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Potential Anticancer Agents From Benzimidazole Derivatives

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ABSTRACT

The usage of heterocyclic compounds in the discipline of Medicinal Chemistry is increasing with each day, because heterocyclic compounds are a component of the structure of many biological materials. Because of its diverse pharmacological properties, benzimidazole, a heterocyclic molecule produced by the fusion of benzene and imidazole, has received substantial importance in the area of medicinal chemistry. Over the last century, scientists have been researching the characteristics of benzimidazole and its derivatives. Benzimidazole derivatives have found practical uses in an array of disciplines and exhibit a wide range of pharmacological actions such as antihypertensive, anticancer, antiviral, antidiabetic, proton pump inhibitors, anthelmintic, anti-microbial, analgesic, and so on.

Keywords: benzimidazole, anticancer, EGFR, chemistry

INTRODUCTION

Non communicable diseases (NCDs) responsible for 71% of all fatalities worldwide. NCDs were predicted to account for 63 percent of all fatalities in India, with tumor being one of the primary causes (9 percent) (1). Cancer is commonly seen as a cellular illness resulting from mutations in genes that govern cell proliferation, death, metabolism, and DNA repair (2). Cancer, a general term used to describe unregulated cell growth caused by disruption or malfunction of regulatory signalling pathways that are typically strictly regulated, among the common causes of mortality globally (3). Incidence of cancer and fatality are increasing quickly over the planet. The reasons are complicated, they do, however, reflect population ageing and expansion, as well as changes in the incidence and distribution of the key cancer risk factors, which are linked to social and economic development. According to a recent WHO study (2018), Cancer claimed the lives of nearly 9.6 million people globally. In low- and middle-income countries, it kills more than 70% of persons. Cancer mortality is expected to grow to 21.6 billion in 2030 from 14.1 billion in 2012(4). Furthermore, the evolution of resistance and major adverse effects of presently utilised therapeutic antitumor medicines and treatments necessitates the creation of effective and promising antitumor options(5).Therapeutic techniques that focus solely on tumor cells usually provide unsatisfactory results, such as treatment failure, tissue invasion, and resistance. Such shortcomings are caused in part by the unanticipated behaviours that develop from cancerous tissues' complex systems(6). Conventional cancer treatment, including chemotherapy and radiotherapy, seems to have produce

harmful consequences, comprising healthy cellular damage, neurodegeneration, cardiotoxicity,

intestinal poisoning, and immunological suppression, results in a worse life quality in people with tumor(7,8).

The quest for novel medications capable of taking the place of chemicals utilized in typical chemotherapeutics have escalated during the last two decades (9). A great variety of drugs operating through various pathways for the cancer therapy are currently available, however the efficiency of several existing treatments is restricted by their cytotoxicity to normal quickly developing cells, which may acquire resistance to that medicine. Another disadvantage is that the majority of medications on the market now are not targeted. As a result, there is a significant need to create novel, antitumor medicines that are more effective and less harmful(10,11). The current COVID-19 epidemic is threatening healthcare. COVID-19 offers more threat to health systems than any other, with a large number of infected people worldwide and a fast-growing number of individuals diagnosed. However, it is equally crucial to recognise that death from several other illnesses, including but not exclusively cancers, left significant. Because of the COVID-19 pandemic, healthcare workers are faced with the difficulty of significantly reorganising health systems at an extraordinary speed, not just to address the COVID-19 epidemic correctly, and without losing focus of other patient safety(12–14).

Because of its extensive pharmacological characteristics, benzimidazole heterocyclic nucleus has been given this name because of its synthesis promise in medicinalal chemistry. the "Master Key." It is one among the five top most prevalent FDA-approved five-membered aromatic nitrogen heterocycles pharmaceutical medicines in the United States. Because of the fused nitrogen nuclei, Benzimidazoles comprise nucleobase structural isosteres that rapidly connect with biomolecular substrates and evoke a variety of biological effects(15). Purine's structure is similar to that of benzimidazole. Woolley found this in 1944. This results in the benzimidazole moiety developing further. Given the nature and significance of this moiety, it was felt that it would be beneficial to create and develop some new benzimidazole derivatives with the oxadiazole moiety and test their biological effect. Over the course of several decades of active study, it has been demonstrated that benzimidazole, as an important pharmacophore, may exhibit a wide variety of antibiotic actions as well as fight against a vast number of bacteria(16,17).It is considered to be among the highest potential moieties with numerous therapeutic activities and has thus become a key structural componentof several useful drugs such as albendazole, astemizole, candesertan, mebendazole, omeprazole, pantoprazole, thiabendazole, triclabendazole, rabeprazole, and others. Benzimidazole-substituted compounds also have antifungal, anthelmintic, antiproliferative, antiviral, antihypertensive, male contraceptive, and anti-infective properties etc. Derivatives of benzimidazole also have considerable cytotoxic action against tumor cell lines including leukaemia, prostate, colon,lung, melanoma, kidneys, breast(18). Benzimidazole is a significant bicyclic hetero-aromatic chemical molecule composed of the benzene ring and the imidazole ring fused at the 4- and 5-positions, with several medicinal uses including antibacterial, antifungal, anti-inflammatory, antiviral, and analgesic properties. Because their structure is similar to the nucleotides present in humans, derivatives of benzimidazole have been extensively researched for usage as novel antitumor agents(19,20).The benzimidazole scaffold is frequently used in the creation of novel anticancer medicines in a variety of biologically active compounds. Several substituted compounds of benzimidazole have been found to exhibit exceptional anticancer efficacy, as well as a variety of other therapeutic features. The structural closeness of the benzimidazole moiety with naturally occurring nucleotides facilitates simple interaction between these chemicals with molecules like DNA, RNA, or proteins in living systems, therefore playing a critical part in their function(21).Because

