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A Current Analysis of Synthesis and Pharmacological Effects of Benzimidazole Derivatives

Joshny Varghese*[a], Anju V[b], Santhosh M Mathews[c] and Justin Jacob Thomas[d]
[a,b,c&d]**Pushpagiri College of Pharmacy, Department of Pharmaceutical Chemistry, Thiruvalla, Kerala - 689107**

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***Corresponding Author Email:** varghesejoshny2016@gmail.com

Abstract
Benzimidazole is an important heterocyclic organic compound having structural analogy to nucleotides found in human body and profound pharmacophore in medicinal chemistry. It is a bicyclic aromatic organic compound which is a fusion of benzene and imidazole ring. Generally, benzimidazole derivatives are synthesized by reaction of o-phenylenediamine with various carboxylic acids. It has been an exciting area of pharmaceutical chemistry to research the biological evaluation of benzimidazole derivatives. In this review article, various synthetic methods of benzimidazole derivatives and their pharmacological activities were described.

Keywords
Benzimidazole, Benzoic acids, Biological activity Carboxylic acids, o-phenylene diamine.

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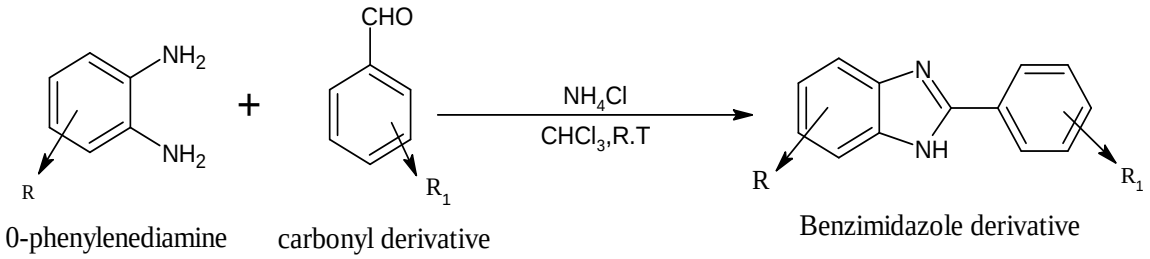
INTRODUCTION:
Benzimidazoles are heteropoly cyclic organic compounds containing a benzene ring fused to an imidazole ring (five-member ring containing a nitrogen atom, 4 carbon atoms, and two double bonds). The hydrogen atom attached to nitrogen in the 1st position of benzimidazole nucleus readily tautomerizes which is responsible for isomerization in the derived compounds. Benzimidazole nucleus substituted at 1, 2, 5 and 6 positions with varied substituents has produced compounds possessing potent analgesic, anti-inflammatory and anti-depressant activity. Various positions of benzimidazole have been subjected to common chemical reactions to derive its derivatives for different medicinal purposes. Substituting the 2nd position with alkyl or bulky lipophilic aryl/ heteroaryl moieties produces compounds with increased pharmacological action. This review is a concise and critical account focusing on the synthesis and properties of pyrazolones as antimicrobial, antidepressant, anti-inflammatory, antioxidant etc.

MATERIALS AND METHODS:
SYNTHETIC METHODS OF BENZIMIDAZOLE DERIVATIVES
Nannapaneni DT *et al*, in presence of ammonium chloride as a catalyst synthesized benzimidazole compounds by the condensation reaction between o-Phenylenediamine and different carbonyl compounds. Ammonium chloride is a reasonable and safe catalyst. The overall yield of the derivatives was discovered to be between 75 and 94%. Melting point and TLC measurements were used to determine the compounds' purity. In addition to elemental analysis, the produced compounds were characterised using IR, NMR, and MASS spectrum data. Using an elevated plus maze model in Wistar rats with Diazepam as standard, the synthesised benzimidazole compounds

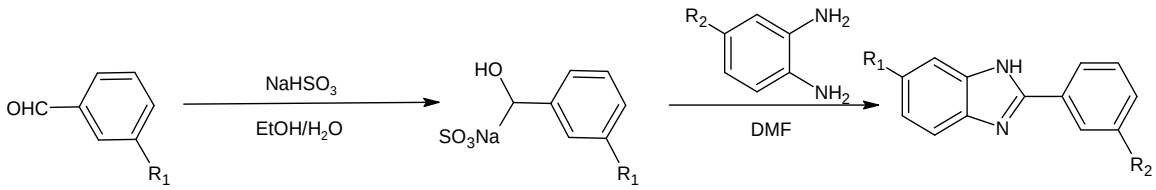
were tested for acute and chronic anti-anxiety effects(1).



0-phenylenediamine carbonyl derivative Benzimidazole derivative

Figure 1: Scheme 1

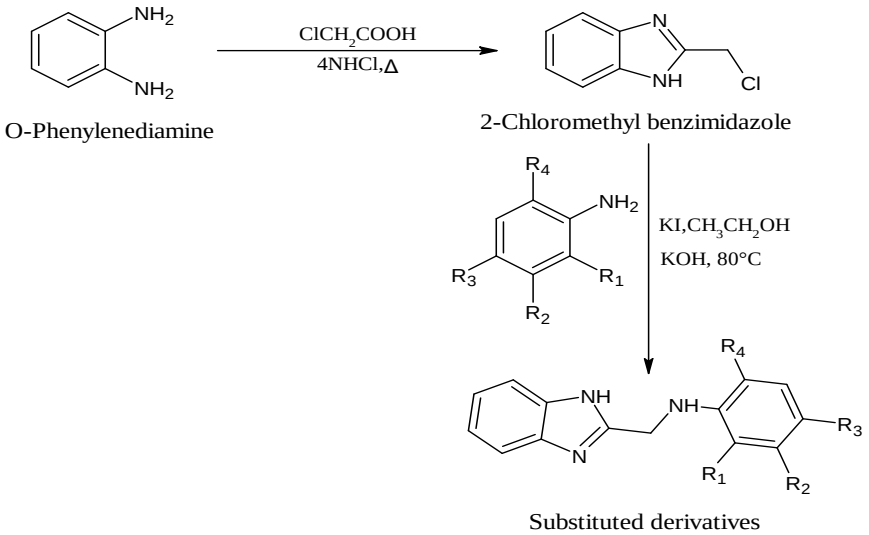
Weijie Si *et al*, generated several new benzimidazole derivatives with chrysanthemum acid moiety and anti-fungal activity of the compounds were investigated(2)



