutical business include the usage of non-environmental organic substances, the employment of high energy synthetic techniques, waste creation, and the use of common harmful technologies. This article offers an overview of the substituted benzimidazoles, including information on their pharmacological effects and environmentally responsible chemical production.

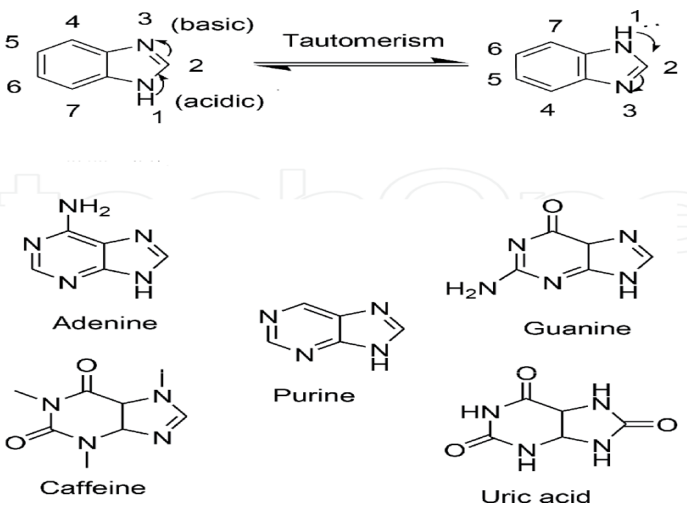
GRAPHICAL ABSTRACT



KEY WORDS: 5,6-dimethylbenzimidazole, US food Drug Administration (FDA), tautomer's, phenylenediamine, polyphosphoric acid

INTRODUCTION-Heterocyclic substance has a ring that contains two or more distinct types of atoms, giving them a cyclic structure. These kinds of substances are found in nature in large quantities and are necessary for life. They are involved in the metabolism of all living cells and include the pyrimidine and purine bases of DNA, proline and histidine, vitamins, and coenzymes, among other essential amino acids. Numerous pharmacologically active heterocyclic compounds exist, many of which are often used in therapeutic settings [1]. Numerous manufactured and naturally existing

heterocyclic substances are used in insecticides, agricultural chemicals, polymers, pharmaceuticals, and other products. Scientists get interested in this and conduct an increasing amount of study, which results in the discovery of new heterocyclic compounds with beneficial biological properties [2]. Because of its versatility in synthesis and wide range of pharmacological action, benzimidazole is one of the significant nitrogen a heterocyclic species among the many heterocyclic systems that have been identified too far. The curative potential of benzimidazole core is widely approved since Woolley postulated within 1944 suggested benzimidazole may work analogous to purines, activating numerous biological responses. After a few decades, Brink learnt because 5,6-dimethylbenzimidazole represents a consequence of the antioxidant vitamin B12 metabolism as well as certain of



Since an axial ligand for cobalt in vitamin B12, N-ribosyl-dimethyl benzimidazole being among the most well-known benzimidazole molecule in environment. Benzimidazole is a synthetic aromatic chemical molecule that has the benzene ring linked together with an imidazole molecules ring at the 4,5-location to generate a bicyclic ring. It is additionally referred to as 1,3-benzodiazole,1H-benzimidazole, benzo glyoxaline, iminazole, and imidazole as shown in Fig. 2 [4]. Benzimidazole, formerly referred to as 2,6-dimethylbenzimidazole, Hobrecker created the initial benzimidazole analogue during 1872. The 1943 scientific study by Goodman and Nancy Hart addressed the pharmacokinetic characteristics of benzimidazole as discuss in Fig. 3. An essential physiologically responsive heterocyclic molecule, benzimidazole belongs to the majority of ten widely used five-membered nitrogen heterocycles, which amongst US food Drug Administration (FDA)-approved medications. Because of similar structural analogy to nucleotides made of purines prevalent in the environment, benzimidazole's are capable of readily interact with the various biological polymers found in living organisms [5].