of its vast variety of biological actions, benzimidazoles have changed the development of new medicines, making this structure a crucial foundation for the development of new therapeutic medicines. As a result of the therapeutic benefits of benzimidazole and associated compounds, scientists have been drawn to create and synthesise more powerful analogues with a broad array of pharmacological actions.Table 1 representing physical properties of benzimidazole.

Table 1: Physical Characteristics of Benzimidazole (22,23)**.**

Molecular Formula	$C_7H_6N_2$
Molecular Weight	118.053 g/mol
Colour	Whitish
Odor	Characteristics
Physical state	Tabular crystals
Boiling point	360 ºC
Melting point	170.5-171.5 ºC
Solubility	Freely soluble in alcohol, sparingly soluble in ether. Soluble in aqueous solutions of acids and strong alkalis.Practically insoluble in benzene, petroleum ether.
Isomerism	Tautomerism

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 anti-tumorgenicity of benzimidazole,Figure1(24). 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 (25). The combination of benzimidazole-pyrazole 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 N-benzylbenzimidazole synthesis through coupled pyrimidine as mild antitumor on MDA-MB-231tumor cell line of breast(26,27). It has been demonstrated that derivatives of benzimidazole can reduce tumor growth and mitosis, cause apoptosis, and suppress HIF-1 expression. As a pivotal pharmacophore in current medication development, benzimidazole has garnered substantial interest in development of antitumor medicines(28).