Benzaldeyde derivative sodium hydroxyphenyl methanesulfonate Benzimidazole derivative

Figure 2: Scheme 2

Guruswamy Mariappan *et al*, by reacting 2-chloro methyl benzimidazole with substituted primary aromatic amines, a novel series of 2-substituted benzimidazole derivatives were created. By using mass spectral data, UV, IR, NMR, and elemental analysis, all the compounds were identified. The synthetic compounds were tested for their anti-inflammatory and analgesic properties and every chemical had a discernible impact, and the experimental data are statistically significant (3).



O-Phenylenediamine 2-Chloromethyl benzimidazole Substituted derivatives

Figure 3: Scheme 3

Keshav Anand and Sharad Wakode *et al*, O-phenylenediamine and benzoic acid were combined to create several benzimidazole derivatives in a single step. TLC and NMR were used to determine the purity and confirm the structure of the produced compounds. The compounds' anti-microbial, anti-fungal, and antioxidant activity was assessed(4).

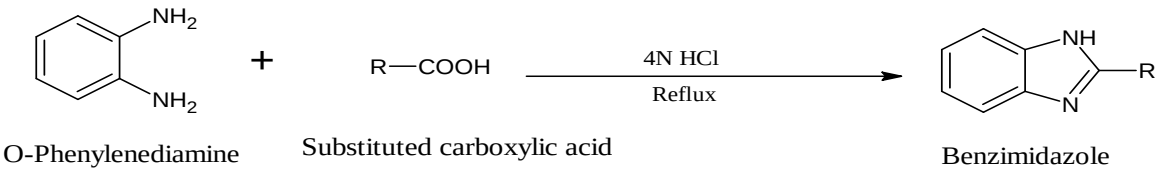


Figure 4: Scheme 4

Fatmah A. S. Alasmary *et al* created a collection of 53 benzimidazole derivatives with substituents at positions 1, 2, and 5 and then tested against several reference strains of bacteria and fungi. The SAR studies revealed that the compound's antibacterial properties were influenced by the substituents affixed to the bicyclic heterocyclic ring system(5).

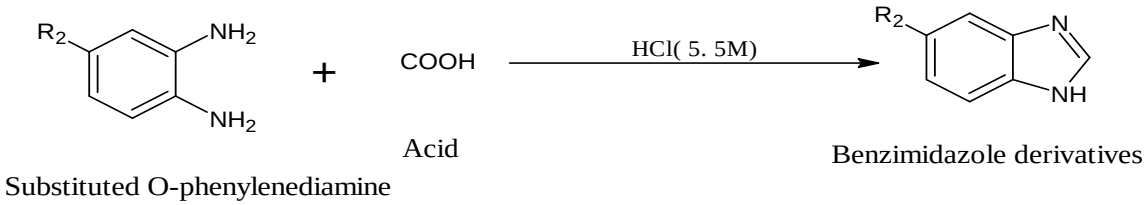


Figure 5: Scheme 5

Hamdan S. Al-Ebaisat *et al* studied several benzimidazole derivatives were produced quickly, cheaply, and simply by employing various ammonium salts. Only the anti-fungal activity of certain of these compounds was identified, described, and evaluated. Most of the chemicals discovered seemed to have antifungal properties(6)

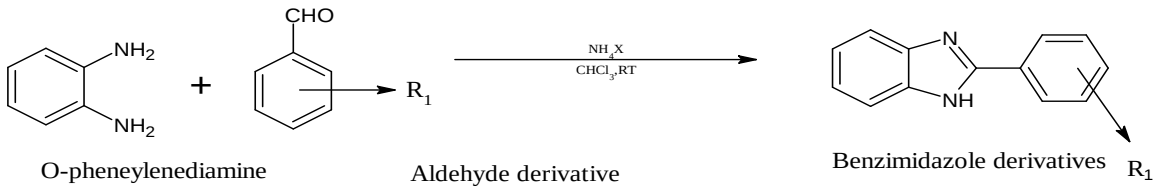


Figure 6: Scheme 6

Shahnaz M., Parminder Kaur, Parkash J., Parsad D. N. *et al* assessed several benzimidazole derivatives' for in-vitro antifungal efficacy. The different amine derivatives of o-phenylenediamine were reacted with carbon disulphide in the presence of potassium hydroxide to produce a variety of benzimidazole derivatives. By using the IR, 1H NMR, and chromatography methods, all the *bis*-derivatives were analysed. By using ciprofloxacin as a reference standard, the antibacterial activity of synthetic compounds was assessed using their MIC and zone of inhibition. The compounds' positive antibacterial activity was found by the microbiological assay(7).