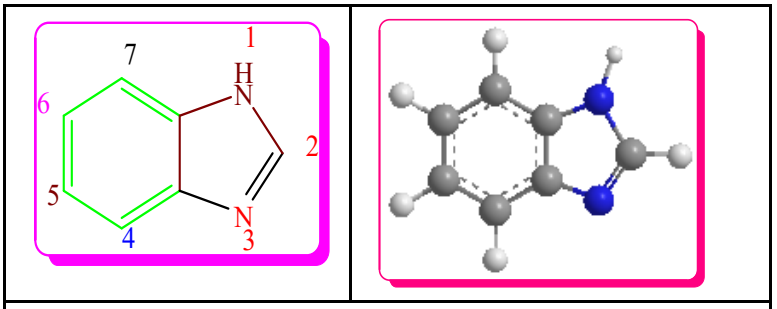


Fig. 2 Structure of 1H-benzimidazole and 3D Model of 1H-benzimidazole

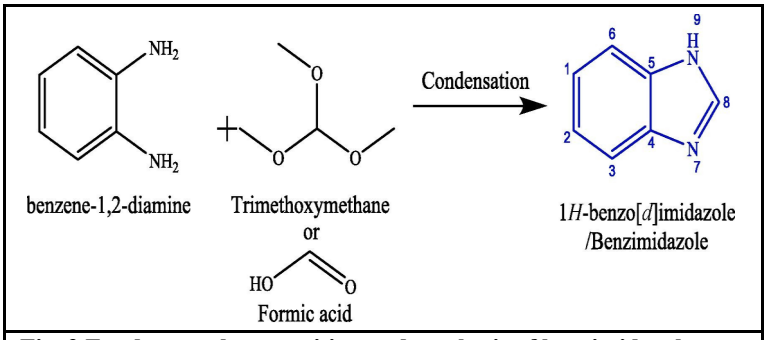


Fig. 3 Fundamental composition and synthesis of benzimidazole

CHEMISTRY OF BENZIMIDAZOLE

An organic compound that is heterocyclic and aromatic is benzimidazoles. The imidazole and benzene rings are combined to form this fused molecule as shown in Fig. 3. According to the diverse array of biological actions exhibited by benzimidazoles and their derivatives, efforts have occasionally been undertaken to build libraries of these compounds. In order to meet customer demands for quantity, purity, and quality, a wide range of synthetic processes have been developed and refined. By converting 2-nitro-4-methyl a compound known as which was possibly 2,5-dimethylbenzimidazole or 2,6-dimethylbenzimidazole, Hoebrecker created the initial form of benzimidazole around 1872 [6].

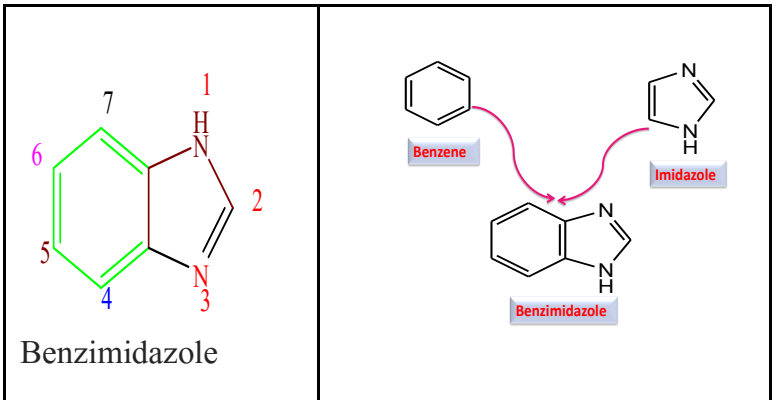


Fig. 4 The basic structure of benzimidazole

ISOMERISM IN BENZIMIDAZOLE-Benzimidazoles which contain a hydrogen molecule attached to nitrogen in the 1st position readily tautomerize. Tautomerism is analogous to that found in the imidazole's and amidines. The benzimidazoles, in fact, may be considered as cyclic analogs of the amidines [7]. Because of this tautomerism in benzimidazoles, certain derivatives which appear at first to be isomers are in reality tautomer's; although two non-equivalent edifices can be written, individual one compound is known. This may be illustrated with 5 (or 6) methyl benzimidazole as shown in Fig. 7 [8].