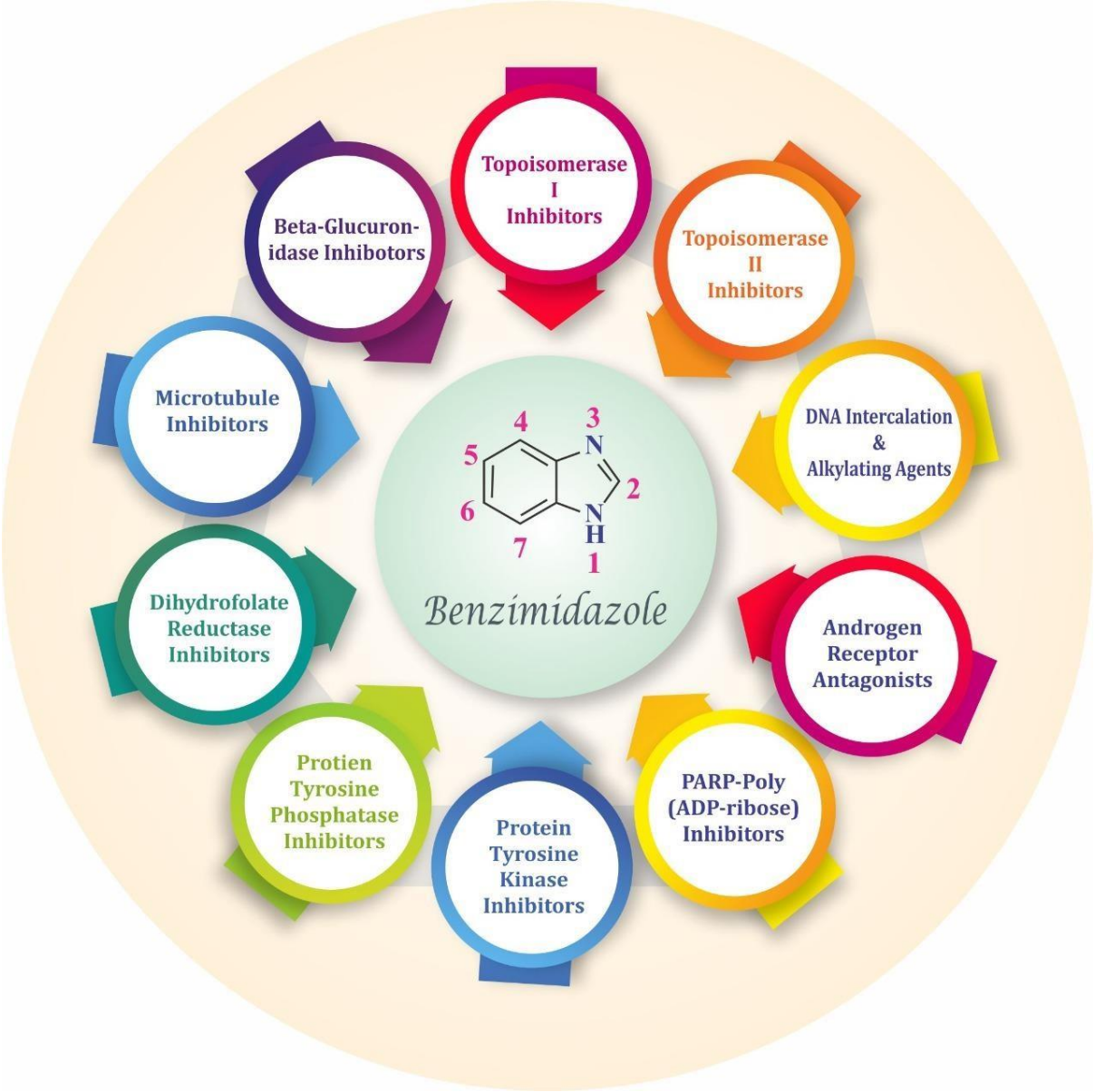

Figure 1. Different targets of benzimidazole as anticancer agents.

ANTICANCER BENZIMIDAZOLES

Chu et al. described the antitumor effect of a chemical, 2-chloro-N-(2-p-tolyl-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(29).

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, N-methylpiperazine, N-phenylpiperazine, 1-(2-pyridyl)piperazine, 1-(2-methoxyphenyl)piperazine, 1-(2-pyrimidinyl)piperazine, and formaldehyde in ethanol. The pyrimido [1,2-a]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)-1,2-dihydro-pyrimido[1,2-a]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 amidino benzimidazoles as antitumor medications. The chemicals were chosen based on their substantial antiproliferative, topoisomerase inhibition, and DNA binding,properties. All compounds show antitumor action, however amidinobenzimidazole substituted isoindolin-1-ones and benzimidazole substituted 1-iminoisoindoline exhibit antitumor activity at submicromolar concentrations. Two of the 1-iminoisoindolines compounds, 1 and 2, seemed to have the greatest DNA binding, with an elevation in melting point of more than 10°C when the drug/base ratio (R) is set to 0.5. The CD spectra of CT-DNA investigations revealed additional high positive induced-CD (ICD) binding of compounds 1 and 2. This is typical of DNA groove binders, which arrange their primary axis along the groove of the DNA helix(32,33).

Twenty congeners of imidazopyridine/imidazopyrimidine-benzimidazole conjugates (11a-t) were synthesised and tested for cytotoxicity against four human tumor cell lines, Hela (cervical), A-549 (lung), B-16 (melonoma), and DU-145 (prostate). At micromolar (µM) concentrations, some of these conjugates displayed considerable cytotoxic action. Two of the most powerful compounds (11i and 11p) demonstrated potential cytotoxic action against the A-549 tumor cell lines (IC50, 1.48 and 1.92 µM, respectively). Flow cytometry demonstrated that these conjugates halted the cell cycle at the G2/M phase. With IC50 values of 2.06µ M and 2.26 µM, respectively, these powerful conjugates (11i and 11p) exert their cytotoxic effect by inhibiting tubulin polymerization. Moreover, Hoechst staining, DNA fragmentation test, caspase-3 activation, and Annexin V-FITC assays revealed that these conjugates cause apoptosis. Furthermore, molecular modelling investigation indicates that these conjugates preferentially bind to tubulin's colchicine binding site. Overall, this study presents the production of imidazopyridine/imidazopyrimidine benzimidazoles conjugates as prospective antitumor drugs capable of triggering apoptosis via tubulin targeting(34).

MTT colorimetric assay was utilized to investigate the anticancer efficacy of benzimidazoles 5-7 against MCF-7 and HL-60 cell lines.The cells were then treated with 5-7 for 48 hours, and the findings are showed as IC50 in µM, with the survival of untreated cells assumed to be 100%.Every

one of the studied compounds had substantial effects against MCF-7 and HL60, which varied depending on the alteration at the benzimidazole ring's 5th place. The benzoyl substituted benzimidazole **6** showed high efficacy (IC50:16.18±0.07 μM forMCF-7 and 15.15±0.05 μM for HL-60), the carboxyl substituted benzimidazole **7** which wasmoderately potent (IC50:19.21±0.08 μM for MCF-7 and18.29±0.06 μM for HL-60),whereas **5**exhibited decreased the effect (IC50:20.48±0.08 μM for MCF-7 and 23.23±0.09 μM for HL-60). When these points were compared to those of cisplatin (IC50:40.45±0.29 μM for MCF-7 and 41.08±0.32 μM for HL-60), it was discovered that all of these complexes (5-7) are more powerful than cisplatin under the current experimental conditions(35,36).

