



A SUMMARY OF THE BIOLOGICAL ACTIVITIES OF BENZIMIDAZOLE

Md Afaque^{1*}, Saddam Hussain¹, Md. Shamsir Alam¹, Md. Anwar Salik¹, Md. Rahat Raza¹, Md. Quamar Niyaz¹

Faculty, School of Pharmacy, Al-karim University, Katihar (Bihar).



***Corresponding Author: Md. Afaque**

Faculty, School of Pharmacy, Al-karim University, Katihar (Bihar).

DOI: <https://doi.org/10.5281/zenodo.19280866>

How to cite this Article: Md. Afaque^{1*}, Saddam Hussain¹, Md. Shamsir Alam¹, Md. Anwar Salik¹, Md. Rahat Raza¹, Md. Quamar Niyaz¹. (2026). A Summary of The Biological Activities of Benzimidazole. European Journal of Biomedical and Pharmaceutical Sciences, 13(4), 52–70.

This work is licensed under Creative Commons Attribution 4.0 International license.



Article Received on 25/02/2026

Article Revised on 17/03/2026

Article Published on 01/04/2026

ABSTRACT

When benzene and an imidazole ring merge, a heterocyclic a compound known as benzoimidazole is formed. Analogs of benzoimidazole are very important due to their biological activity and numerous clinical uses. One potential class of functional heterocyclic substances with several kinds of biological properties is benzoimidazoles. As a flexible heterocyclic a broad range of biological characteristics, along with anti-bacterial, antiviral, anti-diabetics, and anticancer, and various anti-oxidants, anti-parasitics, antihelminthic, antiproliferatives, anti-HIV, anticonvulsants, anti-inflammatory, anti-hypertensives, PP inhibitors, and anti-trichinellosis properties, the work in this article focuses on benzimidazole. Significant biological effects, such as potential anticancer agents and inhibitors of smooth muscle cell proliferation, are possessed by benzomidazoles in a variety of chemistry-related fields.

KEYWORDS: Benzimidazoles, early rationality, SAR and pharmacological activity.

INTRODUCTION

One carbon atom separates the nitrogen atom in imidazole, sometimes referred to as iminazoline, an azapyrrole. Because the German chemist Heinrich Debus initially synthesized this chemical in 1858 from glyoxal, formaldehyde, and ammonia, it was once known as glyoxalin.^[1] Imidazole or iminazoline heterocycles, in which one carbon atom separates the nitrogen atom, involve the azapyrrole component. When it was first made in 1958 using ammonia and glyoxal, it was also known as glyoxalin. Other names for benzomidazole include 1, 3-benzodiazole and 1H-benzimidazole.^[2] In medicinal chemistry, benzoimidazole is a well-known structure having a variety of biological functions. The 5-member ring moiety linked with benzene ring that contains heteroatoms at positions one and three to form a benzannulated ring system. For a century, researcher has examined properties of benzimidazole its analogs. However, because 5, 6-dimethyl-1-(α -dribofuranosyl)Benzimidazole is a fundamental component of vitamin B₁₂, researchers have a particular interest in benzimidazole derivatives.^[3] A kind of bicyclic aromatic chemical molecule, benzoimidazole is benzo analogues of imidazole (**Figure 1**). It consists of a five-member imidazole moiety attached to a 6-member

benzene ring at positions four and five. It is also called 1H-1, 3-Benzimidazole. Its IUPAC designation is 1H-Benzimidazole. Hobrecker cooked it for the first time in 1872.^[4] Purine, histamine, histidine, nucleic acid, and benzimidazole derivatives are among the many natural molecules that have a special place in medicinal chemistry as important ingredients. By attached a lengthy Propyl, Acetamido, Thio, and Thiazole chain amine, and tetra-methyl piperidine or pyridine and analogues of benzimidazole at its N-H with an electron-donating groups, benzimidazole derivatives with high analgesic efficacy were created in 1991. Benzimidazole medications are frequently used to treat and prevent parasitic illnesses Well-known newly discovered benzimidazole medications include **1** esomeprazole **2** Rabeprazole, **3** Lansoprazole, **4** Pantoprazole, **5** esomeprazole. Following its launch, a number of benzimidazoles with comparable properties were introduced to the market, including oxibendazole **10** (OXI), mebendazole (MBZ) **7**, parabendazole (PAR) **8**, and cambendazole (CAM) **9**.^[5] N-ribosyl di-methyl benzimidazole has the highest frequent benzimidazole molecule in natures; it serves as axial ligands for cobalt in vitamins B₁₂.^[6] These days globally, Infective microorganism diseases are presenting problems due to

resistance to various anti-microbial drugs, including vancomycin, beta-lactam antibiotic, macrolides, and quinolones. Numerous clinically significant microorganism species have emerged as a major worldwide health concern.^[7] Benzimidazole-containing medications that are on the market include **1** nocardazole, **2** benda mustine, **3** veliparib, **4** glasdegib, **5** crenolanib, **6** abemaciclib, **7** liarozole, and **8** pracinostat (**Fig. 3**). Malignancy is a collected of harmful conditions identified by unchecked cells growth that attacks surrounding tissue and frequently spreads to other body areas.^[8] In table 1 shown structure activity relationship of benzimidazole derivatives in anticancer drug design. In table 2 displayed Benzimidazole based anticancer drugs

in clinical development. In table 3 screened Pharmacological Activities of 1H-Benzimidazole moiety Containing Drugs.

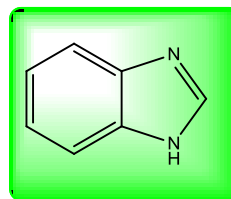
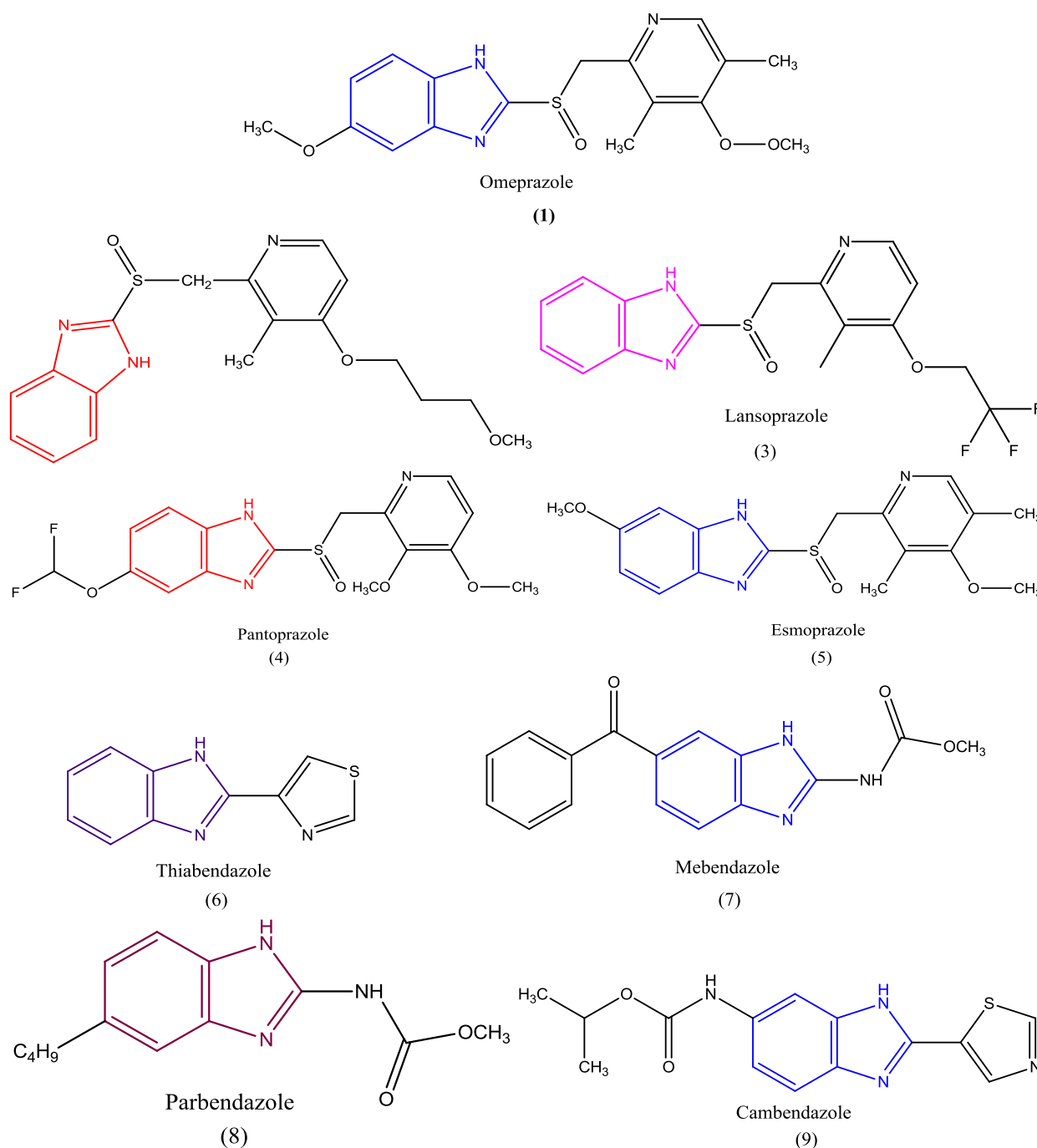
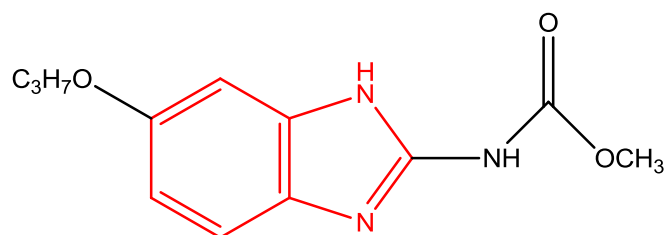


Fig.1 Structure of 1H-Benzimidazole ring





Oxibendazole

(10)

Fig. 2: Early rationally of discovered benzimidazole medicines.