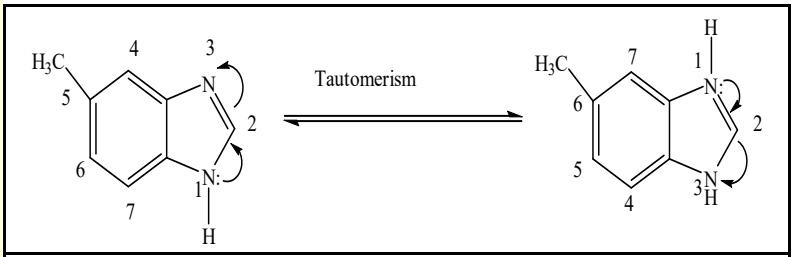
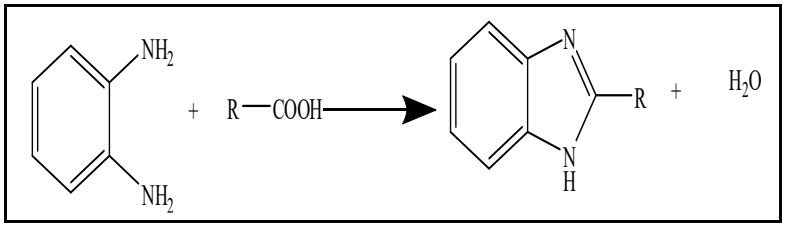


Fig. 4 Tautomerism in benzimidazoles

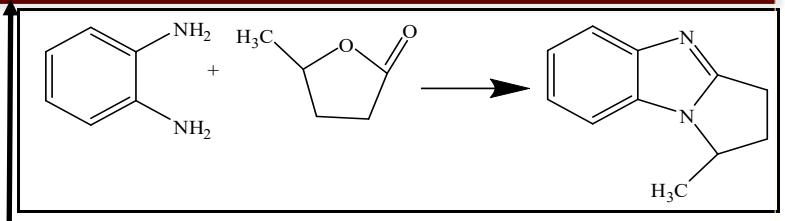
VARIOUS SYNTHESIS METHODS OF BENZIMIDAZOLES-There have been released extensive reviews that address the chemical structure and manufacturing of imidazole's and benzimidazoles. Many different sources of inspiration, some of which are mentioned above, can be used to create benzimidazoles in particular.

- From o-Phenylenediamines
- From o-(N-acylamino–aryol amino)aryl amines and nitroarenes
- From o-Nitro aryl aminesando-dinitroarenes
- From o-substituted-N-benzylideneanilines
- From Amidines
- From Other heterocyclic compounds

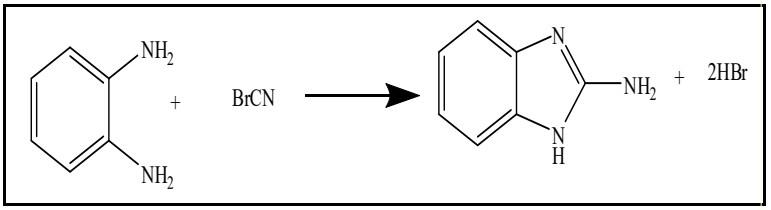
By reaction of carboxylic acid and carboxylic acid derivatives: -*o*-phenylenediamines react readily with most carboxylic acids to give 2-substituted benzimidazoles in very good yield. Also, *o*-phenylenediamines and their dihydrochlorides also react with various carboxylic acid derivatives like anhydrides, ester, amides and acid chlorides to yield the corresponding benzimidazoles [9].



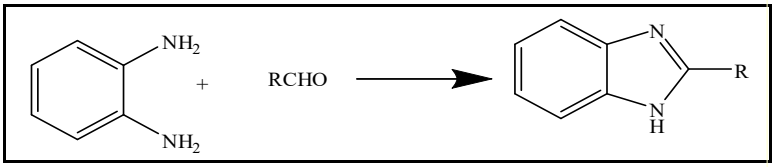
By reaction with lactones:-Valero lactone when refluxed with *o*-phenylenediamines gives only a small yield of 1, 2- (1-methyltrimethylene) benzimidazoles [10].