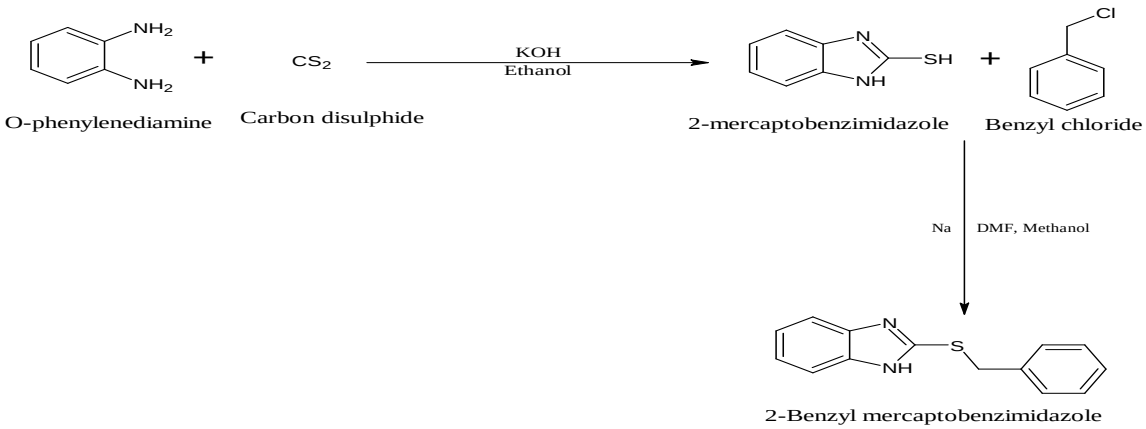


Figure 7: Scheme 7

Chintakunta and Meka *et al*, created 2-substituted benzimidazole derivatives by Phillips reaction, which resulted in condensation of o-phenylenediamine with various amino acids like glycine, alanine, aspartic acid, and L-proline. At high concentrations the synthesised derivatives demonstrated promising antibacterial activity against Bacillus subtilis and Pseudomonas aeruginosa. The medicine of choice was ciprofloxacin. By the recrystallization technique with ethanol, the synthesised benzimidazole derivatives were purified and melting point, TLC, and spectroscopic techniques including 1 H-NMR and FT-IR were used to describe the characteristics of the compound(8).

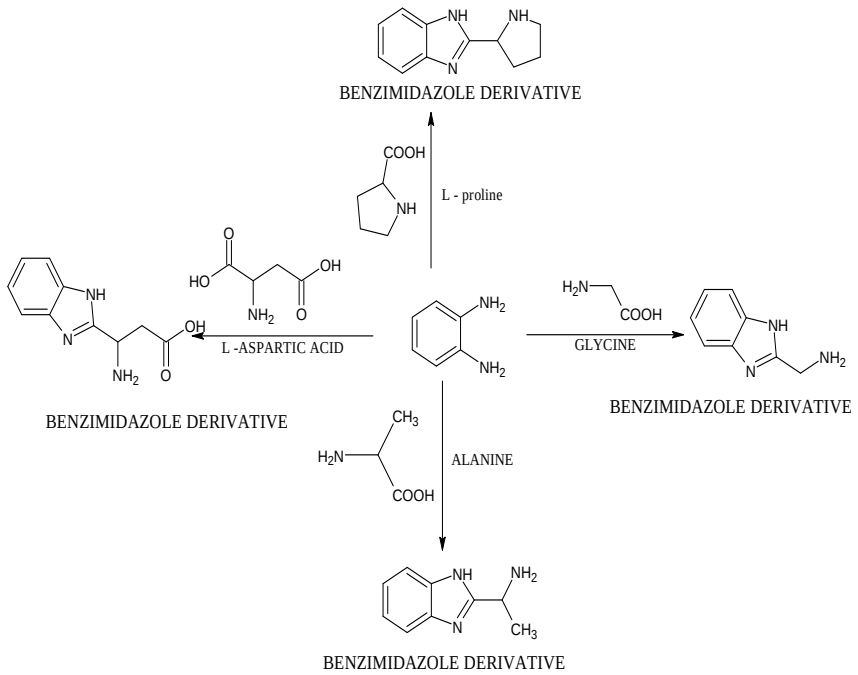


Figure 8: Scheme 8

Yadav *et al.* synthesised and evaluated novel benzimidazole compounds with an alkyl chain acting as a linker at the N-1 position in order to investigate their potential anti-HIV and antibacterial activities. Using spectral data, the structures of the produced compounds were clarified. Using virtual ADME, toxicity prediction, and structure activity relationship (SAR), it was possible to establish a link between the target compounds activities, electronic, and physicochemical properties, as well as their degrees of toxicity(9).

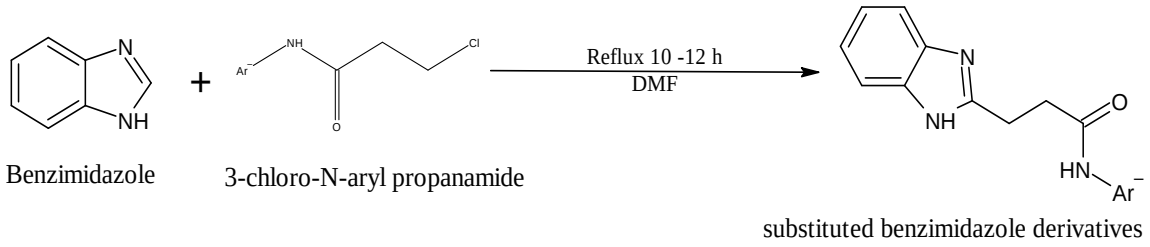


Figure 9: Scheme 9

Ahmed mudhafar mohamod *et al*. by nucleophilic substitution reaction between 5-(un) substituted-2-chloromethyl-1H-benzimidazole and 5-(un) substituted-2-mercapto-1H-benzimidazole in the presence of sodium in methanol, several novel bis benzimidazole derivatives were developed. The structures of the produced compounds were verified using spectral analysis techniques like FT-IR, $_1$H-NMR, and $_{13}$C-NMR. Four bacterial strains, including E. coli and P. aeruginosa, which are gram-negative bacteria, and B. subtilis and S. aureus, which are gram-positive bacteria, were used to test the antibacterial activity of most of the target compounds(10).