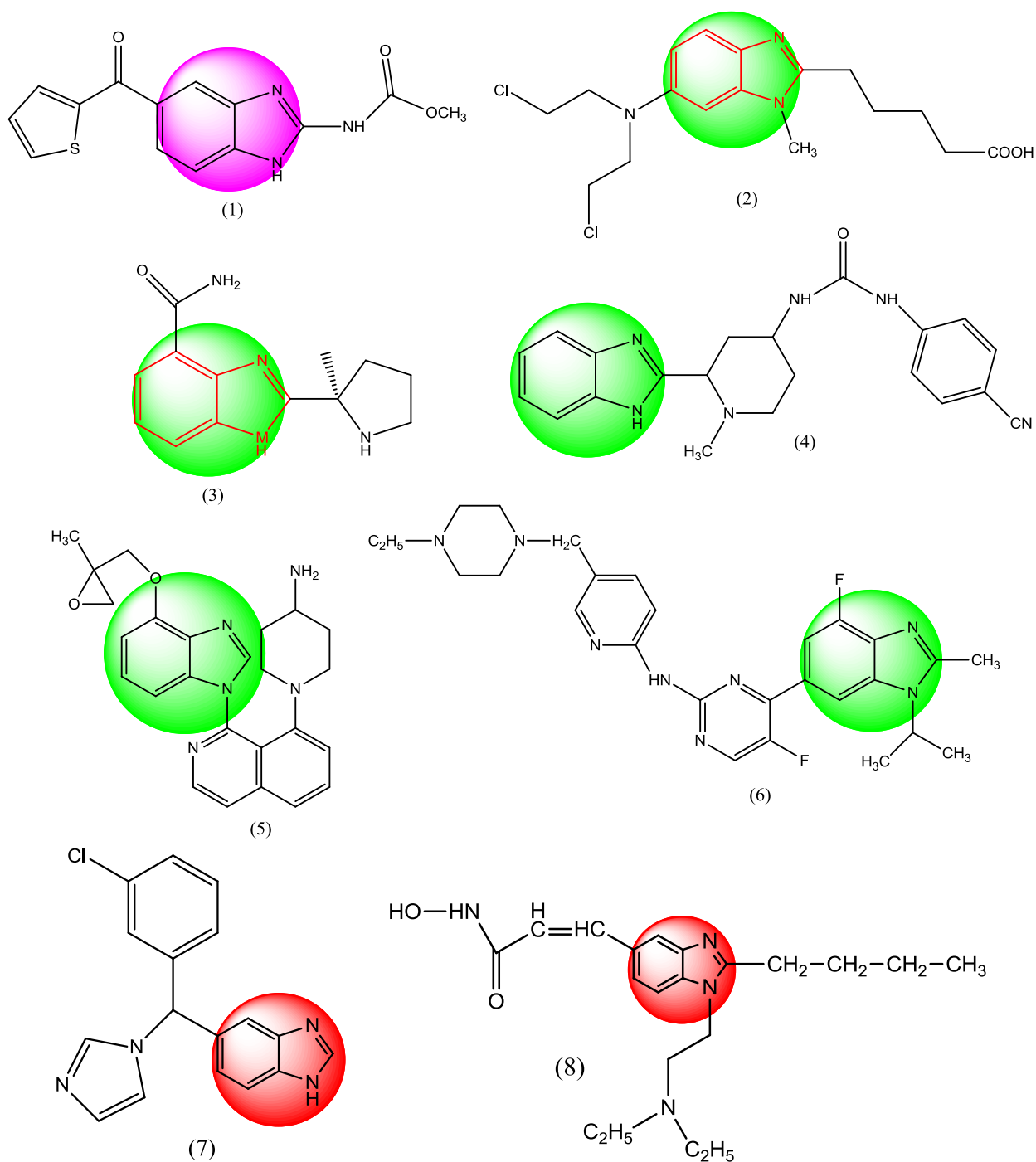


Fig.3 Marketed medicines having benzimidazole constituent.

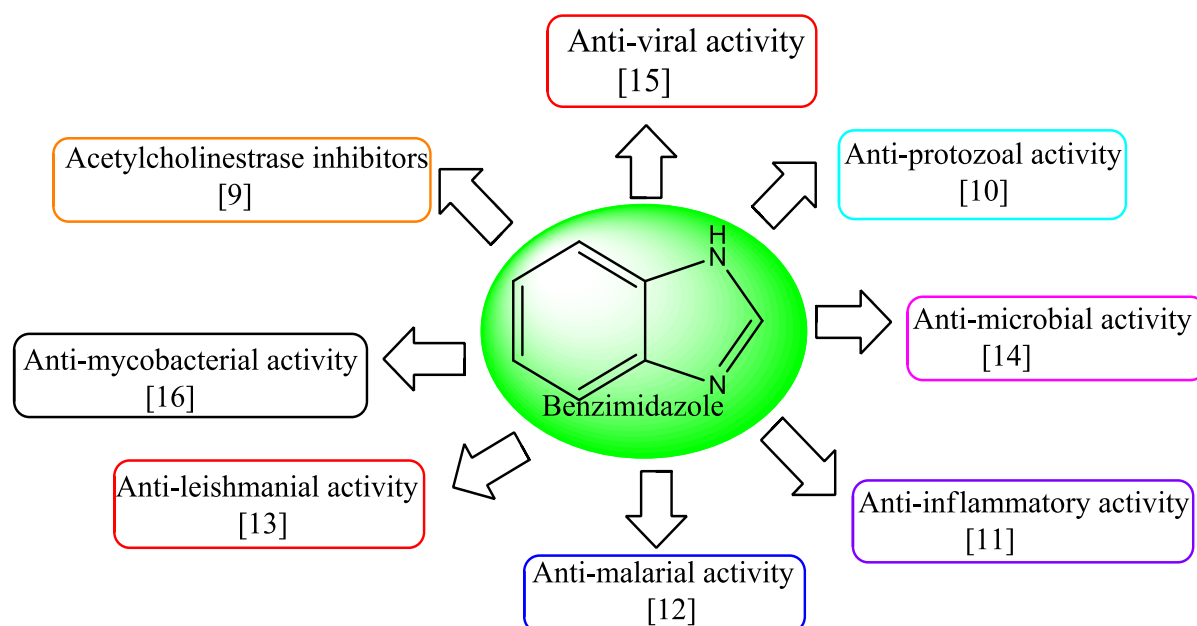


Fig. 4 Biological activity of heterocyclic nucleus of benzimidazole derivatives

PHYSICAL PROPERTIES

Amphoterism

Benzimidazole is amphoteric in nature refers to its ability to function as both a basic and an acid.

Molecular Formula of Benzimidazole is $C_7H_6N_2$

Molecular weight of Benzimidazole is 118.14 g/mol

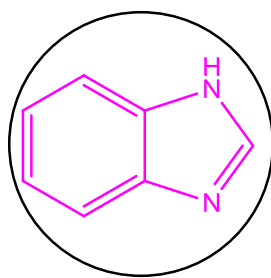
Melting point 171 – 174 °C

Boiling point 360 °C

pKa Values

- **pKa (as a base):** The pKa of benzimidazole as a base is around 12.8. This indicates it's relatively weak, meaning it readily accepts a proton to form its conjugate acid.
- **pKa (as acid):** The pKa of benzimidazole's conjugate acids is around 5.6. This suggests it's a moderately weak acid, meaning it will only partially donate a proton.

Table 1: Structure-Activity Relationship (SAR) of Benzimidazole Derivatives in [17 – 22] Anticancer Drug Design.



Sr. No.	Modification	Effect on Anticancer Activity	Examples
1	Alkylation at N1/N3 (-CH ₃ , C ₂ H ₅)	Improves metabolic stability	Methylbenzimidazoles
2	Halogen substitution (Cl, Br, F)	Increases lipophilicity and enhances cell permeability	5-Chlorobenzimidazole
3	Heterocyclic ring fusion (quinoline, thiazole)	Increases DNA intercalation	Quinoline-fused benzimidazole
4	Electron-withdrawing groups (-NO ₂ , -CN, COOH)	Enhances binding to cancer enzymes	Nitrobenzimidazole derivatives
5	Metal complexation (Pt, Cu)	Enhances ROS generation and apoptosis	Copper-benzimidazole complexes

Table 2: Common benzimidazole derivatives and their biological activities.^[23]

Sr. No.	Benzimidazole derivatives	Biological activity
1.	Albendazole sulfoxide	Anthelmintic, Antiparasitic
2.	Albendazole	Anthelmintic, Antiparasitic
3.	Domperidone	Antiemetic
4.	Itraconazole	Antifungal
5.	Lansoprazole sulfide	Proton pump inhibitor
6.	Clopidogrel	Antiplatelet
7.	Metronidazole	Antiprotozoal, Antibacterial
8.	Pantoprazole	Proton pump inhibitor
9.	Omeprazole	Proton pump inhibitor
10.	Ketoconazole	Antifungal
11.	Niclosamide	Anthelmintic, antiparasitic
12.	Thiabendazole	Antifungal, antiparasitic
13.	Vardenafil	Erectile dysfunction treatment
14.	Praziquantel	Anthelmintic
15.	Flubendazole	Antiparasitic
16.	Tinidazole	Antibacterial, antiprotozoal
17.	Meclizine	Antihistamine, antiemetic
18.	Risperidone	Antipsychotic
19.	Nimorazole	Antibacterial, antiprotozoal

BIOLOGICAL ACTIVITIES

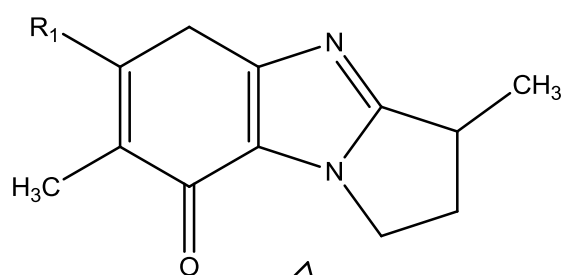
1. Anti-cancer activities

Cancer disease is one of the primary fitness concerns which are influencing a broad the bulk of the populations multiple anti-cancer drugs (also known as anti-tumor, anti-proliferative, and anti-neoplastics) have been used to treat a variety of cancer types. These drugs work in different ways. However, because these drugs are not selective for the aberrant cell, their primary adverse effect is carcinogenic to normal cell. Thus, the hunt for anticancer agents has been ongoing for a long time. As a purine-based nucleic acid isostere and a crucial scaffold in a variety of physiologically active compounds, benzoimidazole is being investigated extensively for the creation of anticancer drugs. One of the earliest groups of anti-cancer drugs, pyrrolo[1,2-a]benzimidazoles 1–3, works by cleaving Guanine and Adenine bases and reductively alkylating Deoxyribonucleic acid.^[24–28] The most effective Bis(benzimidazole) synthetic precursor against human cancer cell lines: A-549, BFTC-905, RD, MES-SA, and HeLa **4**, one of the benzimidazole isosteres that Huang et al. produced.^[29] Ramla et al. made 2-(N-benzyl-2-methyl-1H-Benzimidazol-5-ylimino)-3-(substituted)-thiazolidine-4-ones and 3-(2-methyl-1H-benzimidazol-5-yl)-2-substituted thiazolidines-4-one. They substantially tested them for anticancer effectiveness against EBV-EA activation using Phorbol-13-acetate (12-O-tetradecanoyl) -3-Benzoyl-2-(N-benzyl-(2-methyl-1H-Benzimidazol-5-yl-imino)thiazolidin-4-one **5**.^[30] Vedula and colleagues investigated novel styryl sulfone for anti-neoplastic efficacy towards several cells line. Out of the different compounds synthesized, a single substanc 6-Chloro-1H-(benzo[d]imidazol-2-yl) methyl [(E)-2-(4-chloro-3-methylphenyl)-1-Ethenyl] in mice with HT-29, sulphone **6** inhibited tumor growth by 51% at 400mg/kg orally.^[31] Gellis et al.^[32] produced Benzimidazoles-4, 7-di-ones