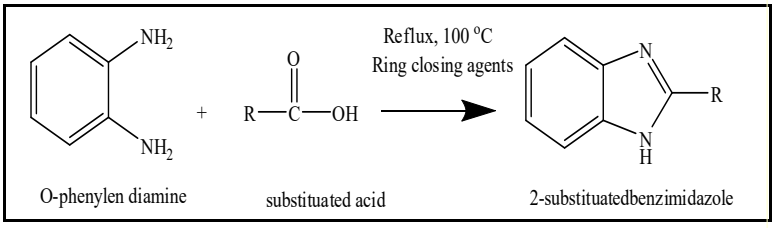
By reaction with nitriles: -Cyanogen bromide reacts with *o*-phenylenediamines to give 2-aminobenzimidazoles in good yield. The reaction is carried out by mixing equimolecular amounts of the reactants in aqueous suspensions [11].



By reaction with aldehydes:-Under the correct conditions aldehydes may reacted with *o*-phenylenediamines to yield 2-substituted benzimidazoles. Due improvement of oxidation reaction was best carried out under oxidative conditions [12].



Universal Method for the Synthesis of 2 - Substituted Benzimidazoles-Ortho phenylenediamine (1mole) was made to condense with carboxylic acid derivatives (1mole) in presence of ring closing agents like hydrochloric acid or polyphosphoric acid (Vaidehi *et al* 2012) [13].



BENZIMIDAZOLE MECHANISM OF ACTION

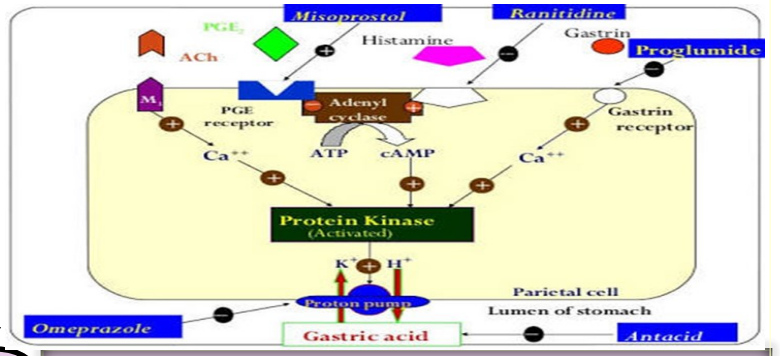
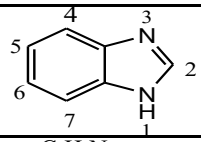


Fig. 5 Mechanism of action of antiulcer agents

Structure	
Molecular formula	$C_7H_6N_2$
Molecular Weight	**118.14 g/mol**
Amphoteric Nature	Benzimidazole serves either simultaneously an acid and a base because of its amphoteric characteristics.
Colour	It has the appearance of a solid white or light-yellow colour
Melting point	172°C
Boiling point	360°C
Solubility	Dissolved in alcohol and just marginally soluble in aqueous. When benzimidazole's include imide nitrogen, they often dissolve better in polar solvents than in organic ones. Using fewer basic strategies, including as the potassium carbonate an approach especially the more acidic benzimidazoles could dissolve.
PKa_1	5.68
PKa_2	12.75 (due to tautomerism)
Acidic Character	Ion Research stabilising via resonance appears to be the cause of the acidic characteristics of both benzimidazole's and imidazole's.

BIOLOGICAL ACTIVITIES -The "The Art Central" of pharmaceutical reactions is the benzimidazole nucleus, which functions as a crucial nucleus in several drugs by acting at multiple locations. Positions 1, 2, and/or 5 (or 6) of most biologically active benzimidazole-based products include groups with functional properties, while a wide range of chemical compounds can be put into any one of the seven sites of the benzimidazole nucleus. These compounds consequently include mono-, di -, or tri-substituted derivatives of the nucleus. Only a handful of the primary actions include antihypertensive, anti-inflammatory, antibacterial, antifungal, anthelmintic, antiviral, antioxidant, antiulcer, antitumor, and pyschoactivity. There are several products that include benzimidazoles, like fig. 9 and 10 [16].

