



Benzimidazole: A Promising Scaffold as Multitargeted Anticancer Agents - A Review of Chemistry and Mechanisms and Therapeutic Prospects

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Abstract

Cancer is still one of the biggest challenges facing global public health, and accounts for the second largest number of deaths globally. The design, discovery, and development of active anticancer agents including antitumor, antiproliferative, and antineoplastic agents therefore has been an important goal of current drug research. A longstanding hurdle in traditional cytotoxic treatment regimens is the poor selectivity for cancer cells, leading to harmful side effects in normal tissues. Given purine's significance in biology, there has been a tremendous amount of research on the substitution of the purine nucleoside scaffold with various bioisosteres, such as benzimidazole, which is considered a bioisostere of the purine nucleoside scaffold, is a privileged pharmacophore in medicinal chemistry due to its wide range of biological activities such as antiulcer, antioxidant, anti-HIV reverse transcriptase (HIV-RT) inhibitor, anticancer, anthelmintic, antimicrobial, and antihistaminic. The benzimidazole scaffold has been widely explored as a template in the development of drugs for cancer and antineoplastic therapeutics. Various transformations at different positions of the benzimidazole core have been obtained leading to the development of a wide range of active compounds exhibiting potent antiproliferative activities. This review provides an inclusive overview of the medicinal chemistry of substituted benzimidazole derivatives with special emphasis on their SAR explanations that influence their cytotoxic activity against diverse human tumor cell lines. Major mechanistic targets investigated include cyclin dependent kinase (CDK) inhibition, DNA topoisomerase inhibition, poly (ADP-ribose) polymerase (PARP) inhibition, dihydrofolate reductase (DHFR) inhibition, protein tyrosine kinase (PTK) inhibition, and microtubule disruption. The discussion also focuses on benzimidazole-based anticancer agents that have been clinically approved as well as potential investigational leads, demonstrating the sustained importance of this scaffold in oncology drug discovery.

Keyword : *benzimidazole; anticancer agents; CDK inhibitors; topoisomerase inhibitors; PARP inhibitors; DHFR inhibitors; tyrosine kinase inhibitors*

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INTRODUCTION

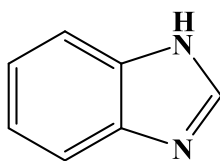
Cancer is a generic term for more than 277 different diseases, all involving abnormal cell growth with the potential to infiltrate and metastasize to other sites. The worldwide burden of cancer is huge; it is the second leading cause of death worldwide and takes millions of lives every year [1]. Several stages have been defined by scientists in cancer pathogenesis to represent the successive stepwise accumulation of genetic and epigenetic changes that lead normal cells to malignant phenotypes [10]. Some cancers are known for rapid proliferation kinetics, while others develop more slowly, yet they both result, ultimately, in severe disorganization of normal physiologic function.

The pathology of most cancers, at a molecular level, is based in genetic changes — germline mutations passed from parent to child or somatic mutations acquired during life — that disrupt the complex networks that regulate normal cellular activities. Among the intrinsic and extrinsic causes of oncogenic mutation are environmental carcinogens, ionizing radiation, chronic inflammation, and replication errors [10]. When mutations occur in proto-oncogenes, tumor suppressor genes, or DNA repair genes, the balance between cellular proliferation and programmed cell death, which is tightly regulated, can be irrevocably tipped toward cancer. Inactivation of tumor-suppressor genes leads to limitless cellular proliferation, and malfunctioning of DNA-repair systems causes further mutagenic events to accumulate unchecked, exacerbating genomic instability [10].

Among cancers, breast, lung, and colorectal cancers approximately contribute to one-third of total cancer burden and related deaths in the world [11]. The main risk factors that can be changed are tobacco use, contact with ionizing radiation and asbestos, and there are genetic predispositions that cannot be changed [11]. In the era of therapeutic advances in surgical oncology, radiotherapy, immunotherapy, and focused therapies, cytotoxic chemotherapy still maintains its place at the core of cancer treatment. Consequently, the discovery and development of new small molecule anticancer agents continues to be area of intense research.

The cell cycle — the ordered sequence of molecular events regulating cell growth, DNA replication, and division — is governed by a complex network of signaling cascades, checkpoint mechanisms, and quality-control mechanisms which are tightly controlled under normal physiological conditions. Crucial to this layer of regulation are the cyclin-dependent kinases (CDKs), a group of serine/threonine kinases whose activity depends on binding to their respective cyclin partners [2,3]. When checkpoint surveillance systems are compromised — through mutations in regulatory proteins — the "molecular switch" regulating cell cycle is locked in the on position, allowing unchecked cellular proliferation and carcinogenesis [2].

Benzimidazole, the condensed system of benzene and imidazole, is an important aromatic moiety which has been utilized in the drug designing and it is considered as a privileged scaffold in pharmaceutical chemistry. Its similarity to purines — the chemical basis of nucleic acids — promotes favorable interactions with many biologically relevant macromolecular targets. In fact, a number of benzimidazole-based compounds are already in the market, which find application in the broad therapeutic areas of gastroenterology (e.g. omeprazole, lansoprazole), parasitology (e.g. albendazole, mebendazole), cardiology (e.g. pimobendan), and oncology (e.g. bendamustine, olaparib) [27,30]. This privileged nature, together with positive synthetic accessibility and the possibility of introduction of the structural modifications to control or tune the pharmacological properties have made the benzimidazole derivative a very useful scaffold for the development of new anticancer agents [8,9].



