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HARNESSING IMIDAZOLE CHEMISTRY IN THE FIGHT AGAINST CANCER: INSIGHTS AND ADVANCES

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ABSTRACT[4]

Imidazole is a five-membered ring containing three carbon atoms and two nitrogen atoms. It is found in many important biological molecules like purines, histamine, and nucleic acids. Imidazole derivatives are significant in medicinal chemistry, especially for cancer treatment. This review focuses on research from 2018 to 2020, highlighting the anticancer properties of imidazole and fused imidazole compounds. Cancer is a major global health challenge, and while advances in targeted therapies have been made, resistance to these treatments is common. One promising compound, compound has shown the ability to kill breast cancer cells while sparing healthy cells, making it a potential aromatase inhibitor. The review discusses how various imidazole derivatives work against cancer by affecting key cellular targets, including microtubules and specific enzymes. Some compounds act through mechanisms that are still not fully understood. Additionally, the review looks at how changes in the structure of these compounds can impact their effectiveness. Overall, this overview aims to highlight recent findings and inspire further research into imidazole-based drugs for cancer treatment, emphasizing their potential to provide new therapeutic options.

KEYWORDS: Imidazole, Anticancer, Tumour, Biological Activity, Kinase inhibitor.

INTRODUCTION[11]

Formulated as C3N2H4, imidazole (ImH) is an organic molecule. It is a colorless or white substance that dissolves in water to form a slightly alkaline solution. It is categorized as a diazole in chemistry and is an aromatic heterocycle with nitrogen atoms that are not

contiguous in meta-substitution. Alkaloids in particular are abundant in natural compounds that contain the imidazole ring. Although this imidazole has different substituents, it nevertheless has a 1,3-C3N2 ring. Important biological building elements like histidine and the related hormone histamine have this ring structure. Numerous medications, including certain antifungals, the antibiotics in the nitroimidazole class, and the sedative midazolam, have an imidazole ring. Breast cancer is one of the most common types of cancer in our country and around the world.[1] Especially in postmenopausal women, the risk of breast cancer increases due to oestrogen secretion in peripheral tissues.[2] Aromatase is a catalytic enzyme involved in the manufacture of oestrogen from androgen. It catalyses the last rate-limiting/crucial/key step in oestrogen biosynthesis.[3,4] Figure 1. demonstrates the action and role of the aromatase enzyme.