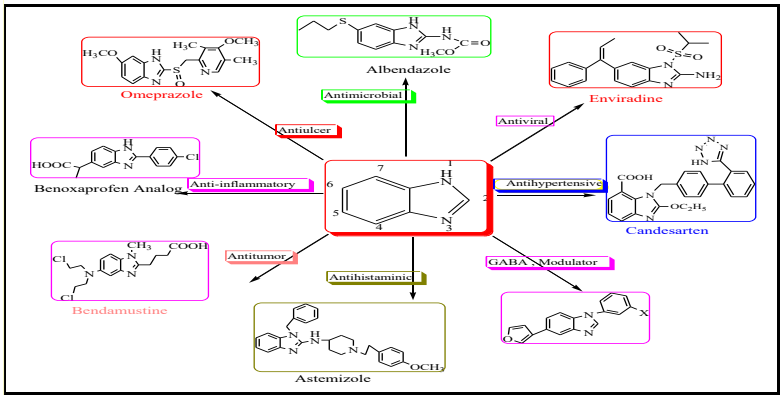


Fig. 6 multifunctional nucleus of benzimidazole

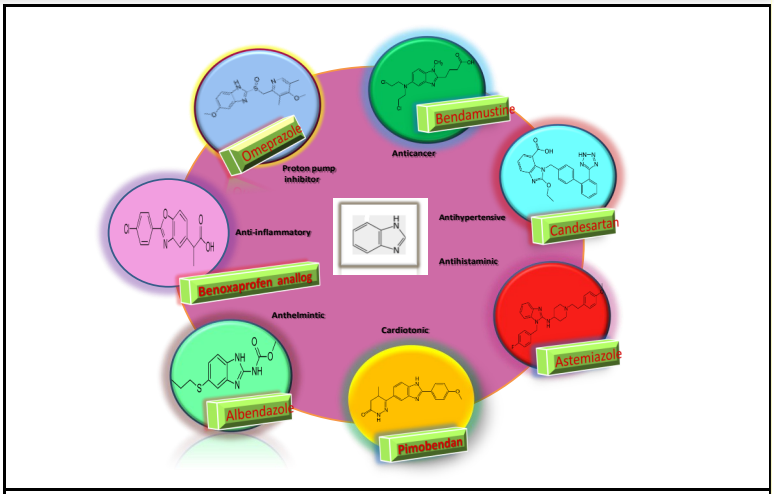


Fig.7

ANTIMICROBIAL INTERVENTIONS-According *to Dokla et al. (2023),* the need for novel antimicrobial drugs will never go away. In order to find new therapies against gram-negative microbes, we previously published a structure-activity-relationship (SAR) investigation on 1,2-disubstituted benzimidazole derivatives. With a MIC value of 2 g/mL, the chemical in Fig. 8 showed considerable activity against to lC-mutant Escherichia coli, suggesting it might be a promising candidate for further optimisation. Based on these findings, 49 novel benzimidazole compounds were synthesised and evaluated for their ability to inhibit Gram-negative bacteria. Three main goals of our design were to improve the primary compound as shown in Fig. 8 by changing the methane sulphonamide moiety, to expand the SAR study to the unknown ring C, and to solve the limiting permeability of our substances and boost their cellular deposition [17]

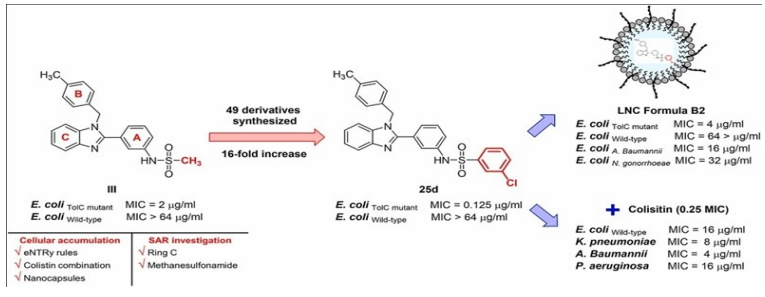


Fig. 8-A range of spectroscopic techniques, such as IR, NMR, and mass spectrometry, among others, are used to verify the synthesis of a class of 2-(1H-imidazol-1-yl)-1 -phenylethyl cinnamates, which includes 2-(1H-benzo [d]imidazol-1-yl)-1-phenylethyl cinnamates, as reported by *Zala et al in 2023*. Furthermore, the in-vitro antifungal and antibacterial activities of the chemicals versus 6 different bacterial strains and gram-positive and gram-

negative strains were assessed. considerable activity against all bacterial strains with MIC values between 12.5 and 50 g/mL and considerable activity against all fungal strains with MFC values between 125 and 200 g/mL were exhibited by the compounds in Fig. 9. It has been suggested by molecular docking research that compounds might attach to the active pocket [18].