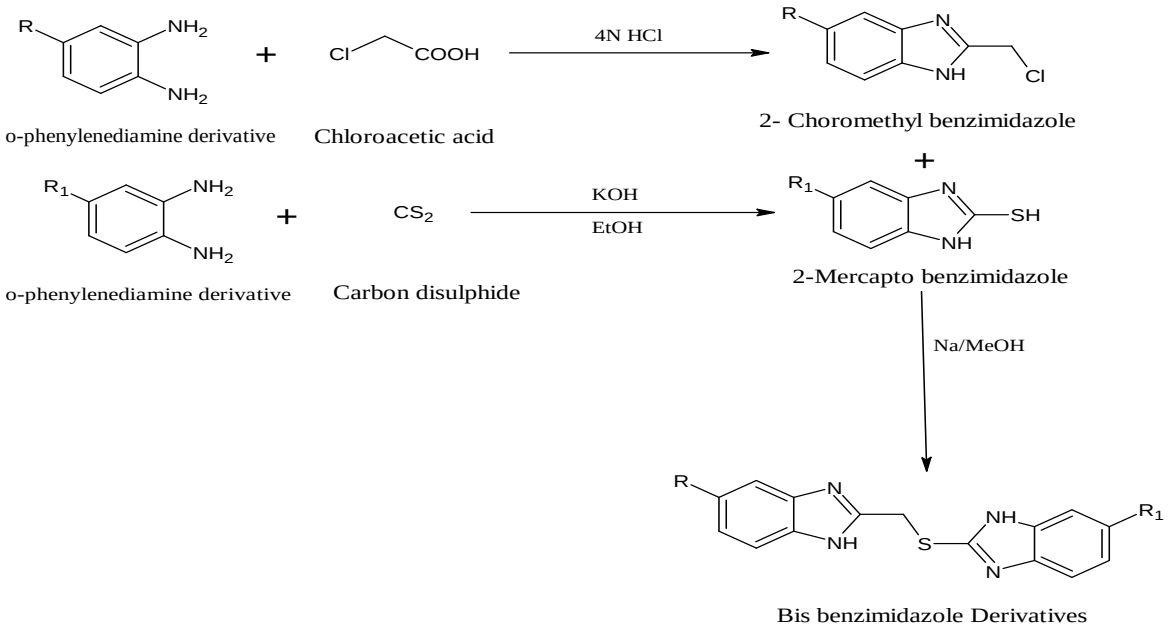


Figure 10: Scheme 10

Muayed ahmed redayan *et al*, synthesized novel benzimidazole derivative that contains a Schiff base moiety. By cycling 4-methyl-1,2-phenylene diamine with a number of amino acids like glycine, alanine, phenyl alanine, and tyrosine, the reaction was carried out to produce derivatives of benzimidazole compounds. The novel benzimidazole compounds with imine groups were produced by condensing these compounds with a range of aromatic aldehydes. FT-IR, $_{1}H$, $_{13}C$-NMR spectroscopy was used to confirm the chemical structure of the produced compounds. By using the disc diffusion method, some chosen compounds were examined in vitro for their antibacterial activities(11).

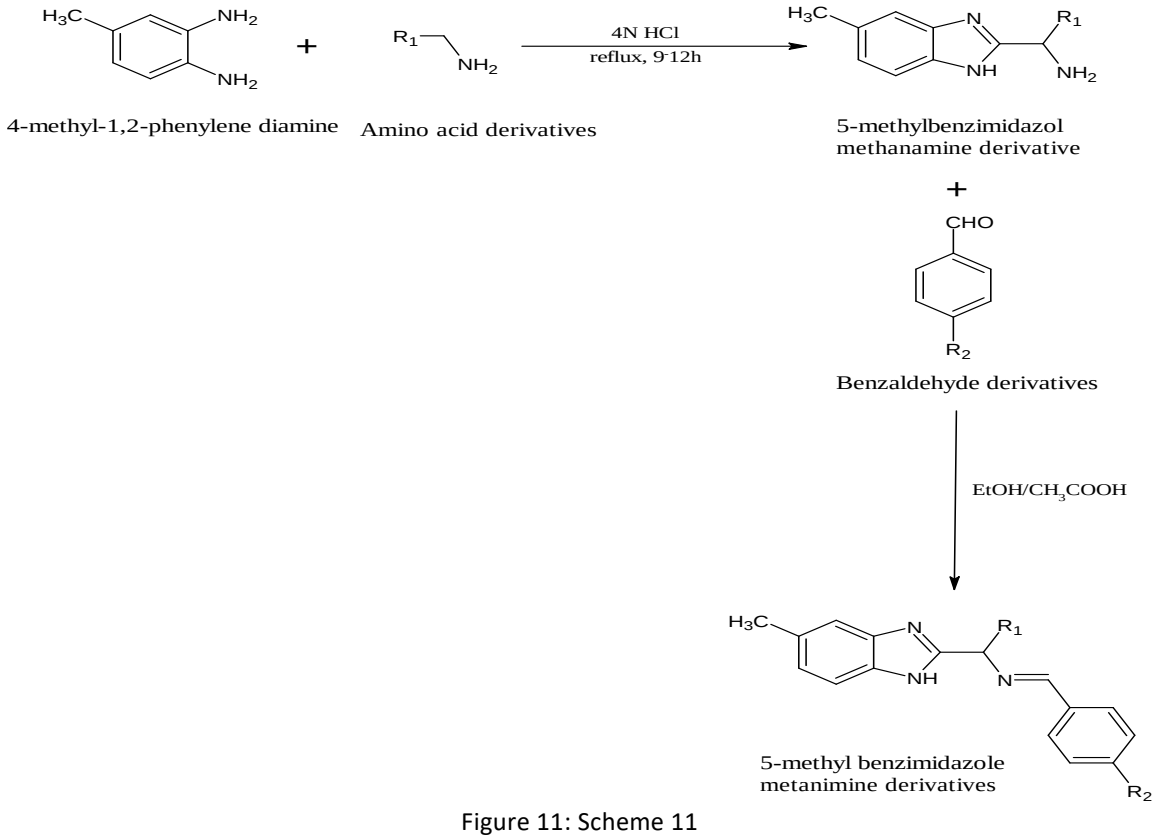


Figure 11: Scheme 11

R1	R2
H	OH
CH_3	Br
$C_6H_5CH_2$	NO_2
OH-C_6H_5-CH_2	-

Table 1

Brishty *et al*, in the current study describes the synthesis and pharmacological assessment of several substituted benzimidazole derivatives. These derivatives were made by condensation of various o-phenylenediamine compounds with the corresponding aldehyde using ammonium salt as a catalyst. By using spectroscopic investigation using the IR and $_1$H NMR, all the derivatives were identified. The analgesic and antioxidant properties of the synthesised benzimidazole derivatives were examined using the DPPH free radical scavenging test and acetic acid-induced writhing inhibition in Swiss albino mice, respectively(12).