The cytotoxic and/or development inhibitory activity of 2-arylbenzimidazoles and pyrazino-benzimidazole derivatives on numerous tumor cell lines were investigated in vitro. Compounds (110) and (111) have exceptional anti-cancer action. Compounds containing methoxy or halogen have greater activity levels than other alternatives. Benzimidazoles containing oxothiazolidine **(112)** and benzimidazolesthioxothiazole**113 (a,b)**, 2-[(4-fluorobenzylidene **114(a,b)** and cyclo-alkylidene) cyanomethyl] benzimidazoles **115 (a,b)**, 2-[(4- or 5-oxothiazolidin-2-ylidene, 4-substitutedthiazolyl-2-ylidene and [1,3]thiazin-2-ylidene)cyanomethyl]benzimidazoles (**116-119**,respectively) were synthesized and screened for in vitro anti-cancer efficacy, and all the tested compounds demonstrated anti-tumoreffect against three human cell lines i.e., breast adenocarcinoma (MCF7), colon carcinoma (HCT 116),and hepatocellular carcinoma (HEPG2), with IC50's < 10 μg/mL.The most powerful compounds with a broad spectrum of action against all three cell lines were 2-thiazolylbenzimidazole derivative (113a), benzylidene cyanomethy lbenzimidazole (114a), and oxothiazolidin-2-ylide-necyanomethylbenzimidazole (118a)(37).

Pyrazole-benzoimidazole-5-carboxylates (129), which inhibited 60 distinct human tumour cell lines, were produced and tested. Products 129(a,b) 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-1,2-dihydroquinolin-3-yl moiety in the structure of SAR improves anticancer efficacy(38). Antiproliferative efficacy of thiazoly lbenzimidazole compounds against SMMC-7721 and A549 cell lines was investigated. The majority of the compounds demonstrated significant anticancer potential, whereas compound (130) 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(39).

The synthesis and evaluation of a new series of N-substituted benzimidazole derivatives containing a functional chalcone group are described. The MTT experiment against OVCAR-3, MCF-7, HEP-G2, and A549 cells indicated significant antitumor therapeutic potential. Compound 23a ((2E)-1-(1-(3-morpholinopropyl)-1H-benzimidazol-2-yl)-3-phenyl-2-propen-1-one) in particular had significant IC50 values on OVCAR-3, MCF-7, HEP-G2, and A549 cells and demonstrated in vitro cytotoxicity equivalent to or superior to cisplatin.For the OVCAR-3 cells, 11 chemicals (20a, 20c, 20d, 21a–21c, 22c, 22d, 23a–23c) showed IC50 values between 10.34 and 14.88 μM, which were lower than 16.04 μM (the IC50 value of cisplatin). According to the MTT results, the nitrogen-containing 5- or 6-membered ring in the N-substituted benzimidazole derivatives might result in improved cytotoxic effects on MCF-7 and OVCAR-3 cells, potentially serving as novel templates in the production and development of effective medicines(40).

BZD9L1 inhibits tumour growth in a dose-dependent mannerby decreasing cell viability, motility, and survival in HCT 116 and HT-29 colorectal cancer cells (CRCC). Our findings demonstrated, BZD9L1 has a stronger affinity for CRCCthan for normal colon cells. The investigation of BZD9L1-mediated CRCC mortality mechanisms has revealed how suppression of mammalian sirtuins (SIRT1 and SIRT2) be used to decrease CRCC progression (41).