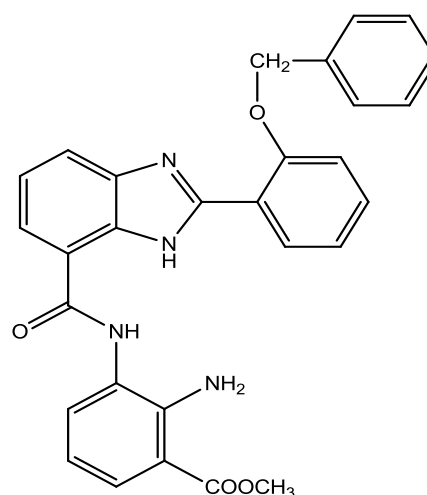
connected at the 2-position by a microwaves-assisted process employing 2-Chloromethyl-1, 5, 6-trimethyl-1H-Benzimidazole-4, 7diones. Anti-cancer properties were tested on colon, breasts, and lungs cancer cells line. Among these, 20 - Bi-(Chloromethyl) Dimethyl-5, 50-bis-(1H-Benzimidazole)-4, 40, 7, 70-tetraones **7** were displayed to have highly significant carcinogenic equivalent to mitomycin C. The title compounds were tested for suppression of MDAMB-231 breast cancer cells proliferation. The chemical 1(4-Fluorobenzyl)-1-(4-cyano-3-(tri-fluoromethyl)-phenyl)-2-(dichlorophenyl)-1H-benzo[d]imidazole-5-carboxamide **8** were shown to be most powerful inhibitors of breasts Thimmegowda et al.^[33] created a new class of trisubstituted benzimidazoles and their precursors cancer cells. N. Perin et al.^[34] manufactured a newly sequence of Acrylonitriles from aromatic aldehydes and N-substituted 2-cyanomethylbenzimidazoles utilizing the microwaves and traditional linear organics processes, and examined them for their in-vitro inhibitory efficacy on the different humans cancer cells lines such as Capan1, HCT-116, NCI-H460, DND-41, HL-60, K-562, MM.1S, and Z-138. The compounds with the most promising anticancer activity (IC₅₀ = 0.2-0.6 μM) were compounds **9** and **10**, which had isobutyl sides chains linked to benzimidazole moiety and cyano and isobutyl substituents, respectively. Additionally, tests showed that these compounds had no effects on normal cancer cells. These substances inhibited tubulin polymerization by breaking down the microtubule network. Furthermore, the computational research showed that the NMe₂ group facilitated binding the most and colchicine is the strongest tubulin binder. This allowed ligand to have optimal bonding interaction in addition to Lys352. The addition of electron-donating group at para-position NMe₂ group attached to the phenyl nucleus significantly enhanced its affinity, according to SAR tests. The potential to participate in the

highest binding with cys-241 was decreased by introducing an electron-drawing cyano group. The possibility for advantageous position rose with the addition of a big *n*-isobutyl group and fell with the inclusion of a smaller *n*-methyl group. 2,4-diarylbenzimidazole derived compounds were produced and biologically assessed by Ya-Liang Zhang *et al.*^[35], who discovered that many of them exhibited anticancer characteristics. With IC₅₀ values of 8.47 μ M and a GI₅₀ values of 0.71-2.41 μ M against HeLa, HepG2, A549, and MCF-7 cells, compound **(11)** shown the strongest anti-tumor activity. It also showed little toxicity to normal cells and the most inhibitory action against microtubules

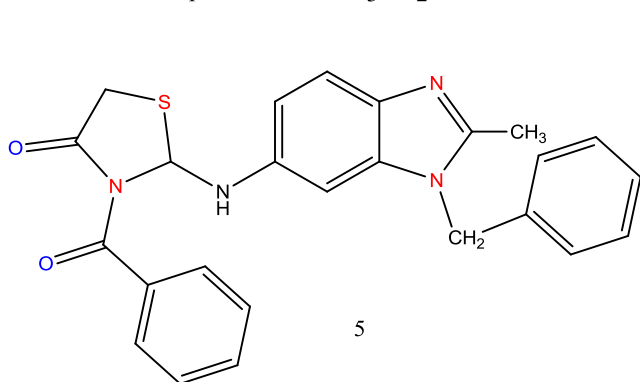
polymerization (IC₅₀ = 8.47 μ M). Compound **(11)**'s ability to attach to tubules crystals was confirmed by molecular docking analysis, and additional research on HepG2 and HeLa cells showed that it caused cancer cells to stop mitotically in the G2/M phase before inducing apoptosis. When the compounds were para-substituted instead of ortho- or meta-substituted, their activity was observed to increase. Afterwards, ortho-para and meta-para disubstituted sites were examined for methoxy and hydroxy substituents. The best activity was seen in 3, 4-(OCH₃)₂, indicating that 3, 4- disubstitution had a strongest action than 2, 4- disubstitution.



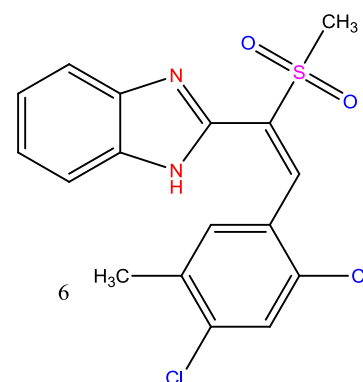
1. X = O, R₁ = HN, R₂ = CH₃
2. X = O, R₁ = NHCOCH₃, R₂ = Ester function
3. X = NH, R₁ = NHCOCH₃, R₂ = Ester function



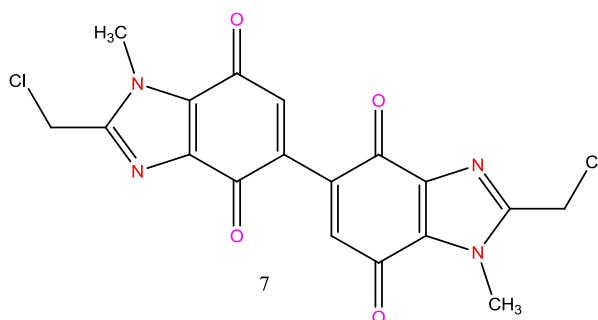
4



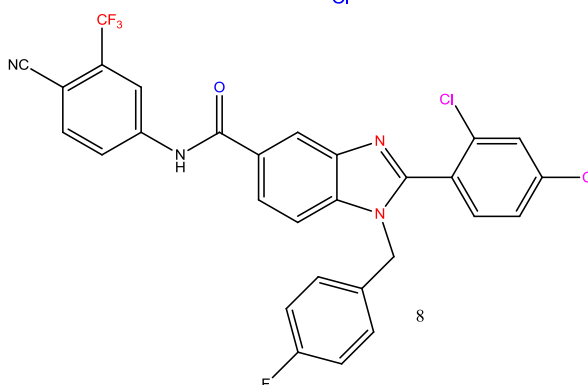
5



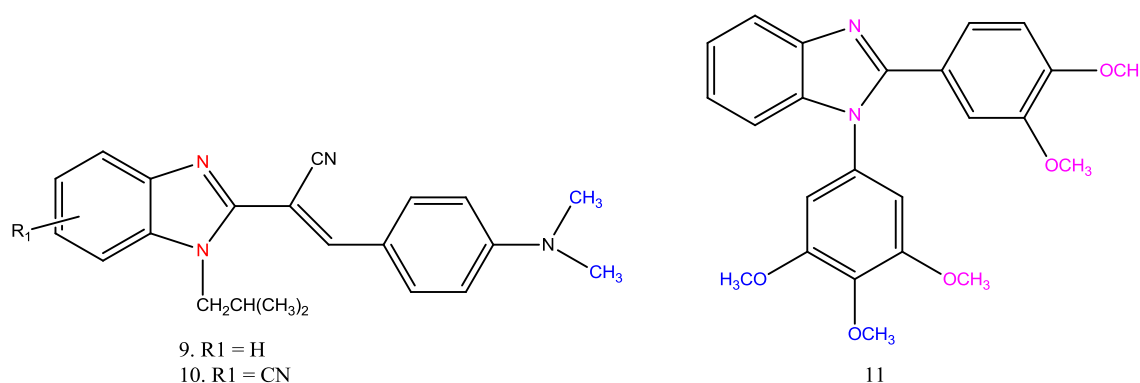
6



7

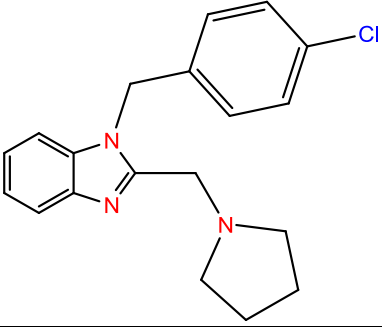
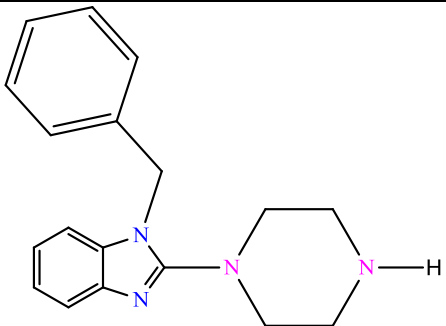
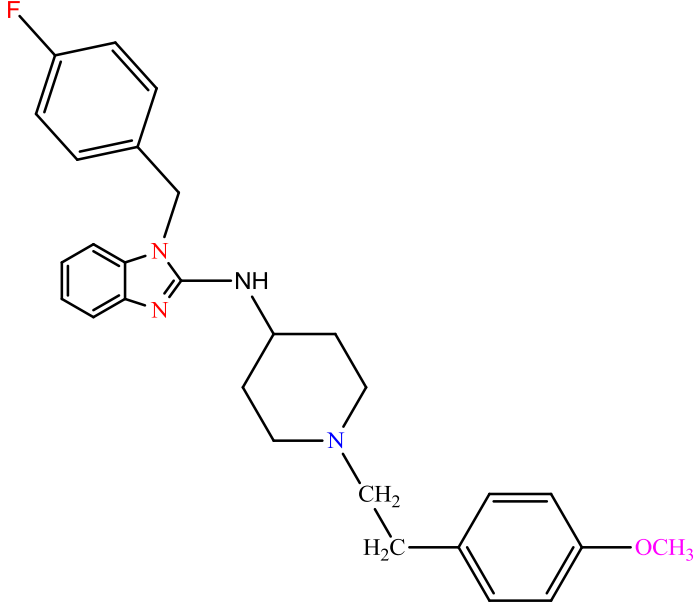
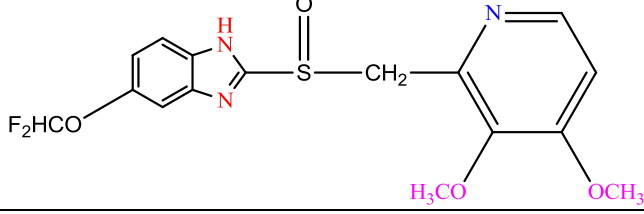
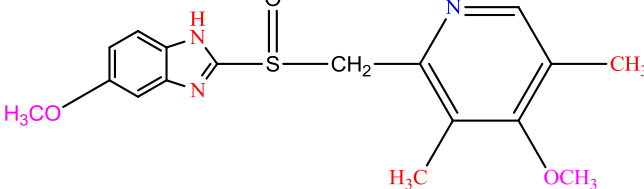


