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Review on Potential Anticancer Agents from Benzimidazole Derivatives

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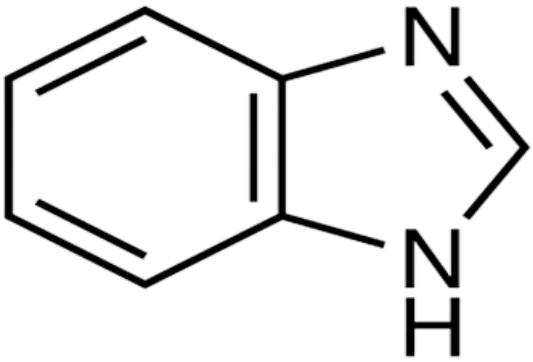
ABSTRACT:

Because heterocyclic compounds constitute a part of the structure of many biological components, the use of heterocyclic compounds in the field of medicinal chemistry is growing daily. The heterocyclic molecule benzimidazole, which is created when benzene and imidazole combine, has gained significant attention in the field of medicinal chemistry because of its wide range of pharmacological properties. Scientists have been studying the properties of benzimidazole and its derivatives for the past century. The pharmacological activities of benzimidazole derivatives, which include antihypertensive, anticancer, antiviral, antidiabetic, proton pump inhibitors, anthelmintic, antibacterial, analgesic, and others, have been applied in a variety of fields.

Keywords: benzimidazole, anticancer, EGFR, chemistry

INTRODUCTION:

Benzimidazole:



Benzimidazole

When Woolley speculated that benzimidazoles resemble purine-like structure and provoke some biological use in 1944, the biological application of benzimidazole nuclei was identified. Thus, isosters of naturally occurring nucleotides were found to have benzimidazole structures, allowing them to interact with living system's biopolymers with ease. Brink later identified 5,6-dimethylbenzimidazole as a vitamin B12 breakdown product and later observed that certain of its analogues had vitamin B12-like action. These early study papers looked on the many ornamented benzimidazole motif discoveries made by the medicinal chemist.

Over the few decades of active research, benzimidazole has evolved as an important heterocyclic nucleus due to its wide range of pharmacological applications. Hence, it's worth to understand the basic chemistry and structure of such a wonderful molecule.

Benzimidazole is formed by the fusion of benzene and imidazole moiety, and numbering system according to the IUPAC is shown in . Historically, the firstly benzimidazole was prepared in 1872 by Hoebrecker, whoobtained 2,5 dimethylbenzimidazole or 2,6dimethylbenzimidazole by the reduction of 2nitro4methylacetanilide. Benzimidazoles which contain a hydrogen atom attached to nitrogen in the 1-position readily tautomerize, and this may shown in . The pharmacological application of benzimidazole analogs found potent inhibitors of various enzymes involved and therapeutic uses including as anticancer, antimicrobial, antiparasitic, analgesics, antiviral, antihistamine activity.

Cancer :

Cancer refers to any one of a large number of diseases characterized by the development of abnormal cells that divide uncontrollably and have the ability to infiltrate and destroy normal body tissue. Cancer often has the ability to spread throughout your body.

Cancer is the second-leading cause of death in the world. But survival rates are improving for many types of cancer, thanks to improvements in cancer screening, treatment and prevention.

Symptoms

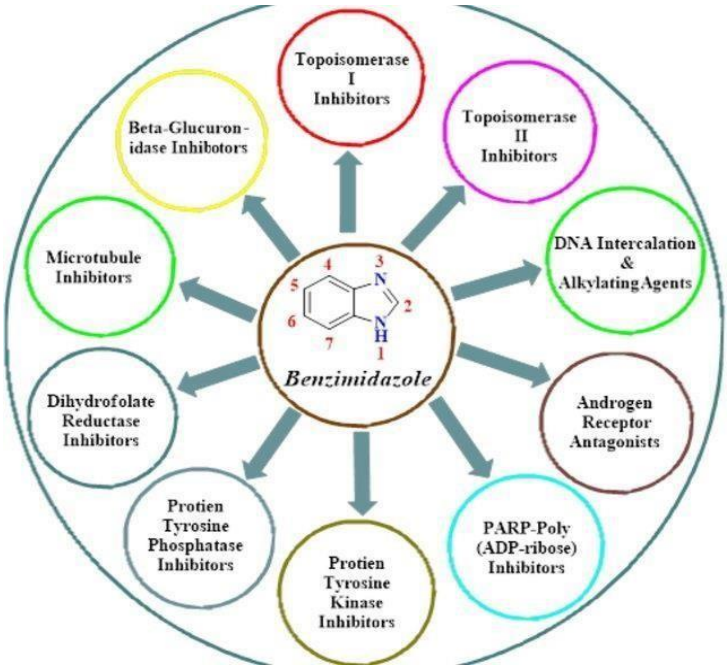
Signs and symptoms caused by cancer will vary depending on what part of the body is affected.