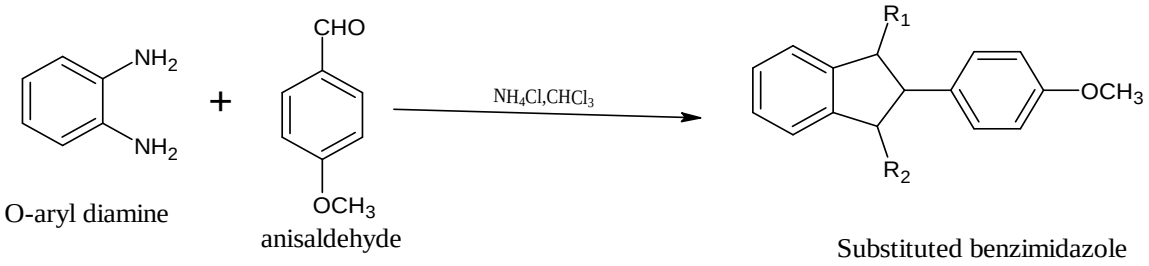


Figure 12: Scheme 12

Sarma *et al*, synthesized benzimidazole nuclei through condensation of o-phenylenediamine with substituted aromatic acids in polyphosphoric acid, which upon reaction with ethyl chloroacetate and hydrazine hydrate in two separate processes produced substituted acetohydrazides. The targeted compounds were created by reacting substituted acetohydrazides with aromatic aldehydes, and they were then tested using the cup-plate method for their antibacterial activity(13).

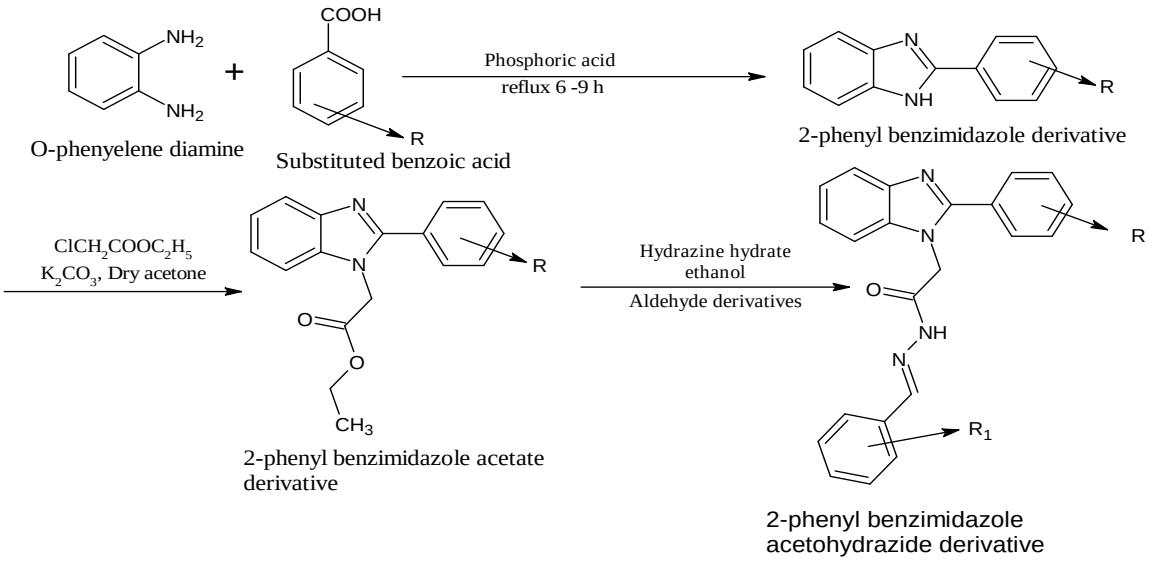
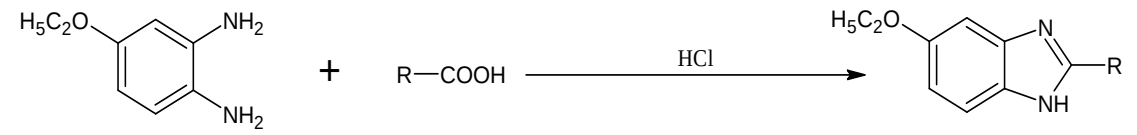