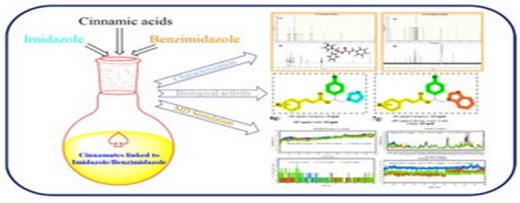


Fig. 9

In 2023, Aaghaz et al. reported Fungus infections are one of the main untreated health issues that are prevalent in developed countries. Based on statistical evidence, approximately 17% of infections in critical care units in the United States and Europe are caused by fungus. Treatment for fungal infections, particularly systemic infections, presents a number of challenges, including high costs and poor to moderate success rates [2, 3, 4]. Furthermore, Fig. 10 illustrates a significant level of immunity to antifungal drugs that are sold commercially. Patients undergoing chemotherapy, neonates, recipients of organ transplants, and burn victims are more susceptible to dermatomycoses, a kind of bacterial infection [19-20]

ANTI-INFLAMETARY AGENTS -Various heterocycle substitutions at N1 of benzimidazole account for the beneficial anti-inflammatory effects of various drugs; the published SAR analysis shows that substitutions at the N1, C2, C5, and C6 locations of the benzimidazole nucleus heavily impact the anti-inflammatory activity [21].

CYCLOOXYGENASE INHIBITORS-Coxibs (COX-1), or cyclooxygenase-2 (COX-2) inhibitors, are a group of nonsteroidal anti-inflammatory drugs (NSAIDs) used to treat inflammation and discomfort. They function by inhibiting the production of prostaglandins, which are responsible for inflammation-induced discomfort and swelling, using the COX-2 enzyme. By combining benzimidazole with anacardic acid, Paramashivappa et al. (2003) synthesised 2-[[2-alkoxy-6-pentadecyl-phenyl) methyl] thio]-1H-benzimidazoles and assessed their COX-2-inhibitory efficacy in humans (Fig. 10) Strong anti-inflammatory action was demonstrated by a molecule wherein R = H and R1 = methoxy moiety. This drug had a 384-fold selectivity for COX-2 over COX-1 inhibition. In contrast, the second molecule exhibited 470-fold selectivity with R = methyl and R1 = H moiety, which is similar to the 375-fold and 200-fold selectivity of celecoxib and rofecoxib, respectively. The significance of benzimidazole's "NH" moiety in its anti-inflammatory action was also validated by the study. On the other hand, –OCHF2 did not exhibit a beneficial inhibitory activity, while substitution of –CH3 or –NO2 at benzimidazole's C5 demonstrated mild inhibition [22