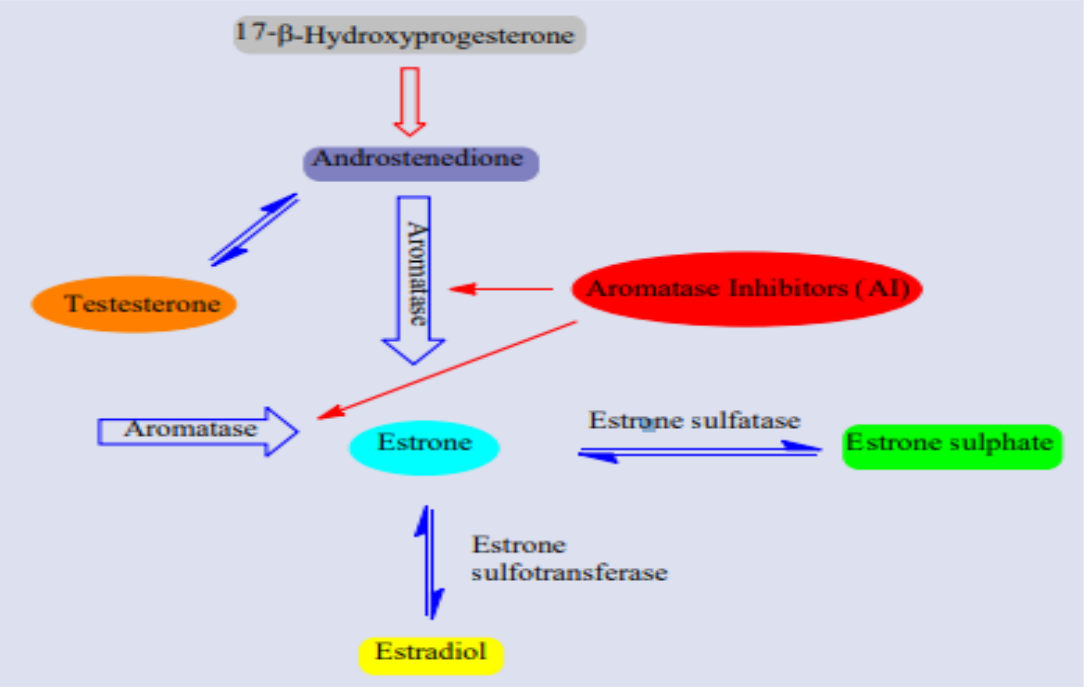


Figure 1.

According to their methods of action, aromatase inhibitors (AIs) can be divided into two classes. The steroidal AIs, such as exemestane and formestane (Figure 2), suppress the aromatase enzyme activity irreversibly. Nonsteroidal AIs, such as letrozole, vorozole, and anastrozole, are the second group of AIs that inhibit aromatase activity and have reversible inhibitory effects.

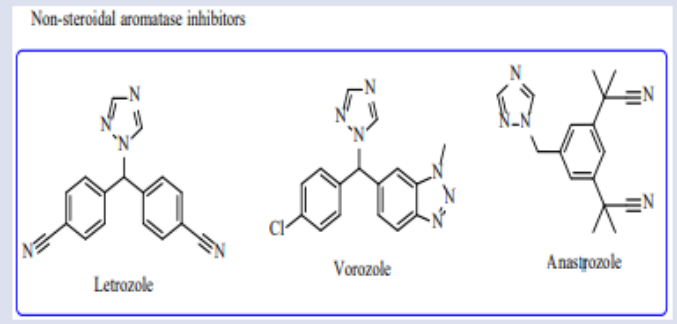
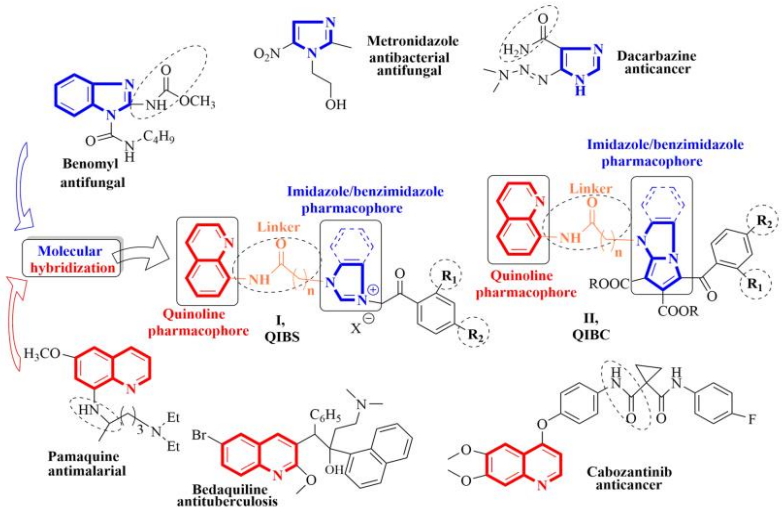


Figure 2.

Cancer is one of the most merciless, serious, and life-threatening disease worldwide, being characterized by the uncontrolled and rapid pathological growth of abnormal cells in the body and spread in different organs (metastasis). According to WHO data, cancer is expected to account for over 10 million deaths globally by 2020, making it the second highest cause of death globally. This will put significant strain on health systems, people, and communities. Another significant threat to human life and health is the spread of infectious diseases brought on by microbes, particularly bacteria and fungi. Treatment of many microbial infections has been severely hampered by the overuse, abuse, and widespread usage of antimicrobials.