Figure 13: Scheme 13

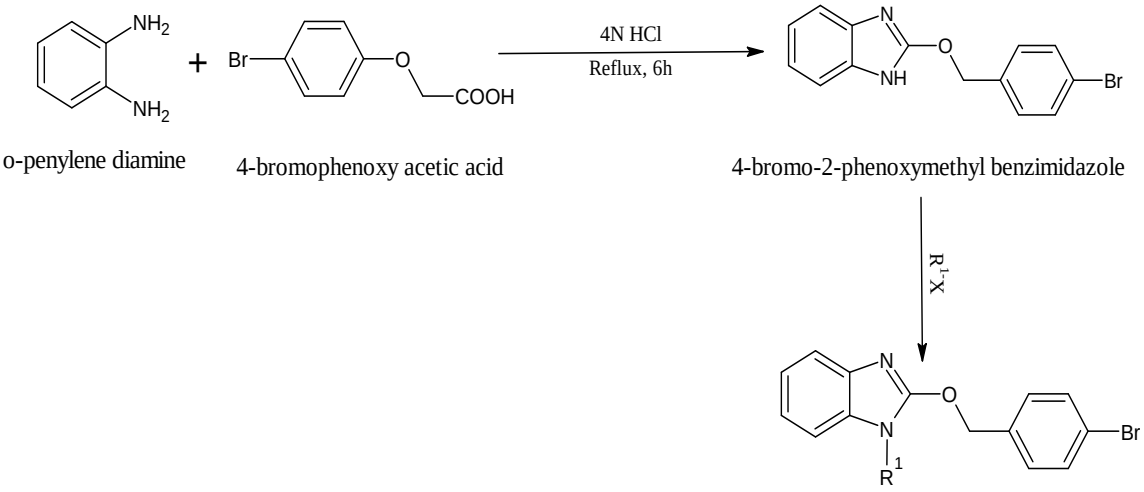
Sunila Patil *et al,* synthesized 5-ethoxy benzimidazole from 5-ethoxy ortho phenylenediamine with substituted acids. Elemental analysis, FT-IR, NMR and Mass spectral analysis were carried out. The synthesized compounds were evaluated for anti-tubercular activity(14).



2-ethoxy ortho phenylenediamine Substituted acids Benzimidazole derivatives

Figure 14: Scheme 14

Gund *et al*, synthesized benzimidazole by condensing o-phenylenediamine with 4 bromo phenoxy acetic acid. The final product was then electrophilically alkylated at the benzimidazole NH with various reagents. These compounds were all identified using FT-IR, 1H NMR, MS, and elemental analysis. These substances were examined for potential antibacterial and antifungal properties(15).

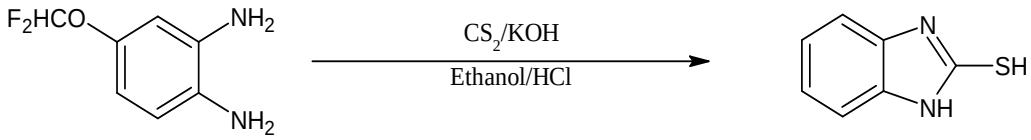


o-penylene diamine 4-bromophenoxy acetic acid 4-bromo-2-phenoxymethyl benzimidazole

N-alkylated derivative of 4-bromo-2-phenoxymethyl benzimidazole

Figure 15: Scheme 15

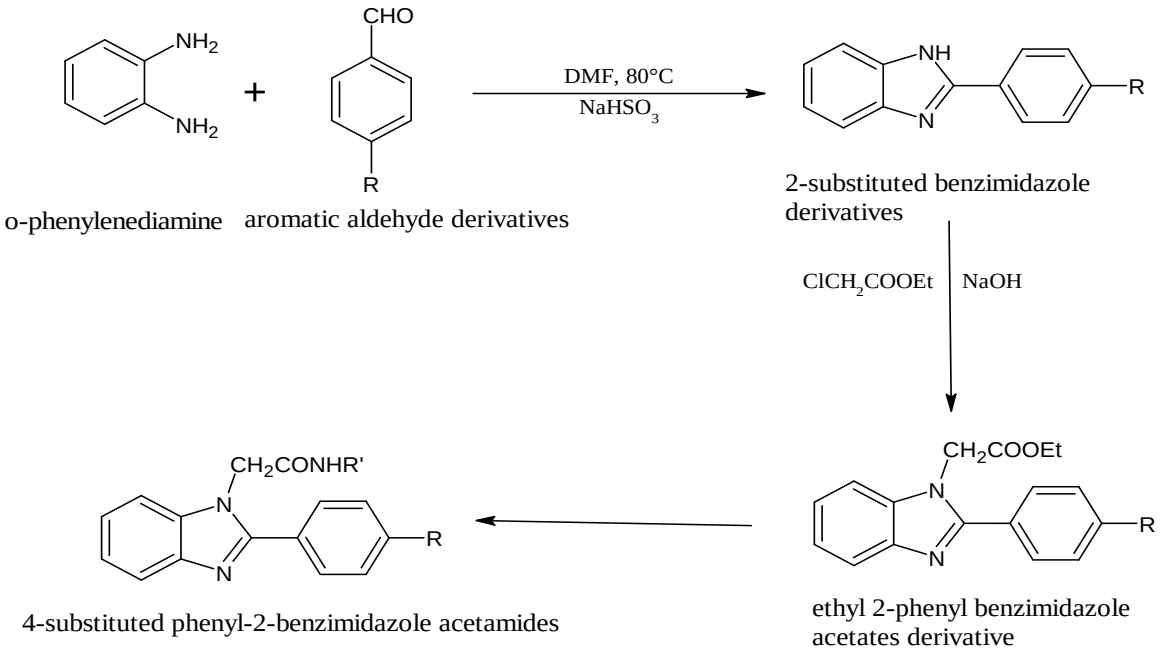
Choudhary Kapil *et al,* conducted this study to examine the Benzimidazole derivatives anti-microbial properties. Several benzimidazole derivatives were synthesized using Ethyl acetate and benzene as the starting materials. It was possible to prepare a series of 1, 2-disubstituted benzimidazoles with pyrimidine and other functional groups, which offers benefits like high yield(16).