The novel copper(II) (1) and zinc(II) (2) complexes were created using a benzimidazole-derived ligand as amoiety that is physiologically active. Our research focused on its therapeutic relevance, namely its antitumor properties. Thus, complexes 1 and 2 were investigated for their tendency to interact withDNA and HSA, which confirmed the strong binding. DNA cleavage tests demonstrated that complex 1 had nuclease function utilising a double-stranded cleavage technique, and that ROS are the cleavage agents. Surprisingly, both the compounds and the ligand were cytotoxic and tested on five various tumour cell lines, and the findings revealed that complex 1 had far better action on tumor cells, having IC50 values equivalent to the standard medication cisplatin. In addition, we investigated adhesion of cell and migratory capabilities of several tumor cell lines in the presence of complex 1. Strong anti-metastatic properties are shown by Complex 1 by blocking tumour cells migration and adhesion, according to our findings. Furthermore, complex 1 and 2 were tested forin vivo toxicitydemonstrated both the compounds' safety profile is efficacious and might be developed as a viable antitumor medication for human utilization(42).Two Zn(II) complexes with benzimidazole-based complexes were synthesised and studied in an attempt to target novel metal complexes as powerful antitumor medicines. Complex 2 is less effective than compound 1 demonstrated by cytotoxic essay in inhibiting the tumor cells proliferation (EC109, MCF7, QBC939, and SHSY5Y), but both the ligands showed no specific increase in inhibitory effecton the cells. Complex 1 interaction investigations with CT-DNA indicate that the binding mechanism of 1 with DNA is not typical intercalation binding. Other biochemical investigations have shown that complex 1 serves as a strong antitumor by generating morphological alterations, accumulation of cell in the G0/G1 phase, increased membrane permeability, and associated with production of mostly apoptotic. According to the findings of our current study, 1 merit further exploration as a possible anticancer medication (43). Eighteen novel Zn(II) and Co(II) benzimidazole metal complexes, as well as three new benzimidazole ligands (V), effectively synthesised, along with antitumor properties tested on human cancer cell lines (A2780 and DU-145). At a concentration of 0.1 M, compounds 1, 3, 4, and 9 outperformed the conventional medication docetaxel in antitumor efficacy against the A2780 cell line. Only 1, 18, and V, on the other hand, had equivalent antitumor effect against DU145 at 100 M concentrations. Several derivates of benzimidazole (5a-l) were created by combining pyrazole at the C-2 position with substituted aryl rings at the C-3 and C-5 positions of pyrazole in order to target their powerful antitumor effect. When the complexes were evaluated for EGFR binding affinity, compound 5a inhibited EGFR at 0.97mM.The cytotoxicity of the newly synthesised compounds exhibited substantial anticancer activity, notably compound 5a,against lung tumor cell lines (A549), with an IC50 range of 2.2mM. Additionally, by triggering apoptosis, compounds 5a caused cell cycle arrest during the G2/M phase(44).

Wanga et al. developed and tested a variety of chrysin benzimidazole derivatives for antitumor properties. Against MFC cells, Compound (1) 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(45).

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 non-substituted benzimidazole 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, HCT-116, 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)(47).

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.

REFERENCES

1. Mathur P, Sathishkumar K, Chaturvedi M, Das P, Sudarshan KL, Santhappan S, et al. Cancer Statistics, 2020: Report From National Cancer Registry Programme, India. JCO Global Oncology. 2020 Nov 16;(6):1063–75.
2. Nia HT, Munn LL, Jain RK. Physical traits of cancer. Science (New York, NY) [Internet]. 2020 Oct 30 [cited 2021 Dec 12];370(6516). Available from: https://pubmed.ncbi.nlm.nih.gov/33122355/
3. Khan MF, Anwer T, Bakht A, Verma G, Akhtar W, Alam MM, et al. Unveiling novel diphenyl-1H-pyrazole based acrylates tethered to 1,2,3-triazole as promising apoptosis inducing cytotoxic and anti-inflammatory agents. Bioorganic Chemistry. 2019 Jun 1;87:667–78.
4. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians [Internet]. 2018 Nov [cited 2021 Dec 12];68(6):394–424. Available from: https://pubmed.ncbi.nlm.nih.gov/30207593/
5. Ruddarraju RR, Murugulla AC, Kotla R, Chandra Babu Tirumalasetty M, Wudayagiri R, Donthabakthuni S, et al. Design, synthesis, anticancer, antimicrobial activities and molecular docking studies of theophylline containing acetylenes and theophylline containing 1,2,3-triazoles with variant nucleoside derivatives. European journal of medicinal chemistry [Internet]. 2016 [cited 2021 Dec 12];123:379–96. Available from: https://pubmed.ncbi.nlm.nih.gov/27487568/