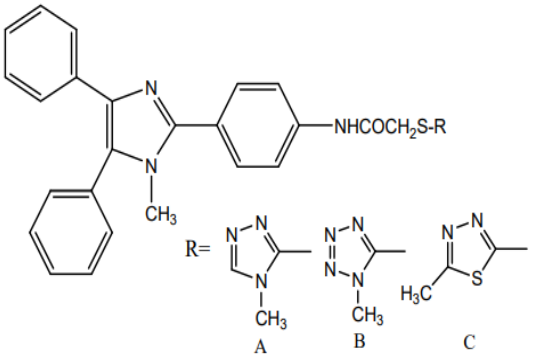
Despite the biggest advancements in microbiotherapy and cancer, the current treatment has se veral significant drawbacks, such as nonspecificity of medications, high costs, drug resistanc, multi-drug resistance, extensively-drug resistance, frequently high toxicity levels, etc.

However, the ongoing quest for improved antibacterial and anticancer medications continues to be a critical component of medicinal chemistry.



STRUCTURE AND PHARMACOLOGICAL ACTIVITIES[7,15]

Imidazole's are well known heterocyclic compounds which are common and have important feature of a variety of medicinal agents. The five-membered planar ring imidazole is soluble in polar solvents such as water. Because the hydrogen atom can be found on either of the two nitrogen atoms, it exists in two equivalent tautomeric forms. Its computed dipole of 3.61D indicates that it is a strongly polar molecule that dissolves completely in water. Because the molecule has a sextet of π-electrons—two from the protonated nitrogen atom and one from each of the other four atoms in the ring—it is categorized as aromatic. Imidazole is amphoteric, i.e. it can function as both an acid and as a base.



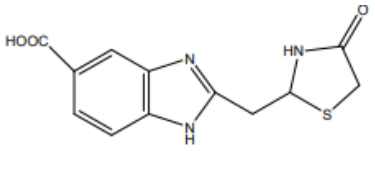
On basis of various literature surveys Imidazole derivatives shows various pharmacological activities

1. Anti-fungal and Anti-bacterial activity
2. Anti-inflammatory activity and analgesic activity
3. Anti -tubercular activity
4. Anti-depressant activity
5. Anti-cancer activity
6. Anti-viral activity
7. Antileishmanial activity

ANTICANCER ACTIVITY[7]

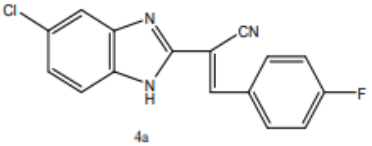
To study the anticancer activity, Yusuf Ozkay et al. synthesized a large number of new imidazole-(Benz) azole and imidazole piperazine derivatives. These were the series' most active chemicals based on anticancer activity screening findings. Cisplatin served as the benchmark medication. A number of 2-substituted benzimidazole series were created by Hanan M. Refaat. A number of the synthesized products were put through anticancer screening, and the results showed that every chemical put through its paces demonstrated

antitumor efficacy against human colon, breast, adenocarcinoma, and hepatocellular carcinoma. The most potent anti-human hepatocellular carcinoma samples were 3a and 4a.



3a

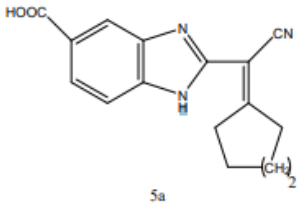
Fig-14



4a

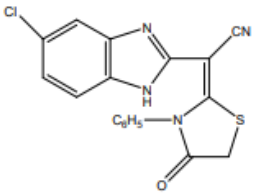
Fig-15

Compounds 5a 6a and 7a were most active against human breast adenocarcinoma.