Some general signs and symptoms associated with, but not specific to, cancer, include:

- Fatigue
- Lump or area of thickening that can be felt under the skin
- Weight changes, including unintended loss or gain
- Skin changes, such as yellowing, darkening or redness of the skin, sores that won't heal, or changes to existing moles
- Changes in bowel or bladder habits
- Persistent cough or trouble breathing
- Difficulty swallowing
- Hoarseness
- Persistent indigestion or discomfort after eating
- Persistent, unexplained muscle or joint pain
- Persistent, unexplained fevers or night sweats
- Unexplained bleeding or bruising

MECHANISM OF ACTION

Antineoplastic implications of benzimidazole are induced through a range of biochemical actions, including decreased colonial development, interrupted tubulin polymerization, triggered apoptotic cell death, G2/M cell cycle arrest, activated differentiation and senescence, hindered drug resistance and transporters, and abnormal glucose utilization. significant signalling mechanisms connected to chemicals therapeutic effects assist the antitumorgenicity of benzimidazole,. The chemical pathway of benzimidazoles is based on particular attachment with tubulin, that disrupted the microtubule functioning, as well as Interference affects secretory vesicle trafficking via microtubules in helminth tissues absorption. Microtubules perform critical part in cell proliferation, trafficking, and eukaryoticmigration, along with tumour cell invasion and metastatic dissemination. Compounds that disrupt the chemotherapeutic strategies have made advantage through microtubule structure for tumor sufferers. These substances have employed as antimitotic, inhibiting the functioning of microtubule during the mitotic stage. The combination of benzimidazolepyrazole has been shown to have efficient action against thetumor cell line of breast (A549) and binding affinity for epidermal growth factor receptor (EGFR). Padhy et al. recently described the Nbenzylbenzimidazole synthesis through coupled pyrimidine as mild antitumor on MDA-MB231tumor cell line of breast. It has been demonstrated that derivatives of benzimidazole can reduce tumor growth and mitosis, cause apoptosis, and suppress HIF-1 expression. As a pivota pharmacophore in current medication development, benzimidazole has garnered substantial interest in development of antitumor medicines.



ANTICANCER BENZIMIDAZOLES :

Chu et al. described the antitumor effect of a chemical, 2chloro-N-(2-ptolyl-1H-benzo[d]imidazol-5-yl) acetamide 33, against breast cancer. They found that this chemical effectively suppressed both HER2 and EGFR effect in vitro and in vivo by lowering HER2 and EGFR and tyrosine phosphorylation and blocking downstream activation of the PI3K/Akt and MEK/Erk pathways. They also discovered that the drug prevented FOXO phosphorylation and encouraged FOXO translocation from the cytoplasm to the nucleus, leading to cellular inhibition and death in the G1 phase. Furthermore, in breast cancer cells, this derivative potently promoted apoptosis via c-Jun N-terminal kinase (JNK)- mediated death receptor 5 upregulation. This derivative's anticancer effect was matched with further findings revealing that it greatly decreased tumor size in nude mice in vivo. This analogue strongly decreased Akt Ser473 and Bad Ser136 phosphorylation and lowered cyclin D3 production in primary breast cancer cell lines with HER2 over expression, according to additional research. Noha et al., produced a series of novel Schiff bases 34 by condensation of certain aromatic aldehydes with 1,2,4-triazole derivatives. Biological testing of the synthesised chemicals against microorganisms was performed, all of the tested compounds shown strong antifungal effect (Candida albicans). Some of the investigated substances shown strong efficacy against both gramme positive and gramme negative bacteria. Three compounds out of numerous investigated derivatives had the best efficacy against breast cancer (MCF-7) and colon carcinoma (HCT116) cell lines at low μg/ml levels. Docking calculations were also performed in order to justify the reported biological data(30). Anna et al. discovered a new class of Mannich bases, derivatives of 2-amino-1H- benzimidazole 35, by condensation of Schiff bases or 2-benzylaminobenzimidazoles with selected secondary amines such as morpholine, piperidine, Nmethylpiperazine, N- phenylpiperazine, 1-(2- pyridyl)piperazine, 1-(2methoxyphenyl)piperazine, 1-(2-pyrimidinyl)piperazine, and formaldehyde in ethanol. The pyrimido [1,2a]benzimidazole derivatives were created by Schiff base reactions with several compounds having active methylene groups, such as acetylacetone, benzoylacetone, and malononitrile. All compounds were evaluated against MV4-11 human leukaemia cells, and the most active ones were subsequently tested against human T47D breast and A549 lung cancer cells, as well as normal mouse fibroblasts