6. Metzcar J, Wang Y, Heiland R, Macklin P. A Review of Cell-Based Computational Modelling in Cancer Biology. JCO Clinical Cancer Informatics. 2019 Dec 4;(3):1–13.
7. Cleeland CS, Allen JD, Roberts SA, Brell JM, Giralt SA, Khakoo AY, et al. Reducing the toxicity of cancer therapy: recognizing needs, taking action. Nature reviews Clinical oncology [Internet]. 2012 Aug [cited 2021 Dec 12];9(8):471–8. Available from: https://pubmed.ncbi.nlm.nih.gov/22751283/
8. Slocum M, Garcia SF, McKoy JM. Cancer drug toxicity: Moving from patient to survivor. Cancer Treatment and Research. 2019;171:107–18.
9. Hernández-Romero D, Rosete-Luna S, López-Monte on A, Chávez-Piña A, Pérez-Hernández N, Marroquín-Flores J, et al. First-row transition metal compounds containing benzimidazole ligands: An overview of their anticancer and antitumor activity. Coordination Chemistry Reviews. 2021 Jul 15;439:213930.
10. Pathare B, Bansode T. Review- biological active benzimidazole derivatives. Results in Chemistry. 2021 Jan 1;3:100200.
11. Bharadwaj SS, Poojary B, Nandish SKM, Kengaiah J, Kirana MP, Shankar MK, et al. Efficient Synthesis and in Silico Studies of the Benzimidazole Hybrid Scaffold with the Quinolinyloxadiazole Skeleton with Potential α-Glucosidase Inhibitory, Anticoagulant, and Antiplatelet Activities for Type-II Diabetes Mellitus Management and Treating Thrombotic Disorders. ACS Omega [Internet]. 2018 Oct 31 [cited 2021 Dec 12];3(10):12562–74. Available from: /pmc/articles/PMC6217529/
12. Shankar A, Saini D, Roy S, Jarrahi AM, Chakraborty A, Bharati SJ, et al. Cancer care delivery challenges amidst coronavirus disease -19 (covid-19) outbreak: Specific precautions for cancer patients and cancer care providers to prevent spread. Asian Pacific Journal of Cancer Prevention. 2020 Mar 1;21(3):569–73.
13. van Zandwijk N, Rasko JEJ. The COVID-19 outbreak: a snapshot from down under. Expert Review of Anticancer Therapy. 2020;433–6.
14. van de Haar J, Hoes LR, Coles CE, Seamon K, Fröhling S, Jäger D, et al. Caring for patients with cancer in the COVID-19 era. Nature medicine [Internet]. 2020 May 1 [cited 2021 Dec 12];26(5):665–71. Available from: https://pubmed.ncbi.nlm.nih.gov/32405058/
15. Goud NS, Kumar P, Bharath RD. Recent Developments of Target-Based Benzimidazole Derivatives as Potential Anticancer Agents. Heterocycles - Synthesis and Biological Activities [Internet]. 2020 Jan 2 [cited 2021 Dec 12]; Available from: https://www.intechopen.com/chapters/70696
16. B V, N M, M V, K M, P K, K B, et al. An insight into the medicinal perspectives of mannich bases of benzimidazole derivatives: A review. International Journal of Research in Pharmaceutical Sciences [Internet]. 2021 Jul 1 [cited 2021 Dec 12];12(3):1895–901. Available from: https://www.pharmascope.org/index.php/ijrps/article/view/4790
17. Brishty SR, Hossain MdJ, Khandaker MU, Faruque MRI, Osman H, Rahman SMA. A Comprehensive Account on Recent Progress in Pharmacological Activities of Benzimidazole Derivatives. Frontiers in Pharmacology [Internet]. 2021 Nov 3 [cited 2021 Dec 12];0:2863. Available from: https://www.frontiersin.org/articles/10.3389/fphar.2021.762807/full
18. Haoran W, Akhtar W, Nainwal LM, Kaushik SK, Akhter M, Shaquiquzzaman M, et al. Synthesis and biological evaluation of benzimidazole pendant cyanopyrimidine derivatives as anticancer agents. Journal of Heterocyclic Chemistry [Internet]. 2020 Sep 1 [cited 2021 Dec 12];57(9):3350–60. Available from:

https://onlinelibrary.wiley.com/doi/full/10.1002/jhet.4052

19. Huynh TKC, Nguyen THA, Tran NHS, Nguyen TD, Hoang TKD. A facile and efficient synthesis of benzimidazole as potential anticancer agents. Journal of Chemical Sciences 2020 132:1 [Internet]. 2020 Jul 8 [cited 2021 Dec 12];132(1):1–9. Available from: https://link.springer.com/article/10.1007/s12039-020-01783-4
20. Faheem M, Rathaur A, Pandey A, Kumar Singh V, Tiwari AK. A Review on the Modern Synthetic Approach of Benzimidazole Candidate. ChemistrySelect [Internet]. 2020 Apr 7 [cited 2021 Dec 12];5(13):3981–94. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/slct.201904832
21. Novak Jovanović I, Jadreško D, Miličević A, Hranjec M, Perin N. An electrochemical study on the redox chemistry of cyclic benzimidazole derivatives with potent anticancer activity. Electrochimica acta [Internet]. 2019 Feb 20 [cited 2021 Dec 12];297:452–62. Available from: https://www.bib.irb.hr/971209
22. Gajanan G, Shital S, Vipul T, Babar V, Dnyaneshwar J, Vaibhav D, et al. A Review on Benzimidazole and it's Biological Activities. Journal of Pharmaceutical Chemistry and Drug Formulation [Internet]. 2021 [cited 2021 Dec 13];3(1):23–32. Available from: https://www.researchgate.net/publication/349812021_A_Review_on_Benzimidazole_and_it's_Biological_Activities
23. Singh V, Parle A. THE INTRIGUING BENZIMIDAZOLE: A REVIEW | INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH. INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH [Internet]. 2019 [cited 2021 Dec 13];10(4):1540–52. Available from: http://ijpsr.com/bft-article/a-comprehensive-review-on-benzimidazole/?view=fulltext
24. Son DS, Lee ES, Adunyah SE. The Antitumor Potentials of Benzimidazole Anthelmintics as Repurposing Drugs. Immune network [Internet]. 2020 Aug 1 [cited 2021 Dec 13];20(4):1–20. Available from: https://pubmed.ncbi.nlm.nih.gov/32895616/
25. Králová V, Hanušová V, Staňková P, Knoppová K, Čáňová K, Skálová L. Antiproliferative effect of benzimidazole anthelmintics albendazole, ricobendazole, and flubendazole in intestinal cancer cell lines. Anti-cancer drugs [Internet]. 2013 Oct [cited 2021 Dec 13];24(9):911–9. Available from: https://pubmed.ncbi.nlm.nih.gov/23884106/
26. Djemoui A, Naouri A, Ouahrani MR, Djemoui D, Lahcene S, Lahrech MB, et al. A step-by-step synthesis of triazole-benzimidazole-chalcone hybrids: Anticancer activity in human cells+. Journal of Molecular Structure. 2020 Mar 15;1204:127487.
27. Padhy GK, Panda J, Behera AK. Synthesis and Characterization of Novel N-Benzylbenzimidazole Linked Pyrimidine Derivatives as Anticancer Agents. Indian Journal of Pharmaceutical Education and Research. 2019 Apr 1;53(2s):S129–34.
28. Wang Z, Deng X, Xiong S, Xiong R, Liu J, Zou L, et al. Design, synthesis and biological evaluation of chrysin benzimidazole derivatives as potential anticancer agents. https://doi.org/101080/1478641920171389940 [Internet]. 2017 Dec 17 [cited 2021 Dec 13];32(24):2900–9. Available from: https://www.tandfonline.com/doi/abs/10.1080/14786419.2017.1389940
29. Chu B, Liu F, Li L, Ding C, Chen K, Sun Q, et al. A benzimidazole derivative exhibiting antitumor activity blocks EGFR and HER2 activity and upregulates DR5 in breast cancer cells. Cell death & disease [Internet]. 2015 [cited 2021 Dec 13];6(3):e1686. Available from: https://pubmed.ncbi.nlm.nih.gov/25766325/

30. Tratrat C, Haroun M, Paparisva A, Geronikaki A, Kamoutsis C, Ćirić A, et al. Design, synthesis and biological evaluation of new substituted 5-benzylideno-2-adamantylthiazol[3,2-b][1,2,4]triazol-6(5H)ones. Pharmacophore models for antifungal activity. Arabian Journal of Chemistry. 2018 May 1;11(4):573–90.
31. Nawrocka W, Sztuba B, Kowalska MW, Liszkiewicz H, Wietrzyk J, Nasulewicz A, et al. Synthesis and antiproliferative activity in vitro of 2-aminobenzimidazole derivatives. Farmaco. 2004;59(2):83–91.
32. Hranjec M, Starčević K, Pavelić SK, Lučin P, Pavelić K, KarminskiZamola G. Synthesis, spectroscopic characterization and antiproliferative evaluation in vitro of novel Schiff bases related to benzimidazoles. European Journal of Medicinal Chemistry. 2011 Jun;46(6):2274–9.
33. Akhtar MdJ, Yar MS, Sharma VK, Khan AA, Ali Z, Haider MDR, et al. Recent Progress of Benzimidazole Hybrids for Anticancer Potential. Current medicinal chemistry [Internet]. 2020 Aug 8 [cited 2021 Dec 13];27(35):5970–6014. Available from: https://pubmed.ncbi.nlm.nih.gov/31393240/
34. Kamal A, Bharath Kumar G, Lakshma Nayak V, Reddy VS, Shaik AB, Rajender, et al. Design, synthesis and biological evaluation of imidazopyridine/imidazopyrimidine-benzimidazole conjugates as potential anticancer agents. MedChemComm [Internet]. 2015 Apr 10 [cited 2021 Dec 13];6(4):606–12. Available from: https://pubs.rsc.org/en/content/articlehtml/2015/md/c4md00400k
35. Hranjec M, Starčević K, Pavelić SK, Lučin P, Pavelić K, KarminskiZamola G. Synthesis, spectroscopic characterization and antiproliferative evaluation in vitro of novel Schiff bases related to benzimidazoles. European Journal of Medicinal Chemistry. 2011 Jun;46(6):2274–9.
36. Nawrocka W, Sztuba B, Kowalska MW, Liszkiewicz H, Wietrzyk J, Nasulewicz A, et al. Synthesis and antiproliferative activity in vitro of 2-aminobenzimidazole derivatives. Farmaco. 2004;59(2):83–91.
37. Keri RS, Hiremathad A, Budagumpi S, Nagaraja BM. Comprehensive Review in Current Developments of Benzimidazole-Based Medicinal Chemistry. Chemical biology & drug design [Internet]. 2015 Jul 1 [cited 2021 Dec 13];86(1):799–845. Available from: https://pubmed.ncbi.nlm.nih.gov/25352112/
38. Abonia R, Cortés E, Insuasty B, Quiroga J, Nogueras M, Cobo J. Synthesis of novel 1,2,5-trisubstituted benzimidazoles as potential antitumor agents. European journal of medicinal chemistry [Internet]. 2011 [cited 2021 Dec 13];46(9):4062–70. Available from: https://pubmed.ncbi.nlm.nih.gov/21719162/
39. Luo Y, Xiao F, Qian S, Lu W, Yang B. Synthesis and in vitro cytotoxic evaluation of some thiazolylbenzimidazole derivatives. European journal of medicinal chemistry [Internet]. 2011 Jan [cited 2021 Dec 13];46(1):417–22. Available from: https://pubmed.ncbi.nlm.nih.gov/21115212/
40. Hsieh CY, Ko PW, Chang YJ, Kapoor M, Liang YC, Chu HL, et al. Design and Synthesis of Benzimidazole-Chalcone Derivatives as Potential Anticancer Agents. Molecules [Internet]. 2019 Sep 6 [cited 2021 Dec 13];24(18). Available from: /pmc/articles/PMC6767017/
41. Tan YJ, Lee YT, Yeong KY, Petersen SH, Kono K, Tan SC, et al. Anticancer activities of a benzimidazole compound through sirtuin inhibition in colorectal cancer. Future medicinal chemistry [Internet]. 2018 [cited 2021 Dec 13];10(17):2039–57. Available from: https://pubmed.ncbi.nlm.nih.gov/30066578/