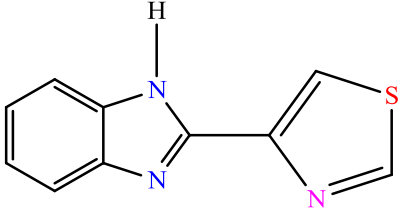
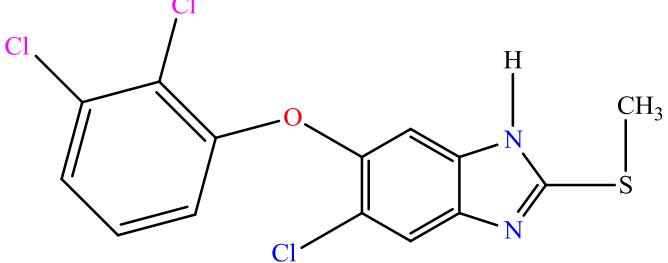
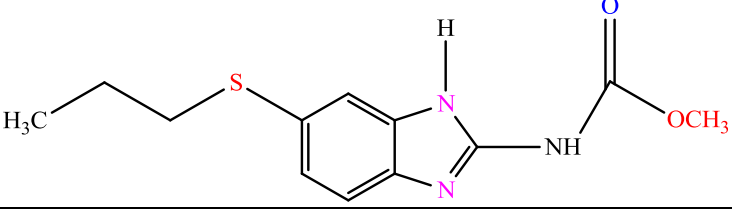
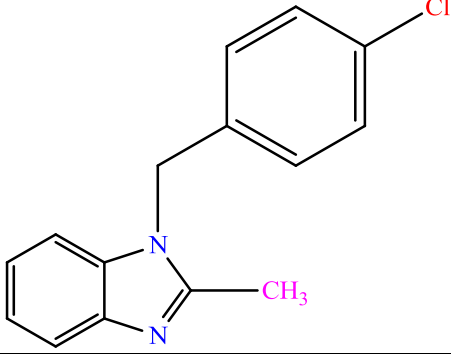
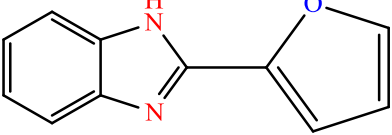
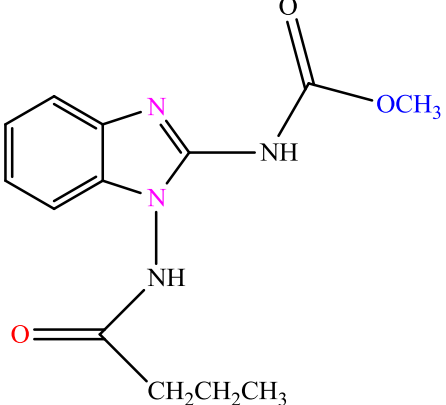
8

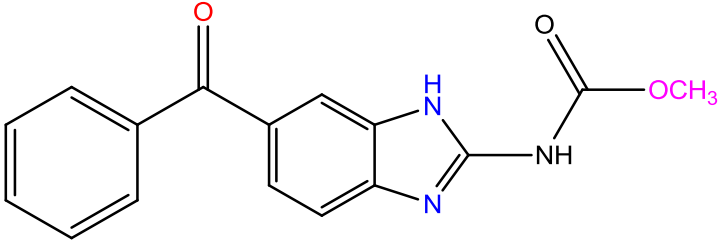
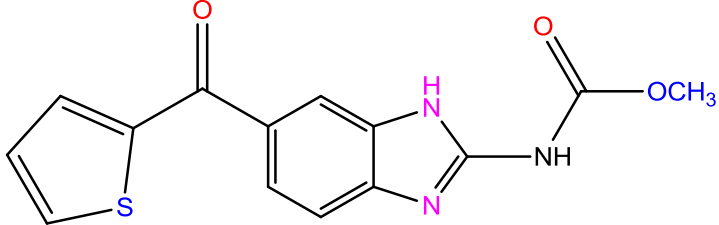
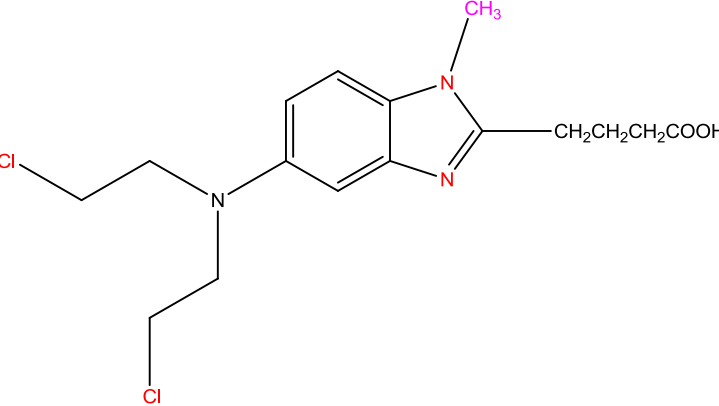
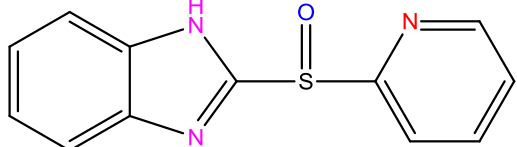
**Table 3: Benzimidazole based anticancer drugs in clinical development.**

Drug	Clinical trial number	Clinical trial study	Date of study	Current status and study phase
Bendamustine ^[36,37]	NCT04217317	CPI-613 in combination with Bendamustine in patients with relapsed or refractory T-cell Non-Hodgkin lymphoma	Last update on August 30,2021	Recruiting Phase 2
	NCT04510636	Study of Pembrolizumab with Bendamustine in Hodgkin lymphoma	Last update on August 30,2021	Not yet Recruiting Phase 2
Binimetinib ^[38,39]	NCT04965818	Phase 1b/2 study of Futibatinib in combination with Binimetinib in patients with advanced KRAS mutant cancer	Last update on September 27, 2021	Recruiting Phase 1b/2
	NCT03170206	Study of CDK4/6 inhibitor Palbociclib in combination with the Binimetinib for patients with advanced KRAS mutant NSCLC	Last update on June 10, 2021	Last update on September 27, 2021
Abemaciclib ^[40,41]	NCT04003896	A study to evaluate Abemaciclib in advanced biliary tract carcinoma who failed prior first line therapy.	Last update on	Active, Not recruiting Phase 2
	NCT04040205	Abemaciclib for bone and soft tissue sarcoma with cyclin dependent kinase (CDK) pathway	February 15, 2021	Recruiting Phase 2
Nazartinib ^[42,43]	NCT02335944	Study and safety and efficacy of Nazartinib in combination with cMET inhibitor INC280 in NSCLC patients with EGFR mutation	Last update on October 4, 2021	Active, not recruiting Phase 1/2
	NCT02108964	A phase I/II, multicentre, open label study of Nazartinib, administered orally in adult patients with EGFR mutated solid malignancies	Last update on August 13, 2021	Active, Not recruiting Phase 1/2
Galeterone ^[44]	NCT04098081	Galeterone with Gemcitabine for patients with metastatic pancreatic adenocarcinoma	Last update on March 10, 2021	Recruiting Phase 2
Dovitinib ^[45]	NCT01635907	Dovitinib in neuroendocrine tumors	Last update on April 14, 2020	Completed Phase 2
Pracinostat ^[46]	NCT03848754	Pracinostat and Gemtuzumab ozogamicin in patients with relapsed or refractory acute myeloid leukemia	Last update on October 18, 2021	Active, not recruiting Phase 1
Veliparib ^[47,48]	NCT02723864	Veliparib and VX-970 in combination with cisplatin in people with refractory solid tumors	Last update on February 5, 2021	Active, Not recruiting Phase 1
	NCT01434316	Dovitinib in neuroendocrine tumors	July 20, 2021	Recruiting Phase 1

Table 4: Pharmacological Activities of 1H-Benzimidazole moiety Containing Drugs.

S.No.	Name of the Drug	Structure	Pharmacological Class
1.	Clemizole		Antihistamine ^[49]
2.	Lerisetron		Antihistamine ^[50]
3.	Astemizole		Antihistamine ^[51]
4.	Pantoprazole		Proton pump inhibitor ^[52]
5.	Omeprazole		Proton pump inhibitor ^[53]

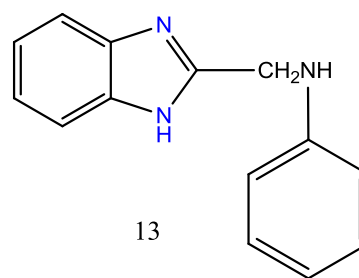
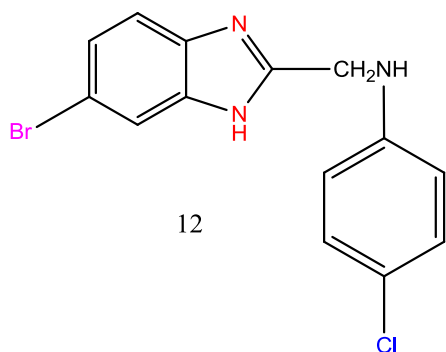
6.	Thiabendazole		Anthelmintic ^[54]
7.	Triclabendazole		Anthelmintic ^[55]
8.	Albendazole		Anthelmintic ^[56]
9.	Chlormidazole		Anti-fungal ^[57]
10.	Fuberidazole		Anti-fungal ^[58]
11.	Benomyl		Anti-fungal ^[59]

12.	Mebendazole		Antiparasitic, Worm infestation ^[60]
13.	Nocodazole		Anticancer ^[61]
14.	Bendamustine		Anticancer ^[62]
15.	Timoprazole		Anti-ulcer ^[63]

1.1. Anti-Inflammatory properties

2-N-((6-Bromo-1H-Benzo[d]imidazol-2-yl)methyl), methylaminobenzimidazole derivative par-chlorobenzenamine **12** and N-((1H-Benzo[d]imidazol-2-yl)methyl) benzenamine **13**, was produced by Achar et al.^[64] These substances had strong analgesic and anti-inflammatory properties when evaluated against nimesulide. Newly 5-linked-1-(phenylsulfonyl)-2-methylbenzimidazole analogues **14** has been prepared by Gaba et al.^[65] Applying indomethacin as a benchmark, these are those components were diagnosed for their anti-inflammatory activity along with their potential to

cause stomach ulcer by inducing edema of the rat paw and acetic acids induced writhing in mice. Numerous research teams have created new anti-inflammatory medications by making substitutions at positions 2 and 5. Utilizing benoxaprofen **16** as the lead chemical, Dunwel et al.^[66] produced compound **15** by bioisosterically replacing the benzoxazole moiety with benzimidazole. However, this compound could not alleviate inflammation in a rat paw edema model, most likely because of decreased solubility or changed drug receptor interactions.