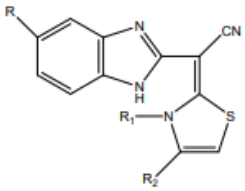
5a

Fig-16



6a

Fig-17

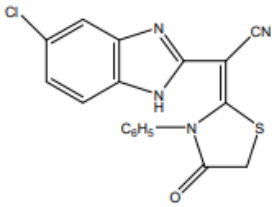


7a

For this compound R=COOH
R_1=4-Br-C_6H_4
R_2=2-OCH_3-C_6H_4

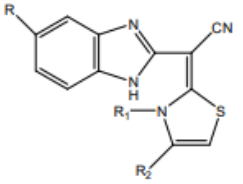
Fig-18

8a and 9a were moderately potent against human colon carcinoma.



8a

Fig-19



9a For this compound R=COOH
R_1=4-Br-C_6H_4
R_2=2-OCH_3-C_6H_4

Fig-20

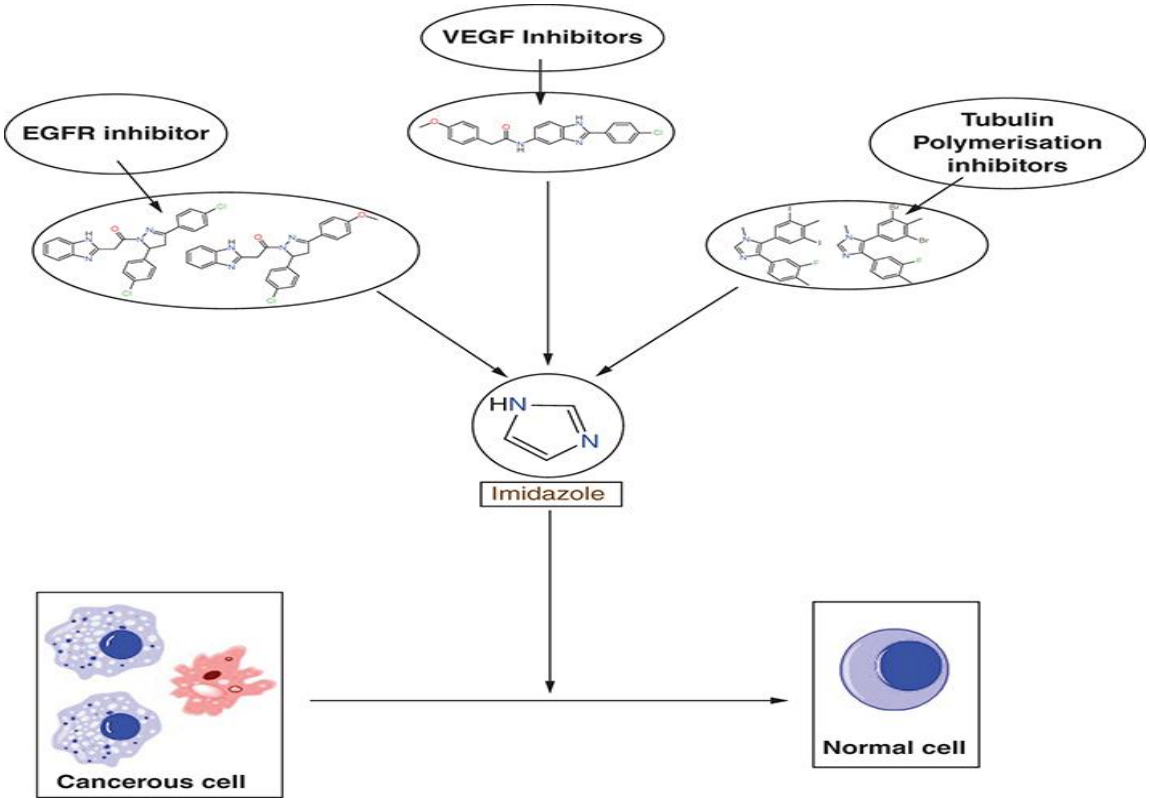
ANTI-CANCER PROPERTIES OF IMIDAZOLE DERIVATIVES

After heart disease, cancer ranks as the second leading cause of mortality both domestically and globally. An estimated 439.2 new cases per 100,000 persons occur each year.4 By 2040, there will be about 27.5 million new instances of cancer year if the current worldwide rate of cancer incidence continues to rise.5. Even though the precise cause of cancer is still unknown, it is generally accepted to be a hereditary disease that begins with aberrant and uncontrollably growing cells and has the potential to spread. The available chemotherapeutic drugs, such as methotrexate, etoposide, and paclitaxel, have shown strong activity and, in some cases, good survival rates. Nevertheless, a number of obstacles must be addressed, including drug resistance, toxicity, and unbearable side effects. According to some reported studies, imidazole has the potential to overcome the unresolved disadvantages of currently