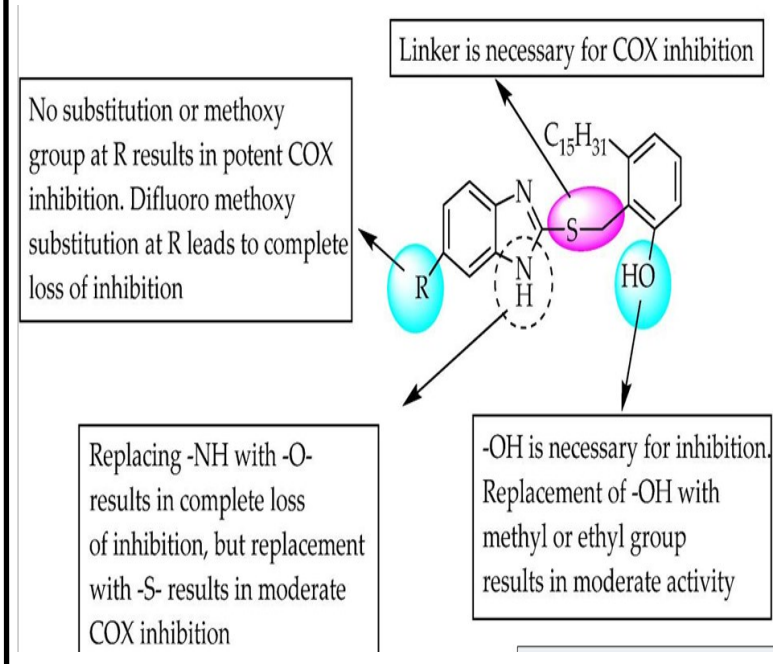


Fig. 10

Bukhari et al. discovered in 2016 how a few 2-phenyl-substituted benzimidazoles inhibited COX and 5-lipoxygenase. (Fig.14, 15) illustrates that for the inhibition of COX-1 and 2, as well as 5-lipoxygenase, unsubstituted at R2, R3, and R4 is preferable; in contrast, the amine group at R1 increased the inhibition of all three enzymes. On the other hand, a hydrophilic group increases COX-2 inhibition, a methoxy substitution promotes 5-lipoxygenase inhibition, and the lipophilic group at R5 favours COX-1 inhibition. With an IC50 of 0.72 ± 0.77 µM, one of the compounds containing R2–CH3, R1–NH2, R3 and R4–H demonstrated superior COX-1 inhibition. Nevertheless, a further substance having a nitrile group at position R5 was a dual inhibitor of COX-1 and -2, with IC50 values of 8.17 ± 2.85 and 6.79 ± 1.46 µM, in that order. containing an IC50 of 8.41 ± 1.22 µM, another molecule containing 2-aminopyridin-4-yl at R5 demonstrated superior inhibition of 5-lipoxygenase. Overall, strong inhibition of COX-1, COX-2, and 5-lipoxygenase is favoured by substituting the suggested groups at the aforementioned location. (Fig. 11, 12) displays the compounds' SAR [26-28].

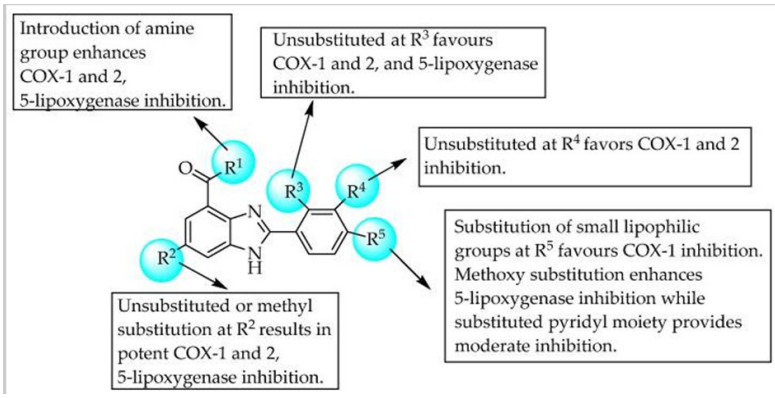


Fig. 11 show SAR of benzimidazole as Cox-1 and Cox -2 Inhibiters

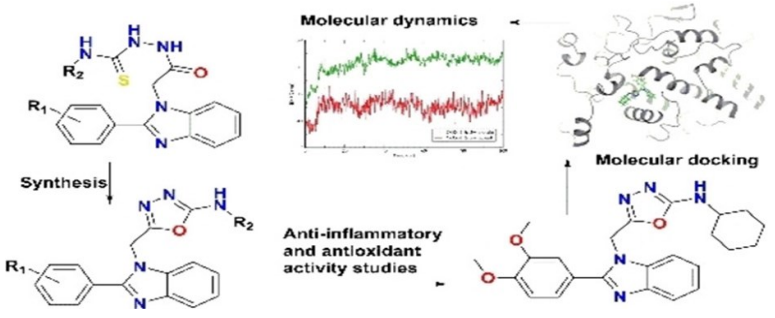
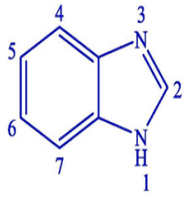