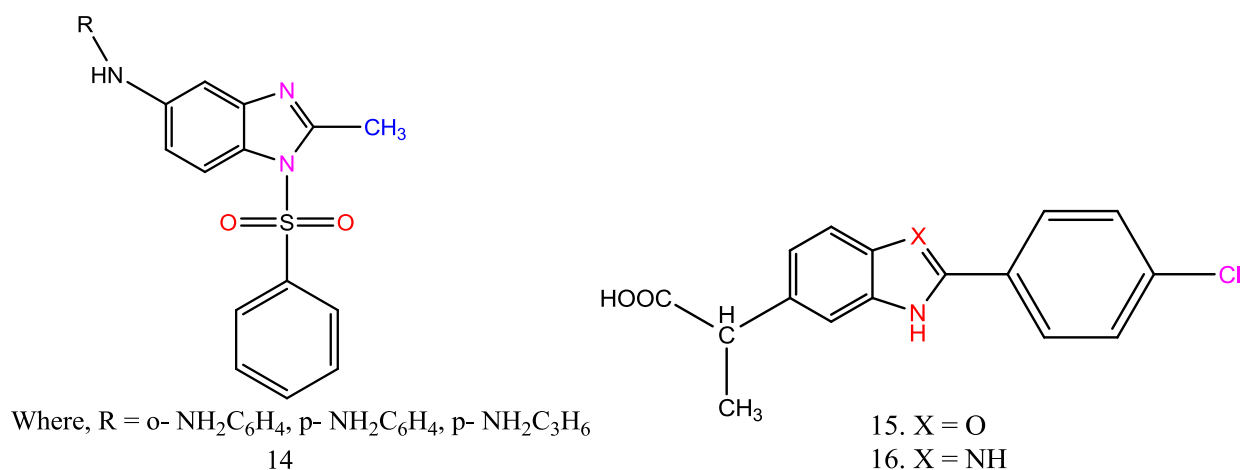
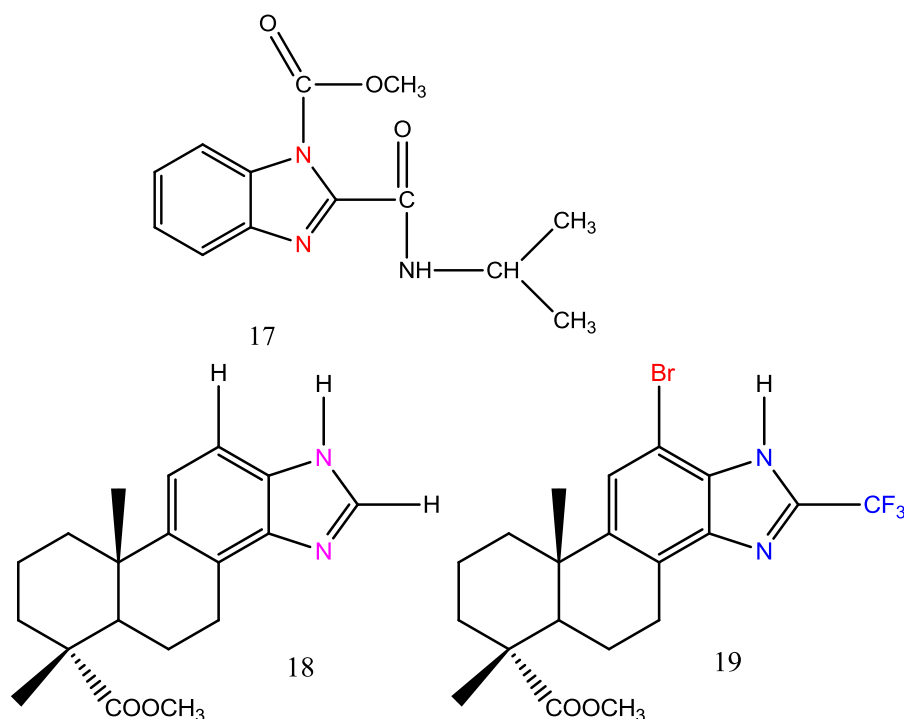


Fig. 6: New benzimidazole derivatives as an anti-inflammatory activities.

1.1 Anti-viral activity

Several 2-substituted benzimidazole-N-carbamates have been identified by Garuti *et al.* as strong antiviral agents; the iso-propylcarboxamide group attached at position-2 **17** had highest action.^[67] VZV and CMV replication are inhibited by dehydroabietic acids analogues of benzimidazoles, as demonstrated by examples **18** and **19**, at concentration significantly lesser than their lethal concentration.^[68] By replacing different types of heterocyclic moiety at Carbon-2 position, Kristina *et al.* created a series of 2-linked-5-amidinobenzimidazole **20** analogues with an amidino substituent at carbon-5 position of Benzimidazole moiety. Their anti-viral action toward coxsackie and echo viruses was assessed. The molecule with pyridine ring at carbon-2 position showed the highest selective action towards coxsackie and echo

viruses.^[69] Vitale *et al.* found a newly family of 2-arylbenzimidazole **21**. They evaluated their anti-viral and anti-proliferative properties. Substances were displayed against members of the flaviviridae family, which includes Herpesviridae, Poxviridae, Retroviridae, Picornaviridae, Paramyxoviridae, Rhabdo-viridae, and Reoviridae. Moderate activity against the Yellow Fevers Virus was demonstrated by compounds **21a**, **21b**, and **21c**.^[70] Applying 2-Arylbenzimidazole as a leads, 2-diphenyl analogues of benzimidazoles are created; nevertheless, all examined viruses did not exhibit any activity against the majority of the compounds, with the exception of **22** and **23**.^[71] Derivatives of 1[H]-benzimidazole-4 carboxamide with an aryl moiety at the carboxamide nitrogen and a furyl at the 2-position exhibit strong inhibitory action.^[72,73]



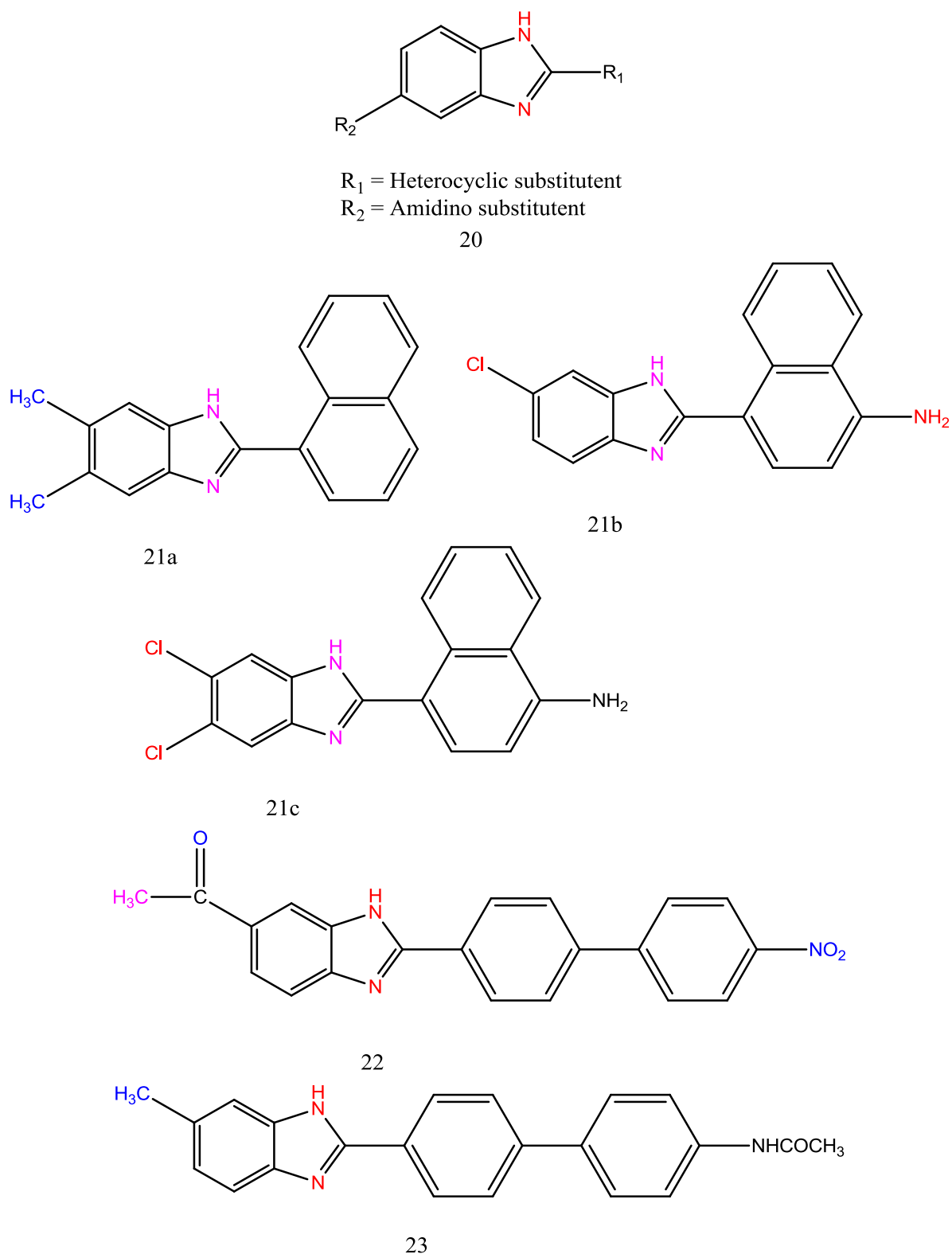


Fig. 7: Benzimidazole as anti-viral activity.

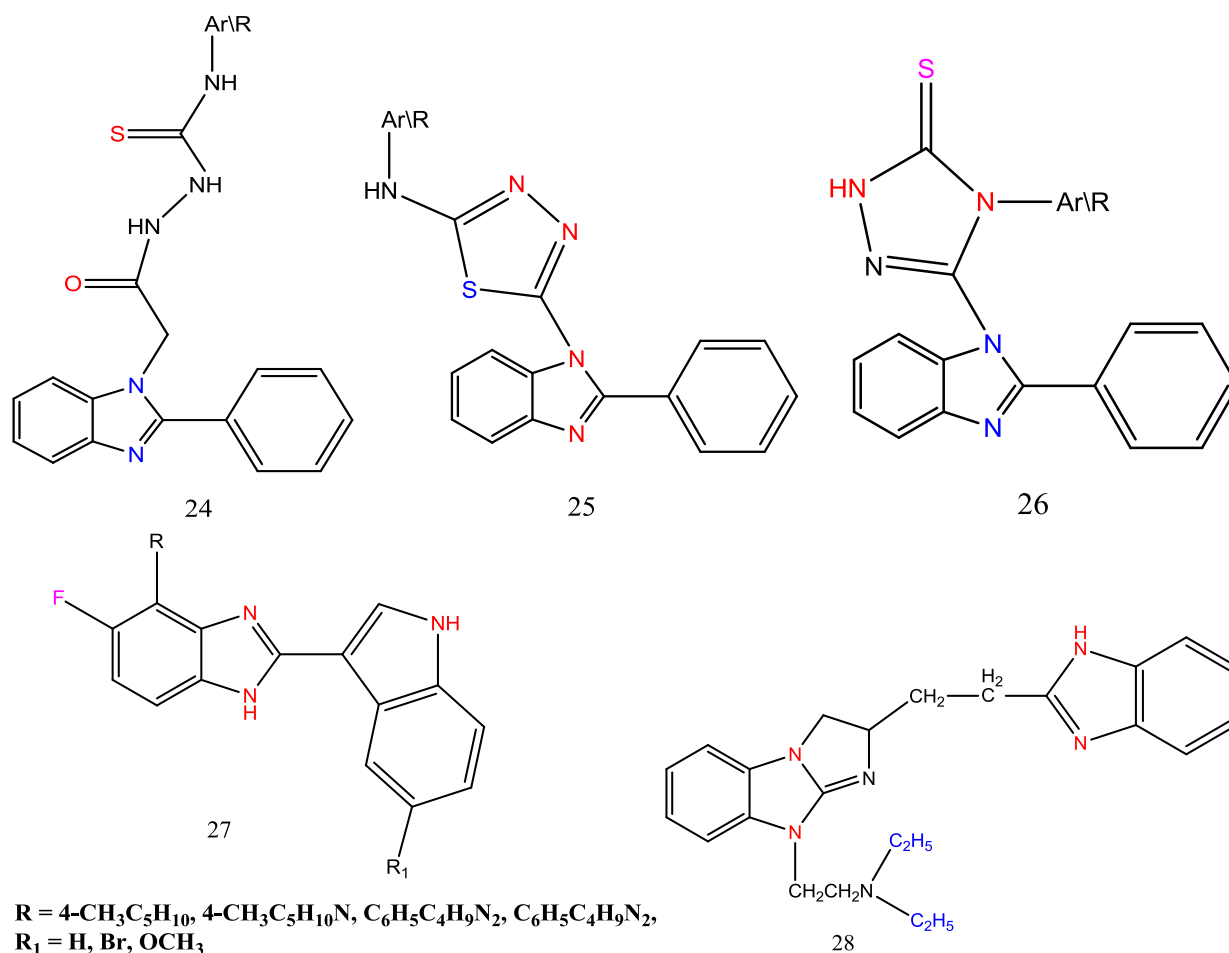
1.2 Antioxidant Activity

The compounds 5-hydroxybenzimidazole and 5-hydroxy-2-methylbenzimidazole have been identified as strong anti-oxidants by Cole *et al.*^[74] Drugs with antioxidant and free radical scavenging activities are used to treat a variety of illnesses linked to the body's insufficient antioxidant capacity. Antioxidant activity is

increased when thia-diazoles, tri-azoles, and thio-semicarbazides are substituted at position-1 of benzimidazole. Potent antioxidants **24-26** were also produced by a variety of aromatic and alkyl group substituent on these heterocyclic moieties at position-1. The DPPH model and lipid peroxidation levels were both more strongly inhibited by semicarbazide

derivatives.^[75,76] Alagoz et al. manufactured a certain 6-fluoro-5-linked benzimidazole **27**, which was examined for antioxidant activity. At a dosage of 0.001M, compound **27e** had a substantial anti-oxidant impact on superoxide anion.^[77] In an invitro model of ascorbates

dependence lipids peroxidation, Anisimova et al. described a group of 2-(heteroaromatic)-imidazo [1, 2-a]Benzimidazoles that possess n-methyl benzimidazol-2-yl **28** and 5-Bromo-2-thienyl **29** at R₂ with varying dialkylaminoalkyl substituent at R₁ as anti-oxidants.^[78]



6-fluoro-5-substituted benzimidazole derivatives (**27**)

Fig. 8: Benzimidazole as an antioxidant activity.