available clinical drugs and could be utilized as a chemical scaffold for novel anticancer agents with several potential mechanisms of action. As a result, the various processes underlying the anti-cancer activity of various imidazole derivatives will be covered in the sections that follow.

In another study, Chung et al found that only eleven compounds among the twenty-six imidazole derivatives showed good activity against human umbilical vein endothelial cells (HUVECs) and smooth muscle cells (SMCs), using mycophenolic acid as a standard control. The results suggested that only three compounds, including compound C6, activated the p38 signaling pathway, and were selective inhibitors of endothelial cell proliferation specifically for human umbilical vein endothelial cells (HUVECs). According to a recent report conducted by Ali et al, the synthesized imidazole derivatives were investigated for potential anti-cancer activity on human cancer cells using Dabrafenib as a reference agent. In a work reported in 2020, anti-cancer activity of a newly synthesized novel imidazole derivatives was investigated against multiple cancer cell lines including human colon carcinoma (Caco-2 and HCT-116), human cervical carcinoma (HeLa), and human breast adenocarcinoma (MCF-7).

GRAPHICAL MECHANSIM OF ACTION OF IMIDAZOLE



1. Kinase Inhibition

- **Mechanism**: Imidazole compounds often target specific kinases involved in signaling pathways critical for cancer cell proliferation and survival. By binding to the ATP-binding site of kinases, they can effectively block downstream signaling.
- **Examples**: Some imidazole derivatives have shown activity against key kinases such as BRAF, VEGFR, and PI3K, which are implicated in various cancer types.

2. Microtubule Disruption

- **Mechanism**: Imidazole derivatives can disrupt microtubule polymerization, which is essential for mitotic spindle formation during cell division. This results in cell cycle arrest, particularly at the metaphase stage.
- **Examples**: Compounds that mimic the action of taxanes or Vinca alkaloids can effectively inhibit cancer cell growth by preventing proper mitosis.

3.Apoptosis Induction

- **Mechanism**: Many imidazole derivatives activate intrinsic apoptotic pathways by increasing the release of cytochrome c from mitochondria, leading to caspase activation and cell death.
- **Examples**: Some imidazole compounds have been shown to upregulate pro-apoptotic proteins (like Bax) and downregulate anti-apoptotic proteins (like Bcl-2).

THE IMPACT OF DNA MUTATIONS ON CANCER TREATMENT[10]

THE BREAST CANCER EXAMPLE Breast cancer is the most common cancer in women worldwide . In 2017, an estimated 255,180 new cases of invasive breast cancer are expected to be diagnosed in women in the USA, along with 63,410 new cases of non-invasive (in situ) breast cancer. On a histological level, breast cancer is a heterogeneous disease with a range of diverse subtypes , whereas on a molecular level, genetic sub-typing describes the following breast cancers; luminal A, luminal B, HER2-enriched, and basal-like breast cancer (BLBC) with the triple-negative breast cancer (TNBC) being a sub-group of BLBC that itself has six sub-types, reviewed in . This molecular sub-grouping is important in order to diagnose and define the appropriate treatment options currently available to breast cancer patients. In recent decades, breast cancer treatment has evolved to a more target-directed approach and the objective here is to underline, through an example in HER2-type breast cancer, the major steps followed in the development of targeted drugs to see how the attribution of driver/passenger roles to the DNA mutations observed in cancer has influenced our approach

towards treatment. The chronological order in the development of the drugs listed below is not as important as to what drugs have been designed and used to treat HER2-type breast cancer.