Fig.12

MEDICATIONS WITH FUNGICIDES-A growing variety of oligonucleotide benzimidazole counterparts have been developed over the years, but 5,6-dichloro-l-(β-d-ribophorins) benzimidazole (DRB) derivatives have received attention because of their antiviral capabilities, especially against RNA viruses like human cytomegalovirus (HCMV). By inhibiting RNA polymerase II, these benzimidazoles effectively prevent the production of viral RNA. Even while DRB compounds have anti-viral properties, their significant cytotoxicity frequently makes them unsuitable for use as medications

Positions unfavorable for substitution

For better activity to experience locant numbers 3, 6,7 should remain unsubstituted



Positions favorable for substitution

Position 1: Insertion of a homologous series of hydrocarbon often enhances permeability. An arylhydrazone at this location promotes antioxidant effect by n fold. In addition it brings about neuroprotection as well.

Position 2: Increase in electron density, preferentially with coumarin evolves into a dual acting (anti-oxidant and antiinflammatory) agent.

Position 5: Substitution with an electron rich fragment, methanesulphonamido yielded both antioxidant and antiinflammatory agent

Fig. 13 SAR of benzimidazole nucleus

ANTIVIRAL ACTIVITY-5,6-dichloro-l-(β-d-ribofuranosyl) benzimidazole (DRB) derivatives have acquired popularity among the many oligonucleotide benzimidazole compounds that have been created over the years because of their effectiveness as antivirus medicines, particularly against human cytomegalovirus (HCMV) and other RNA viruses. These benzimidazoles obstruct RNA polymerase II, thereby inhibiting the production of viral RNA. DRB compounds have anti-viral action, however their significant cytotoxicity makes them unsuitable for use as pharmaceuticals as discuss in Fig 14 [30-31].

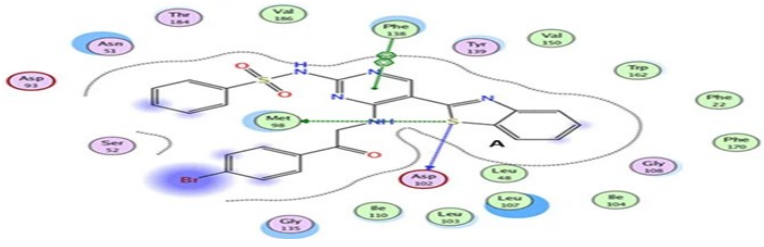


Fig. 14 The most effective docking location of A in the Hsp90 interaction space

CONCLUSION -The best variables for benzimidazole derivatives' antiulcer efficacy include steric impact, pka significance, and degree of nucleophilicity. The pyridine and benzimidazole electron-donating and -withdrawing groups, as well as the connecting chain, are crucial for the stability and structure of benzimidazole derivatives. Inhibitors of the proton pump that prevent the production of gastric acid for an extended period of time have been linked to some apparent side effects, including hypergastrinemia, water retention, tumours, and an affinity for cytochrome 450, as well as an indirect the pharmacodynamic consequence known as ECL-cell hyperplasia. Because of this, scientists have been drawn to creating acid pump antagonists that are reversible, shorter acting, and more potent. The nitrogen-borne fused heterocycle benzimidazole is an essential component of many compounds that are used therapeutically and aids in the treatment of a wide range of illnesses. The creation of novel therapeutically active compounds to treat a range of medical disorders has garnered noticeable attention in recent years, and there has been a significant amount of work done so far on the development of target-based BZ derivatives. The fact that target-based BZs have been the subject of much research to far can be used to explain both of these developments. A number of artificially created substances with encouraging pharmacological potential frequently fall short of their intended market worth. It is necessary to remove this obstacle as a result.

This study has focused on the current state of the BZ moiety, specifically focussing on the surface area ratio (SAR) of BZ-based many molecular templates that have been found by researchers worldwide. To our knowledge, this is the most thorough and in-depth study on the biology and therapeutic potential of BZ compounds that has been conducted to date. To accomplish our goal, we collected information from a vast collection of publications in order to provide scientists, medicinal chemists, and drug developers with a solid basis on which to build the next wave of secure and efficient BZ-based treatments.

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