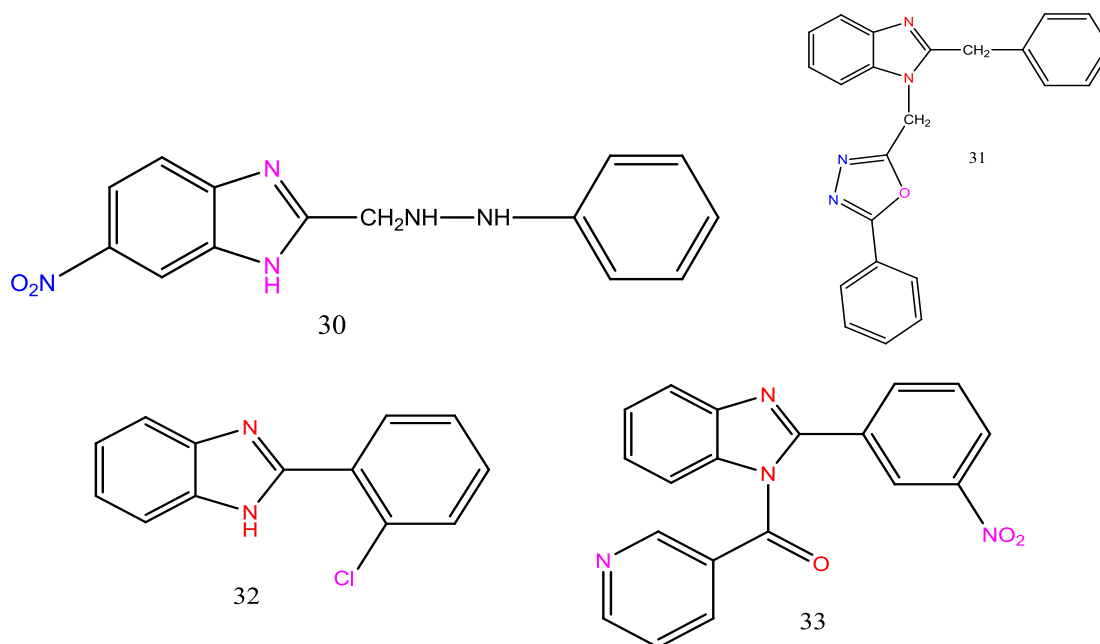
1.3 Anti-microbial activity

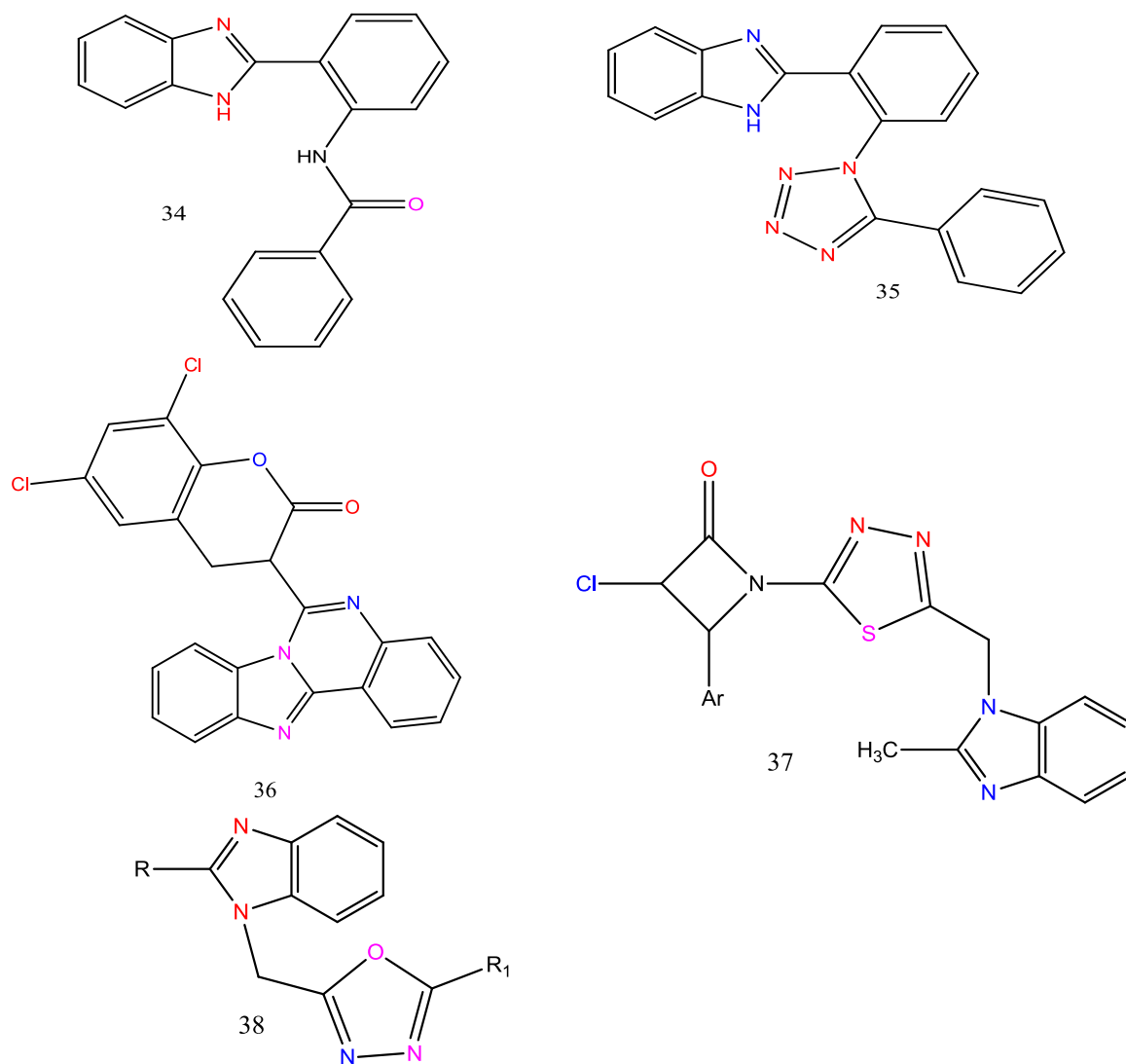
Ortho-phenylenediamine and chloroacetic acids reacted to produce 2-Chloromethyl benzimidazole, which was then used to create benzimidazole derivatives connected to phenylhydrazine. The equivalent N, N'-disubstituted hydrazines are obtained by further replacing the halide with phenylhydrazines. The antibacterial qualities of the

newly created analogues were tested towards *S. aureus*, *Enterobacter* cocci and *E. coli* of the compounds that were produced, compound **30** exhibited superior actions.^[79] Numerous 2-substituted benzimidazole compounds were created, with 1, 3, and 4 oxadiazole further substituting at position 1. While all of the recently created derivatives have demonstrated strong

antibacterial qualities, compound **31** outperformed normal nitrofurazone in terms of activity.^[80] In 2009, Sharma and his colleague produced a number of novel benzimidazole derivatives, including [2-(3-Nitrophenyl)-benzimidazol-1-yl]pyridin-3-yl methanone **33** and 2-(chlorophenyl)benzimidazole **32**. The produced analogues demonstrated strong antibacterial properties.^[81] Using the disc diffusion approach, Ahamed and his colleague produced a number of newly Benzimidazole analogues and assessed their antibacterial qualities. Compounds **34** and **35** had strong antibacterial properties.^[82] Benzimidazo-[1, 2-c]-quinazolin-5-yl-chromene analogues **36** has been described by Kuarmet al. as an antibacterial agent.^[83] The compound became antifungal when the chloro groups were swapped out for bromo ones. The antimicrobial properties of several 2, 6- and 2, 5-disubstituted benzimidazole analogues have also been investigated. After the year 2000, a lot of study was done on the creation of anti-microbials from the benzimidazole moiety. Numerous chemical entities included in antimicrobial agents have the ability to combat a wide value of micro-organisms, including viruses, fungus, helminths (worms), bacteria, and protozoa. Although antiviral drugs have been studied separately, numerous research groups have simultaneously assessed anti-bacterial, anti-protozoal, anthelmintic, and anti-fungal properties.^[84] Newly

azetidine-2-one derivatives **37** were manufactured by Ansari et al.^[85] And their anti-bacterial efficacy against Escherichia coli, Bacillus subtilis, and Candida albicans, Aspergillus niger, and Aspergillus flavus was assessed. When it comes to Gram-positive bacteria, the tested chemicals are more effective. The development of antimicrobial properties is significantly influenced by the molecule's strong lipophilic nature. By nucleophilically substituting benzimidazole 2-substituted-1-[(5-substituted-alkyl/aryl) 1, 3, 4-oxadiazolyl 2-yl]} **38**, several benzimidazole analogues were created, and their antibacterial action towards for both Gram-negative and Gram-positive bacteria were assessed. The synthesis of 1-substituted benzoimidazole analogues has been reported by Afaf H et al. A newly synthesized compound's antibacterial activity was assessed using two dilution methods to combat Staphylococcus aureus, Bacillus subtilis, E-coil, and pseudomonas aeruginosa (Gram Negative), as well as Candida. It was discovered that 3-(2-methylbenzimidazol-1-yl)propionic acids hydrazide was a more potent antibacterial than the others. Oxadiazole was produced using the Mannich reaction of CS₂/KOH. Acids produced **10** and **39a-39c**, respectively, after component **2** was reacted with hydrazine hydrates with both the aldehydes and acetic anhydride.^[86]





R= H or OCH₃

R₁ = CH₃, C₂H₅, CH₂Cl, C₆H₅, 2-ClC₆H₄, 4-ClC₆H₄, 2-OHC₆H₄, 4-OHC₆H₄

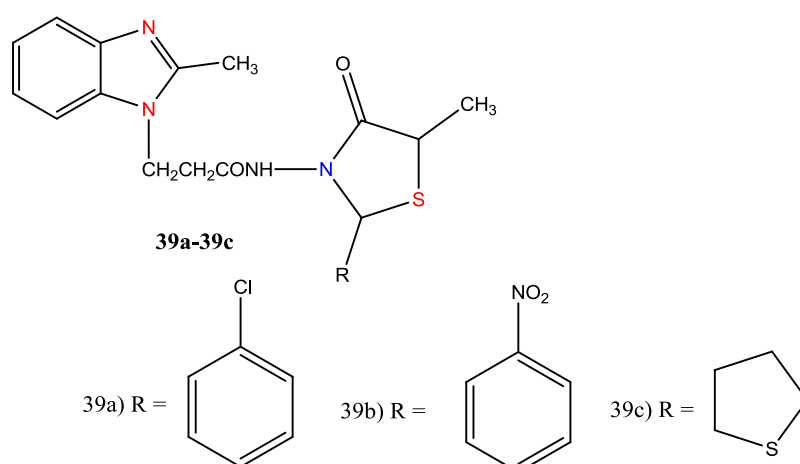


Fig. 9: Benzimidazole as an anti-microbial activity.