42. Alajmi MF, Hussain A, Rehman MT, Khan AA, Sheikh PA, Khan RA. Design, Synthesis, and Biological Evaluation of Benzimidazole-Derived Biocompatible Copper(II) and Zinc(II) Complexes as Anticancer Chemotherapeutics. International journal of molecular sciences [Internet]. 2018 May 16 [cited 2021 Dec 13];19(5). Available from: https://pubmed.ncbi.nlm.nih.gov/29772746/
43. Zhao J, Guo Y, Hu J, Yu H, Zhi S, Zhang J. Potential anticancer activity of benzimidazole-based mono/dinuclear Zn(II) complexes towards human carcinoma cells. Polyhedron [Internet]. 2015 Dec 14 [cited 2021 Dec 13];C(102):163–72. Available from: https://www.infona.pl//resource/bwmeta1.element.elsevier-4a4c8df6-bcb3-3d9e-bfb7-ddc23dc6a183
44. Yılmaz Ü, Tekin S, Buğday N, Yavuz K, Küçükbay H, Sandal S. Synthesis and evaluation of anticancer properties of novel benzimidazole ligand and their cobalt(II) and zinc(II) complexes against cancer cell lines A-2780 and DU-145. INORGANICA CHIMICA ACTA [Internet]. 2019 Sep 1 [cited 2021 Dec 13];495. Available from: https://avesis.inonu.edu.tr/yayin/f6a1ad81-e672-4cce-b9db-0e933f6d5e05/synthesis-and-evaluation-of-anticancer-properties-of-novel-benzimidazole-ligand-and-their-cobaltii-and-zincii-complexes-against-cancer-cell-lines-a-2780-and-du-145
45. Wang Z, Deng X, Xiong S, Xiong R, Liu J, Zou L, et al. Design, synthesis and biological evaluation of chrysin benzimidazole derivatives as potential anticancer agents. Natural product research [Internet]. 2018 Dec 17 [cited 2021 Dec 13];32(24):2900–9. Available from: https://pubmed.ncbi.nlm.nih.gov/29063798/
46. Morais GR, Palma E, Marques F, Gano L, Oliveira MC, Abrunhosa A, et al. Synthesis and Biological Evaluation of Novel 2-Aryl Benzimidazoles as Chemotherapeutic Agents. Journal of Heterocyclic Chemistry [Internet]. 2017 Jan 1 [cited 2021 Dec 13];54(1):255–67. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/jhet.2575
47. Shaker YM, Omar MA, Mahmoud K, Elhallouty SM, El-Senousy WM, Ali MM, et al. Synthesis, in vitro and in vivo antitumor and antiviral activity of novel 1-substituted benzimidazole derivatives. Journal of enzyme inhibition and medicinal chemistry [Internet]. 2015 Sep 3 [cited 2021 Dec 13];30(5):826–45. Available from: https://pubmed.ncbi.nlm.nih.gov/25567722/