(BALB/3T3). The most potent chemical towards tumor cell lines was 4- amino-3-cyano-2-(4-hydroxyphenylene)-1,2dihydro-pyrimido[1,2a]benzimidazole (IC50 0.230±05 μg/ml over MV4-11 cells), with extremely minimal cytotoxicity against mouse fibroblasts. The control medication was cisplatin. Sovic et al. (2018) presented new isoindolines modified with cyano and amidinobenzimidazoles as antitumor medications. The chemicals were chosen based on their substantial antiproliferative, topoisomerase inhibition, and DNA binding,properties.

Pyrazole-benzoimidazole-5-carboxylates), which inhibited 60 distinct human tumour cell lines, were produced and tested. Products) had the strongest efficacy against severaltumor cell lines, with outstanding values in leukemia panels, non-small lung tumor cell, and melanoma with GI50 ranges of 1.15-7.33 μM and 0.167-

7.59 μM, respectively. The inclusion of the 2-oxo-1,2dihydroquinolin-3-yl moiety in the structure of SAR improves anticancer efficacy. Antiproliferative efficacy of thiazolylbenzimidazole compounds against SMMC7721 and A549 cell lines was investigated. The majority of the compounds demonstrated significant anticancer potential, where as compound shown significant in vitro antitumor effect equivalent to taxol. From SAR, cytotoxicity was reduced somewhat when the elastic basic side chain was replaced with a phenyl group., while replacing the 2-diethylamino-ethyl side chain with a hydrophilic cyclohexyl ring resulted in a 12-fold effective weaken against SMMC-7721 and a 2-fold decrease in efficacy against A549 cells. The hydrophilic property of the amide groups was critical for anticancer efficacy.

Wanga et al. developed and tested a variety of chrysinbenzimidazole derivatives for antitumor properties. Against MFC cells, Compound had effective anti-proliferative action, with IC50 values of 25.72±3.95 μM. Results of flow cytometry showed that drug (1) induces apoptosis in MFC cells in a dose-dependent manner. The antitumor action was also investigated in tumor-bearing rats, and it was discovered that compound (1) inhibits cancer development. Morais et al. produced and tested for anticancer activity a number of benzimidazole derivatives with fluorinated or hydroxylated alkyl substituents. Among the substances studied, (2) had the most antitumor action. Compound (2), The compound, which comprises of a nonsubstitutedbenzimidazole core and a 2-fluoroethyl chain at the aniline nitrogenagainst U87 glioblastoma cell line, showed a moderate cytotoxic impact (IC50 = 45.2±13.0 μM) in contrast to DOX (IC50 = 16.6±2.5 μM), a typical anticancer medication(46). Shaker et al. created and tested 1-substituted benzimidazole derivatives for cytotoxicity. In terms of cytotoxicity, against A- 549, HCT116, and MCF-7, doxorubicin is less effective than compound (3), with an IC50 value of 28.29 μM. Compounds (4) and (5) (IC50 = 134.90 and 123.70 mM, respectively) shown efficacy comparable to doxorubicin (IC50 = 84.10 Mm).

CONCLUSION :

Benzimidazole has several pharmacological effects, including antibacterial, antifungal, antioxidant, antiviral, anticancer, and anti-inflammatory action. As a result, we can state that benzimidazole is a molecule that has demonstrated diversity in pharmacological activity and has the capability to investigate further pharmacological properties. In current drug research, benzimidazole plays the role as a key pharmacophore. Benzimidazole derivatives synthesis as a source of novel biological vectors has received increasing attention. The benzimidazole derivatives will be useful in future therapeutic research.Various studies have found that are structural isosteres of nucleotides and substituted benzimidazoles and heterocycles, may easily engage in the biopolymers interaction and have pharmacological action with lesser toxicity. Changes in the structure of benzimidazole resulted in significant therapeutic activity, which have demonstrated effective in the creation of novel pharmaceutical drugs with higher potency and lower toxicity.

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