CONCLUSION

A heterocyclic compound having a broad spectrum of pharmacological actions is benzimidazole. Research on the synthesized of various benzimidazole analogues and

an analysis of their biological properties are therefore required.

REFERENCE

- H. Debus, *Annalen der Chemie und Pharmacie*, 1858; 107(2): 199-208. DOI: 10.1002/jlac.18581070209.
- Congiu, C.; Cocco, M.T.; Onnis, V. Design, synthesis, and in vitro antitumor activity of new 1,4-diarylimidazole-2-ones and their 2-thione analogues. *Bioorg. Med. Chem. Lett.*, 2008; 18: 989-993.
- Spasov A.A. and Yozhitsa I.N., Benzimidazole derivatives: spectrum of pharmacological activity and toxicological properties, *J. Pharm. Chem.*, 1999; 33: 232-243.
- F. Hobrecker, *Ber.*, 1872; 5(2): 920-924. DOI: 10.1002/cber.18720050295.
- Pandey, K.B.; Syed, I.R. Anti-oxidative action of resveratrol: Implications for human health. *Arabian Journal of Chemistry*, 2011; 4: 293-298.
- S. Choudhary, M. Arora, H. Verma, M. Kumar, O. Silakari, *Eur. J. Pharmacol*, 2021; 899: 174027. DOI: 10.1016/j.ejphar.2021.174027.
- Yun H, Baogen W, Yang J, Robinson D, Risen L, Ranken R, Blyn L, Eric SS. and Swayze E. 2-Piperidin-4-yl benzimidazoles with Broad Spectrum antibacterial activities. *Bioorg Med Chem Lett.*, 2003; 13: 3253-3256.
- Rashid M, Husain A, Mishra R. Synthesis of benzimidazoles bearing oxadiazole nucleus as anticancer agents. *Eur J Med Chem.*, 2012; 54: 855-866.
- Tahlan S, Ramasamy K, Lim SM, Shah SAA, Mani V, Narasimhan B. (2-(1H-Benzo[d]imidazol-2-ylthio)acetamido)-N-(substituted phenyl) benzamides: design, synthesis and biological evaluation. *BMC Chem.*, 2019; 3(12): 1-16.
- Alpan AS, Parlar S, Carlino L, Tarikogullari AH, Alptuzun V, Gunes HS Synthesis biological activity and molecular modeling studies on 1H-benzimidazole derivatives as acetylcholinesterase inhibitors. *Bioorg Med Chem.*, 2013; 21: 4928-4937.
- Andrzejewskaa M, Yopez-Mulia L, Tapia A, Cedillo-Rivera R, Laudy AE, Starosciak BJ, Kazimierczuk Z. Synthesis and antiprotozoal and antibacterial activities of S-substituted 4,6-dibromo- and 4,6-dichloro-2-mercaptobenzimidazoles. *Eur J Pharm Sci.*, 2004; 21: 323-329.
- Salahuddin Shaharyar M, Mazumder A. Benzimidazoles: a biologically active compounds. *Arab J Chem.*, 2017; 10: S157-S173.
- Navarrete-Vazquez G, Rojano-Vilchis MM, Yopez-Mulia L, Melendez V, Gerena L, Hernandez-Campos A, Castillo R, Hernandez-Luis F. Synthesis and antiprotozoal activity of some 2-(trifluoromethyl)-1H-benzimidazole bioisosteres. *Eur J Med Chem.*, 2006; 41: 135-141.
- Yoon YK, Ali MA, Wei AC, Choon TS, Ismail R. Synthesis and evaluation of antimycobacterial activity of new benzimidazole aminoesters. *Eur J Med Chem.*, 2015; 93: 614-624.
- Tahlan S, Narasimhan B, Lim SM, Ramasamy K, Mani V, Shah SAA (2018) Mercaptobenzimidazole Schiff bases: design, synthesis, antimicrobial studies and anticancer activity on HCT-116 cell line. *Mini-Rev Med Chem.* <https://doi.org/10.2174/1389557518666181009151008>
- Sharma N, Kumari R, Kumar S, Saxena AK, Prasad DN. Synthesis and anticancer evaluation of hybrid benzimidazole-pyrazole scaffolds. *Bioorg Chem.*, 2020; 97: 103672. doi:10.1016/j.bioorg.2020.103672
- Wu LT, Jiang Z, Shen JJ, Yi H, Zhan YC, Sha MQ, et al. Design, synthesis and biological evaluation of novel benzimidazole-2-substituted phenyl or pyridine propyl ketene derivatives as antitumor agents. *Eur J Med Chem.*, 2016; 114: 328-336.
- Hu Z, Ou L, Li S, Yang L. Synthesis and biological evaluation of 1-cyano-2-amino-benzimidazole derivatives as a novel class of antitumor agents. *Eur J Med Chem.*, 2013; 65: 1-8.
- Sondhi SM, Rani R, Singh J, Roy P, Agrawal SK, Saxena AK. Solvent-free synthesis, anti-inflammatory, and anticancer activity evaluation of tricyclic benzimidazole derivatives. *Bioorg Med Chem Lett.*, 2010; 20(7): 2306-2310.
- Hsieh CY, Ko PW, Chang YJ, Kapoor M, Liang YC, Chu HL, et al. Design and synthesis of benzimidazole-chalcone derivative as potential anticancer agents. *Bioorg Med Chem Lett.*, 2012; 22(7): 2520-2525.
- Choi HS, Ko YS, Jin H, Kang KM, Ha IB, Jeong H, et al. Anticancer effect of benzimidazole derivatives, especially mebendazole, on triple-negative breast cancer (TNBC) and radiotherapy-resistant TNBC in vivo and in vitro. *Cancer Lett.*, 2019; 444: 1-13.
- Sondhi, S. M.; Singh, N.; Kumar, A.; Lozach, O.; Meijer, L. *Bioorg. Med. Chem.*, 2006; 14: 3758.
- Makovec, F.; Giordani, A.; Artusi, R.; Mandelli, S.; Verpiliq, I.; Zanzola, S.; Rovati, L. C. U.S. Patent Application. US 2010/0120802, 2010.
- de Dios, A.; Shih, C.; Lopez de Uralde, B.; Sanchez, C.; del Prado, M.; Cabrejas, L. M. M.; Pleite, S.; Blanco-Urgoiti, J.; Lorite, M. J.; Nevill, C. R., Jr.; Bonjouklian, R.; York, J.; Vieth, M.; Wang, Y.; Magnus, N.; Campbell, R. M.; Anderson, B. D.; McCann, D. J.; Giera, D. D.; Lee, P. A.; Schultz, R. M.; Li, L. C.; Johnson, L. M.; Wolos, J. A. *J. Med. Chem.*, 2005; 48: 2270.
- Mader, M.; de Dios, A.; Shih, C.; Bonjouklian, R.; Li, T.; White, W.; de Uralde, B. L.; Sa'nchez-Martinez, C.; del Prado, M.; Jaramillo, C.; de Diego, E.; Cabrejas, L. M. M.; Dominguez, C.; Montero, C.; Shepherd, T.; Dally, R.; Toth, J. E.; Chatterjee, A.; Pleite, S.; Blanco-Urgoiti, J.; Perez, L.; Barberis, M.; Lorite, M. J.; Jambrina, E.; Nevill, R. C., Jr.; Lee, P. A.; Schultz, R. C.; Wolos, J. A.; Li, L. C.; Campbell, R. M.; Anderson, B. D. *Bioorg. Med. Chem. Lett.*, 2008; 18: 179.