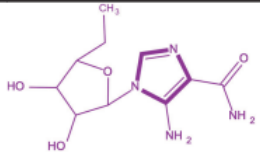
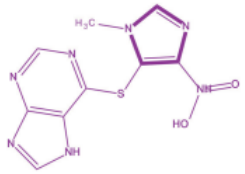
IMIDAZOLES AS ANTICANCER AGENTS

Many research papers have revealed that imidazoles possess anticancer drug potentials. The success of imidazoles as anticancer agents started with dacarbazine, which triggered interest in the development of imidazole agents. Several classes of various structured heterocyclic molecules, which include imidazoles, for different types of cancer treatment have been designed and developed to cure cancer via various targets.12 Imidazoles have the potential to overcome the various drawbacks of currently available clinical drugs and to develop anticancer agents. Therefore, attempts have been made to highlight some important classes of imidazoles based on mechanisms of action via various targets like DNA, VEGF, mitotic spindle microtubules, histone deacetylases, receptor tyrosine kinases, topoisomerases, CYP26A1 enzyme, rapid accelerated fibrosarcoma (RAF) kinases, etc

MARKET STATUS OF IMIDAZOLE-BASED ANTICANCER DRUGS[1]

Imidazole-based anticancer drugs possess remarkable potential due to their ability to interfere first with DNA synthesis and then halt the cell growth and division. Until now, many imidazole-based anticancer drugs: azathioprine, misonidazole, pimonidazole, nilotinib, tipifarnib, fadrozole, indimitecan, acadesine, bleomycin, bombesin, dacarbazine, zoledronic acid, clotrimazole, mitozolomide, mercaptopurine, pilocarpine, radotinib, plinabulin, SB-431542, temozolomide, etanidazole and bendamustine, have been developed and play an important role in the clinic (Table 1).

Table 1 The chemical structures and applications of imidazole drugs in cancer chemotherapy

S. no	Drugs	Structures and chemical names	Brand names	Market status	Applications
1	Acadesine	 5-Amino-1-[(2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-1*H*-imidazole-4-carboxamide	—	Phase III	Acute lymphoblastic leukemia
2	Azathioprine	 6-[(1-Methyl-4-nitro-1*H*-imidazol-5-yl)sulfanyl]-7*H*-purine	Imuran	Phase I	Childhood acute lymphoblastic leukemia

Dacarbazine is an alkylating agent that destroys cancer cells by adding an alkyl group to DNA. It has applications for metastatic malignant melanoma, hodgkin lymphoma, sarcoma and islet cell carcinoma of the pancreas.201 Azathioprine is a prodrug of mercaptopurine that has applications for the treatment of childhood acute lymphoblastic leukemia.202 Moreover, 2-nitroimidazoles (misonidazole, etanidazole and pimonidazole) act as radiosensitizers of hypoxic tumor cells.203 Pimonidazole is reduced in hypoxic environments, as in tumor cells, and it can be used as a hypoxia marker.

CONCLUSION

In conclusion, imidazole (C3N2H4) is an important class of chemical molecules with a wide range of pharmacological uses, especially in the field of cancer therapy. Imidazole's special characteristics enable it to interact with a variety of biological targets as a structural component of vital biomolecules including histidine and histamine, demonstrating its promise as a scaffold for novel anticancer medicines. The worth of imidazole derivatives in medicinal chemistry is highlighted by their potential anticancer activity as well as their capacity to overcome the drawbacks of current chemotherapeutics.

Considering the growing incidence of cancer worldwide, especially breast cancer, continued study into imidazole-based chemicals may result in novel therapeutics. We may be able to overcome problems like drug resistance and toxicity if we understand the mechanisms by which these substances work. The ongoing investigation of imidazole derivatives not only strengthens our defenses against cancer but also raises the prospect of more effective treatment approaches to tackle this widespread illness. Imidazole thus sticks out as an essential substance for upcoming studies and advancements in the battle against cancer and other grave health risks.

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