4-difluouomethoxy bezene-1,2-diamine 5-difluoromethoxybenzimidazole-2-thiol

Figure 16: Scheme 16

R. Sawant and D. Kawade, synthesized a series of 2-phenyl benzimidazole-1-acetamide derivatives and evaluated the anti-anthelminthic activity using standard drug(17).



o-phenylenediamine aromatic aldehyde derivatives

2-substituted benzimidazole derivatives

ethyl 2-phenyl benzimidazole acetates derivative

4-substituted phenyl-2-benzimidazole acetamides

Figure 17: Scheme 17

BIOLOGICAL ACTIVITY OF BENZIMIDAZOLE DERIVATIVES

Anti-bacterial

Endale Mulugeta and Yoseph Samuel (18), in this study outlines the process for creating benzimidazole-sulfonyl hybrids and the candidates' potential bioactivity, such as their antibacterial properties. Strong antibacterial activity has been shown by benzimidazole-sulfonyl derivatives, **1a, 1b and 1c** against both Gram-positive and Gram-negative bacterial strains. Presence of the p-nitrophenyl methyl ether group at position 2 of N-toluene-sulfonyl Bromo benzimidazole gives good anti-bacterial activity.

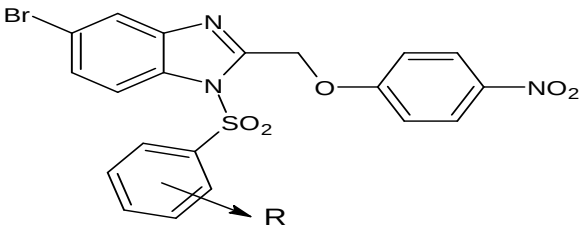
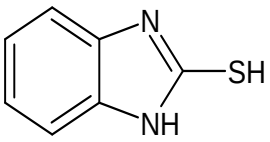


Figure 18: 1a, 1b and 1c

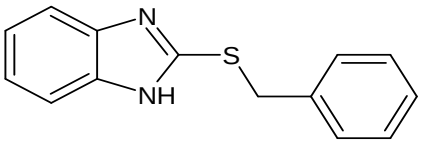
NO.	R
1a	2,5-F
1b	6-NO_2
1c	6-Cl

Table 2

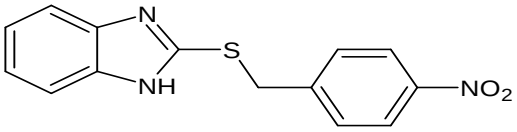
Shahnaz et al (7)Using Ciprofloxacin as the reference, the in vitro antibacterial activity of 2-substituted benzimidazole derivatives were assessed against Staphylococcus aureus, Bacillus subtilis, and Escherichia coli. The synthesized derivatives 2**a, 2b, 2c** exhibited a modest level of antibacterial activity.



2-mercaptobenzimidazole (**2a**)



2-benzyl mercapto benzimidazole (**2b**)



2-(p-nitro) benzyl mercapto benzimidazole (**2c**)

Figure 19: 2a, 2b and 2c

Verma *et al*,(19) created new benzimidazole derivatives which underwent for in-vitro testing for antibacterial activity against both Gram-Positive bacteria Staphylococcus aureus and Gram-Negative bacteria Escherichia coli using several techniques. The results of the antimicrobial screening show that derivatives **3a, 3b and 3c** had good action against every strain.

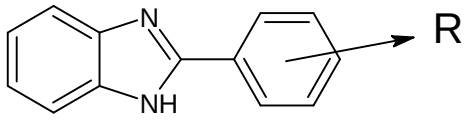


Figure 20

NO.	R
3a	C_6H_5
3b	2-Cl- C_6H_5
3c	4-Cl- C_6H_5

Table 3

Chintakunta and Meka ((8)In the current work, benzimidazole analogues were synthesized and the MIC method was used to test them for antibacterial activity and the **4a** is quite active against B. subtilis when compared with other derivatives.

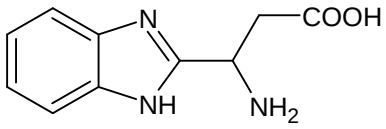


Figure 21: 4a

Muayed ahmed redayan et al(11), synthesized various benzimidazole derivatives and *in-vitro* anti-microbial activity were evaluated. Among the synthesized compounds, **5a, 5b and 5c** was found to be active against both gram positive and gram-negative bacterial strains

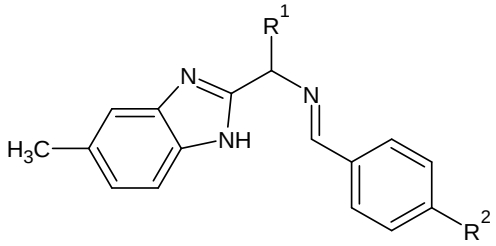


Figure 22: 5a, 5b and 5c

No.	R_1	R_2
5a	H	Br
5b	CH_3	OH
5c	C_6H_5 -CH_2	NO_2

Table 4

Sarma *et al*, (13) with the help of IR, NMR, mass spectrometry, and elemental analysis, a novel series of N-(substituted benzylidene)-2- [(2-(substituted phenyl)-1H-benzimidazol-1-yl) acetohydrazide derivatives were created. The resulting compounds were tested using the cup-plate method for *in vitro* antibacterial activity against both Gram-positive and Gram-negative strains of bacteria using ciprofloxacin as standard. The compounds **6a–6f** have superior bacterial growth inhibitory activity among the other synthesized compounds.

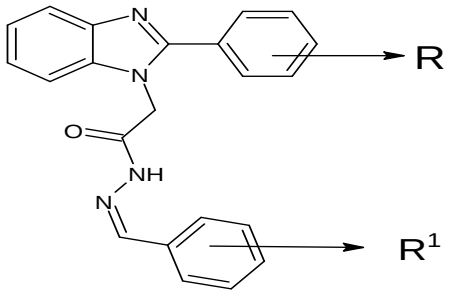


Figure 23

NO.	R^1	R
6a	C_6H_5	C_6H_5
6b	2-OH-C_6H_5	C_6H_5
6c	2-Cl- C_6H_5	C_6H_5
6d	-C_6H_5	2-OH-C_6H_5
6e	2-OH-C_6H_5	2-OH- C_6H_5
6f	2-Cl- C_6H_5	2-OH- C_6H_5

Table 5

Anti-fungal

Endale Mulugeta and Yoseph Samuel (18)developed benzimidazole sulfonyl derivatives and evaluated their anti-fungal activities. On evaluation it was confirmed that compound **7a** was found to be more active among the developed derivatives.