26. Gaba, M.; Singh, D.; Singh, S.; Sharma, V.; Gaba, P. *Eur. J. Med. Chem.*, 2010; 45: 2245.
27. Huang, S. T.; Hseib, I. J.; Chena, C. *Bioorg. Med. Chem.*, 2006; 14: 6106.
28. Ramla MM, Omar MA, Tokuda H, El-Diwani HI Synthesis and inhibitory activity of new benzimidazole derivatives against Burkitt's lymphoma promotion, *Bioorg Med Chem.*, 2007; 15(19): 6489–6496.
29. Vedula MS, Pulipaka AB, Venna C, Chintakunta VC, Jinnapally S, Kattuboina VA, Vallakati RK, Basetti V, Akella V, Rajgopal S, Reka AK, Teepireddy SK, Mamnoon PK, Rajagopalan R, Bulusu G, Khandelwal A, Upreti VV, Mamidi SR New styryl sulfones as anticancer agents, *Eur J Med Chem.*, 2003; 38(9): 811–824.
30. Brishty SR, Hossain MJ, Khandaker MU, Faruque MR, Osman H, Rahman SA. A comprehensive account on recent progress in pharmacological activities of benzimidazole derivatives. *Frontiers in pharmacology*, Nov. 3, 2021; 12: 762807.
31. Gellis, A.; Kovacic, H.; Boufatah, N.; Vanelle, P. Synthesis and cytotoxicity evaluation of some benzimidazole-4,7-diones as bioreductive anticancer agents. *Eur. J. Med. Chem.*, 2008; 43: 1858.
32. Thimmegowda, N.R.; Swamy, S.N.; Kumar, C.S.A. Synthesis, characterization and evaluation of benzimidazole derivative and its precursors as inhibitors of MDA-MB-231 human breast cancer cell proliferation. *Bioorg. Med. Chem. Lett.*, 2008; 18: 432.
33. N Perin, L Hok, A Beč, L Persoons, E Vanstreels, D Daelemans, R Vianello, M Hranjec, *Eur. J. Med. Chem.*, 2021; 211: 113003. DOI: 10.1016/j.ejmech.2020.113003.
34. Y. Zhang, R. Yanga, L. Xia, R. Mana, Y. Chu, A. Jiang, Z. Wang, H. Zhu, *Bioorg. Chem.*, 2019; 92: 103219. DOI: 10.1016/j.bioorg.2019.103219.
35. Balfour JA, Goa KL. Bendamustine. *Drugs*, 2001; 61(5): 631-638.
36. Yamshon S, Martin P. Are novel agents ready to assume the mantle in the frontline treatment of mantle cell lymphoma? *Clinical Advances in Hematology & Oncology: H&O*, 2021; 19(6): 376-382.
37. Kopetz S, Grothey A, Yaeger R, Van Cutsem E, Desai J, Yoshino T, et al. Encorafenib, binimetinib, and cetuximab in BRAF V600E-mutated colorectal cancer. *New England Journal of Medicine*, 2019; 381(17): 1632-1643.
38. Grothey A, Tabernero J, Taieb J, Yaeger R, Yoshino T, Maiello E, et al. LBA-5 ANCHOR CRC: A single-arm, phase 2 study of encorafenib, binimetinib plus cetuximab in previously untreated BRAF V600E-mutant metastatic colorectal cancer. *Annals of Oncology*, 2020; 31: S242-S243.
39. Cuyun Carter G, Sheffield KM, Gossai A, Huang YJ, Zhu YE, Bowman L, et al. Real-world treatment patterns and outcomes of abemaciclib for the treatment of HR+, HER2-metastatic breast cancer. *Current Medical Research and Opinion*, 2021; 1: 37.
40. Toi M, Inoue K, Masuda N, Iwata H, Sohn J, Park IH, et al. Abemaciclib in combination with endocrine therapy for East Asian patients with HR+, HER2- advanced breast cancer: MONARCH 2 & 3 trials. *Cancer Science*, 2021; 112(6): 2381.
41. Jassem J, Dziadziuszko R. Nazartinib in EGFR Thr790Met-mutant non-small-cell lung cancer. *The Lancet Respiratory Medicine*, 2020; 8(6): 528-529.
42. Liu C, Lu H, Wang H, Loo A, Zhang X, Yang G, et al. Combinations with allosteric SHP2 inhibitor TNO155 to block receptor tyrosine kinase signaling. *Clinical Cancer Research*, 2021; 27(1): 342-354.
43. Xu Y, Liao S, Wang L, Wang Y, Wei W, Su K, et al. Galeterone sensitizes breast cancer to chemotherapy via targeting MNK/eIF4E and β -catenin. *Cancer Chemotherapy and Pharmacology*, 2021; 87(1): 85-93.
44. Choi YJ, Kim HS, Park SH, Kim BS, Kim KH, Lee HJ, et al. Phase II study of dovitinib in patients with castration-resistant prostate cancer (KCSG-GU11-05). *Cancer Research and Treatment: Official Journal of Korean Cancer Association*, 2018; 50(4): 1252.
45. Chen J, Li N, Liu B, Ling J, Yang W, Pang X, et al. Pracinostat (SB939), a histone deacetylase inhibitor, suppresses breast cancer metastasis and growth by inactivating the IL-6/STAT3 signalling pathways. *Life Sciences*, 2020; 248: 117469.
46. Boussios S, Karihtala P, Moschetta M, Abson C, Karathanasi A, Zakyntinakis-Kyriakou N, et al. Veliparib in ovarian cancer: A new synthetically lethal therapeutic approach. *Investigational New Drugs*, 2020; 38(1): 181-193
47. Ghisoni E, Giannone G, Tuninetti V, Genta S, Scotto G, Aglietta M, et al. Veliparib: A new therapeutic option in ovarian cancer? *Future Oncology*, 2019; 15(17): 1975-1987
48. S. Khokra, D. Choudhary, *Asian J Biochem Pharm Res.*, 2011; 3(1): 476-486.
49. S. Tahlan, S. Kumar, B. Narasimhan, *BMC Chem.*, 2019; 13: 101. DOI: 10.1186/s13065 019-0625-4.
50. R. Jakhar, S. Paul, M. Bhardwaj, S.C. Kang, *Cancer. Lett.*, 2016; 372(1): 89-100. DOI: 10.1016/j.canlet.2015.12.024.
51. K. Anand, S. Wakode, *Int. J. Chem. Stud*, 2017; 5(2): 350-362.
52. M. Koukoulaa, Y. Dotsikasa, E. Moloub, K.H. Schulpisc, G. Thodib, M. Chat-Zidakib, O. Triantafyllib, Y.L. Loukas, *J. Chromatogr. B.*, 2017; 1047: 173-179. DOI: 10.1016/j.jchromb.2016.06.046.
53. A.J.M. Horvat, S. Babic, D.M. Pavlovic, D. Asperger, S. Pelko, M.K. Macan, M. Petrovic, A.D. Mance, *Trends. Anal. Chem.*, 2012; 31: 61-84. DOI: 10.1016/j.trac.2011.06.023.
54. P.A.A. Shareef, G.P. Brennanb, P. McVeighb, M.A.H. Khana, R.M. Morphewc, A. Mousleyb, N.J. Marks, M.K. Saifullaha, P.M. Brophyc, A.G.

- Mauleb, S.M.A. Abidi, *Acta. Trop.*, 2014; 136: 108-117. DOI: 10.1016/j.actatropica.2014.04.011
55. S. Tahlan, S. Kumar, B. Narasimhan, *BMC Chem.*, 2019; 13: 101. DOI: 10.1186/s13065 019-0625-4.
56. K. Anand, S. Wakode, *Int. J. Chem. Stud*, 2017; 5(2): 350-362.
57. A.J.M. Horvat, S. Babic, D.M. Pavlovic, D. Asperger, S. Pelko, M.K. Macan, M. Petrovic, A.D. Mance, *Trends. Anal. Chem.*, 2012; 31: 61-84. DOI: 10.1016/j.trac.2011.06.023.
58. A.J.M. Horvat, S. Babic, D.M. Pavlovic, D. Asperger, S. Pelko, M.K. Macan, M. Petrovic, A.D. Mance, *Trends. Anal. Chem.*, 2012; 31: 61-84. DOI: 10.1016/j.trac.2011.06.023.
59. N.L. Calvo, T.S. Kaufman, Ruben M. Maggio, *J. Pharm. Biomed. Anal.*, 2016; 122(15): 157-165. DOI: 10.1016/j.jpba.2016.01.035
60. S. Tahlan, S. Kumar, B. Narasimhan, *BMC Chem.*, 2019; 13: 101. DOI: 10.1186/s13065 019-0625-4.
61. S. Hubera, F. Antonia, C. Schickanederb, H. Schickaneder, G. Bernhardta, A. Buschauer, *J. Pharm. Biomed. Anal.*, 2015; 104(10): 137-143. DOI: 10.1016/j.jpba.2014.11.038.
62. D. Vasquez, J.A. Rodriguez, C. Theoduloz, P.B. Calderon, J.A. Valderrama, *Eur. J. Med. Chem.*, 2010; 45(11): 5234-5242. DOI: 10.1016/j.ejmech.2010.08.040
63. Achar, K.C.S.; Hosamani, K.M.; Seetharamareddy, H.R. In-vivo analgesic and anti-inflammatory activities of newly synthesized benzimidazole derivatives. *Eur. J. Med. Chem.*, 2010; 45: 2048-2054.
64. Gaba, M.; Sing, D.; Singh, S.; Sharma, V.; Gaba, P. Synthesis and pharmacological evaluation of novel 5-substituted-1-(phenylsulfonyl) 2-methylbenzimidazole derivatives as anti-inflammatory and analgesic agents. *Eur. J. Med. Chem.*, 2010; 45: 2245.
65. Dunwel, D.W.; Evans, D.; Smith, C.E.; Williamson, W.R.N. Synthesis and antiinflammatory activity of some-2-substituted alpha-methyl-5-benzimidazoleacetic acids. *J. Med. Chem.*, 1975; 18: 692.
66. Garuti, L.; Roberti, M.; Gentilomi, G. *Il Farmaco*, 2000; 55: 35.
67. Fonseca, T.; Gigante, B.; Marques, M. M.; Gilchrist, T. L.; Clercq, E. D. *Bioorg. Med. Chem.*, 2004; 12: 103.
68. Kristina S., Marijeta M., Katja E., Ivan S., Magdalena G., Kresimir P., Grace, K. Z., Synthesis, antiviral and antitumor activity of 2-substituted-5-amidino-benzimidazoles, *Bioorg. Med. Chem.*, 2007; 15: 4419-4422.
69. Vitale G., Carta A., Loriga M., Paglietti G., Colla P., Busonera B., Collu D., Loddo R., 2-Arylbenzimidazoles as Anti-viral and Anti-proliferative Agents-Part 1, *Med. Chem.*, 2008; 4: 605-615. DOI PMid:18991746
70. Vitale, G.; Corona, P.; Loriga, M.; Carta, A.; Pagliettia, G.; Collab, P.L.; Busonera, B.; Marongiu, E.; Collu, D.; Loddo, R. 2 Arylbenzimidazoles as antiviral and antiproliferative agents-Part 2. *Med. Chem.*, 2009; 5: 507.
71. Cheng, J.; Xie, J.T.; Luo, X.J. Synthesis and antiviral activity against Cocksackie virus B3 of some novel benzimidazole derivatives. *Bioorg. Med. Chem. Lett.*, 2005; 15: 267.
72. Li, Y.F.; Wang, G.F.; He, P.L.; Huang, W.G.; Zhu, F.H.; Gao, H.Y.; Tang, W. Synthesis and anti-hepatitis B virus activity of novel benzimidazole derivatives. *J. Med. Chem.*, 2006; 49: 4790-4794.
73. Cole, E.R.; Crank, G.; Salam-Sheikh, A. Antioxidant properties of benzimidazoles. *J. Agr. Food Chem.*, 1974; 22: 918.
74. Kus, C.; Ayhan-Kilcigil, G.; Eke, B.C.; Iscan, M. Synthesis and antioxidant properties of some novel benzimidazole derivatives on lipid peroxidation in the rat liver. *Arch. Pharm. Res.*, 2004; 27: 156.
75. Kus, C.; Ayhan-Kilcigil, G.; Ozbey, S.; Betu, F.; Kaynak, I.; Kaya, M.; Coban, T.; Can-Eke, B. Synthesis and antioxidant properties of novel N-methyl-1,3,4-thiadiazol-2-amine and 4-methyl-2H-1,2,4 triazole-3(4H)-thione derivatives of benzimidazole class. *Bioorg. Med. Chem.*, 2008; 16: 4294.
76. ZA Alagoz; C Kus T Coban., Synthesis and antioxidant properties of novel benzimidazoles containing substituted indoles, *J. Enz. Inhib. Med. Chem.*, 2004; 20(3): 325-331.
77. Anisimova, V. A.; Tolpygin, I. E.; Spasov, A. A.; Kosolapov, V. A.; Stepanov, A. V.; Kucheryavenko, A. F. *Pharm. Chem. J.*, 2006; 40: 261.
78. Venkataramana HC, Singh A, Tiwari A, Tiwari V. Synthesis of phenyl hydrazine substituted benzimidazole derivatives and their biological activity. *Int J Pharm Sci Res.*, 2010; 1(1): 34-8.
79. Gowda J, Khadar AM, Kalluraya B, Kumari NS. Microwave assisted synthesis of 1, 3, 4-oxadiazoles carrying benzimidazole moiety and their antimicrobial properties. *Int J Pharm Sci Res.*, 2010; 1(1): 34-8.
80. Sharma D, Narasimhan B, Kumar P, Jalbout A. Synthesis and QSAR evaluation of 2-(substituted phenyl)-1H benzimidazoles and [2-(substituted phenyl)-benzimidazol-1-yl]-pyridin-3-yl-methanones. *Eur J Med Chem.*, 2009; 44(3): 1119-27.
81. Jafar AA, Vijayakumar KN, Venkatraman BR, Venkatesh G. Synthesis, characterization and biological activity of some novel benzimidazole derivatives. *Orbit: Electro J Chem.*, 2010; 1(4): 306-9.
82. Kuarm, B. S.; Reddy, Y. T.; Madhav, J. V.; Crooks, P. A.; Rajitha, B. *Bioorg. Med. Chem. Lett.* 2011; 21: 524.
83. Bansal, Y.; Silakari, O. The therapeutic journey of benzimidazoles: a review. *Bioorg. Med. Chem.*, 2012; 20: 6208-6236.
84. Ansari, K.F.; Lal, C. Synthesis, physicochemical properties and antimicrobial activity of some new

- benzimidazole derivatives. *Eur. J. Med. Chem.*, 2009; 44: 2294.
85. Afaf H.et.al.Synthesis and Antimicrobial Activity of Some New Benzimidazole Derivatives.*Molecules*, 2000; 5: 1429–1438.