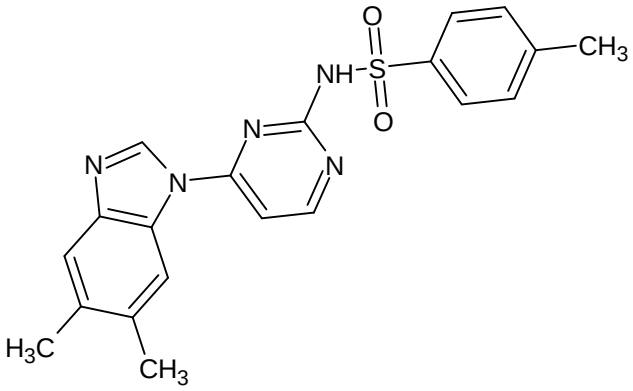


Figure 24: 7a

Al-Ebaisat *et al* (6)synthesized various benzimidazole derivatives and purity of the developed compounds was determined using TLC and MS, IR, and NMR spectral analyses were used to further confirm the assigned structures. Strong anti-fungal activity was discovered in some of the produced compounds, comparing **8a** to other benzimidazole compounds, they showed greater activity. As a result, it can be concluded that the benzimidazole derivatives may one day be used as effective anti-fungal drugs.

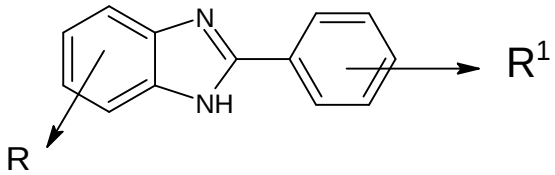


Figure 25: 8a **R^1 = 4 -CH_3**

Anti-poliferative activity

Ronak Haj Ersan(20) conducted the design and synthesis of several 2-(benzyl/phenylethyl/phenoxy methyl) benzimidazole derivatives with diverse substituents. By comparing the results with the standard antiproliferative medication, methotrexate, the derivatives demonstrated strong antiproliferative activity against five human cancer cell lines. Results of the antiproliferative activity test showed that substituted benzimidazole derivatives had an advantageous effect. Based on the results of the investigation, it can be said that the compounds with aliphatic linkers, **9a** exhibit good to robust antiproliferative activity and high selectivity.

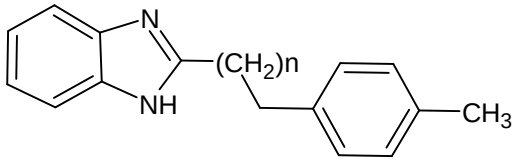
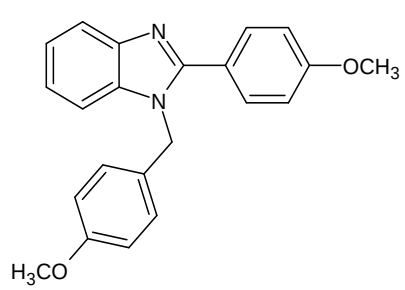


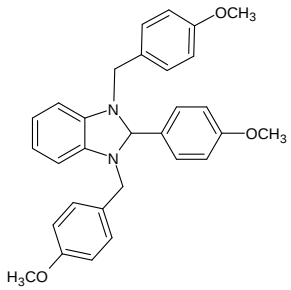
Figure 26: 9a

Anti-oxidant

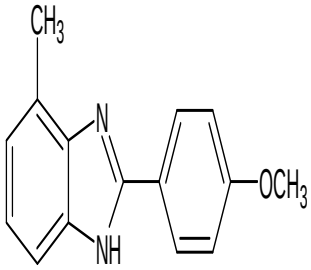
Brishty *et al*, developed various derivatives of benzimidazole nucleus among which compounds **10a, 10b, 10c** outperformed standard BHT in the evaluation of antioxidant property. The presence of the p-methoxybenzyl group on the imidazole nitrogen of compounds may have boosted their antioxidant capacity compared to the standard, making them the most promising antioxidant agents.



10a



10b



10c

Figure 27: 10a, 10b and 10c

Anti-inflammatory

Mariappan, G. *et al*,(3) synthesized various benzimidazole derivatives and *in-vivo* anti-inflammatory properties of all synthesised compounds were examined, and most of them **11a, 11b and 11c** were found to have notable analgesic and anti-inflammatory effects**.**

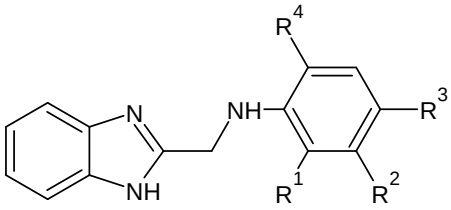


Figure 28: 11a, 11b and 11c

NO.	R_1	R_2	R_3	R_4
11a	Cl	Cl	H	H
11b	H	H	NO_2	H
11c	H	H	F	H

Table 6

CONCLUSION:

Benzimidazole are the important class of heterocyclic aromatic organic compounds which share a fundamental structural characteristic of six-membered benzene fused to five-membered imidazole moiety. Molecules having benzimidazole motifs showed promising application in biological and clinical studies. Nowadays it is a moiety of choice which possesses many pharmacological properties extensively explored with a potent inhibitor of various enzymes involved in a wide range of therapeutic uses. The increased interest for benzimidazole compounds has been due to their excellent properties, like increased stability, bioavailability, and significant biological activity. This review mainly discussed recent synthetic methods developed for the benzimidazole derivatives and their pharmacological properties exemplified on several derivatives.

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