1H-benzo[d]imidazole

This review attempts to present a focused yet holistic view on the anticancer potential of benzimidazole derivatives most noteworthy in the clinical and preclinical stages, and their mechanism of action, important targets, structure-activity relationship and clinical implications in detail. Drawing on accounts from current literature, this review is intended to provide a prospective view for drug discovery and convey future insights into the design of next-generation benzimidazole-based anticancer agents.

KEY MOLECULAR TARGETS IN CANCER THERAPY

The basis for selective molecular targeting in cancer treatment lies in the principle of oncogene addiction — i.e., an observation that cancer cells appear to be addicted to the activity of a limited number of signaling molecules for their survival and proliferation. Some of these targets have been successfully taken advantage of in the design of benzimidazole-based anticancer agent that are reported in the following subsections.

Cyclin-Dependent Kinases (CDKs)

Cyclin-dependent kinases (CDKs) are serine/threonine kinases that function as master regulators of the eukaryotic cell cycle [3]. Their enzymatic activity is highly dependent on binding to regulatory components called cyclins, for which the expression level has a periodic rhythm following the cell cycle. CDK-cyclin complexes also facilitate the phosphorylation of critical targets, such as retinoblastoma protein (Rb) to promote cell cycle stage transitions ($G1 \rightarrow S$, $G2 \rightarrow M$) [2,4].

In human cancers, the activity of CDK is often deregulated due to CDK gene amplification, overexpression of cyclins, loss of endogenous CDK inhibitors (such as p16INK4a, p21CIP1), or mutations in Rb that result in loss-of-function [4,5]. This long-lasting CDK hyperactivity leads to an increasing proliferation, establishing CDKs as enticing targets for therapy. In such context, CDK inhibition has become a promising anticancer pharmacological strategy with proven clinical relevance — as demonstrated by the FDA approval of the CDK4/6 inhibitors palbociclib, ribociclib, and abemaciclib for hormone receptor-positive breast cancer [16].

CDK8 (cyclin-dependent kinase 8), a subunit of the Mediator transcriptional coactivator complex and part of the RNA polymerase II holoenzyme, was specifically involved in the development of acute lymphoblastic leukemia and colorectal cancer and thus is a highly relevant target for design of benzimidazole-based inhibitors [6]. CDK2, an important regulator for the G1/S and S phase in cell cycle, is overexpressed in various solid tumors and attracted great attention in the field of new anticancer drugs [7].

DNA Topoisomerases

DNA topoisomerases are evolutionary conserved nuclear enzymes that play a vital role in genomic stability through the removal of topological constraints, including supercoiling, knotting, and catenation, generated in the processes of DNA replication, transcription, and chromosome segregation [17]. There are two classes that are structurally and mechanistically different: Type I topoisomerases (Topo I) unwind DNA supercoiling by forming transient single-strand DNA breaks, whereas Type II topoisomerases (Topo II) function through transient double-strand DNA breaks to allow passage of an intact DNA duplex through the break [17].

Because of its essential function to decatenate chromosomes before mitosis, Topo II is especially important as an anticancer target. Topo II inhibitors can be divided according to their mechanisms of action into "poisons," which stabilize the covalent Topo II-DNA cleavage complex and induce cytotoxic double-strand breaks, or "catalytic inhibitors," which inhibit other steps of the catalytic cycle without stabilization of the cleavable complex. Catalytic inhibitors are believed to be less genotoxic and may bypass certain resistance mechanisms to classical topoisomerase poisons [17]. A number of clinically relevant anticancer drugs, such as etoposide, doxorubicin, and mitoxantrone, derive most of their cytotoxicity from inhibition of Topo II.

Poly(ADP-Ribose) Polymerase (PARP)

ADP-ribosylation in the nucleus is catalyzed by poly(ADP-ribose) polymerases (PARPs), a family of enzymes that use NAD⁺ as a substrate to form ADP-ribose-containing polymers on nuclear proteins. The most abundant isoform, PARP-1, is an essential DNA single-strand break sensor and a

key player in the base excision repair (BER) pathway [18]. Once strand breaks are recognized, PARP-1 is activated and recruits DNA repair enzymes by poly(ADP-ribosyl)ating histones, itself, and additional nuclear proteins.

The therapeutic leverage of PARP inhibition is illustrated by the concept of synthetic lethality in tumors with homo-logous recombination repair defects — with BRCA1 or BRCA2 mutations being a prime example. In those cells, PARP inhibition leads to accumulation of unrepaired single-strand breaks, which are converted to double-strand breaks during replication, breaks that cannot be adequately repaired because of the underlying HR defect, selectively inducing death of cancer cells [19]. The effectiveness of PARP inhibitors (PARPi) such as olaparib, niraparib, rucaparib and talazoparib in BRCA mutated breast and ovarian cancers is very impressive, and these agents are truly a paradigm shifting breakthrough in targeted oncology [19].

Dihydrofolate Reductase (DHFR)

Dihydrofolate reductase (DHFR) is a key enzyme in the folate metabolism pathway and catalyzes NADPH-dependent reduction of the DHF to THF, which is a key cofactor in one-carbon transfer reactions that are needed for de novo biosynthesis of purines, thymidylate, and certain amino acids [20]. DHFR is a well-validated therapeutic target as rapidly dividing cancer cells have greatly increased demand for nucleotide precursors to sustain rapid DNA replication. DHFR expression is maximal at the G1/S transition of the cell cycle, which is in accordance with its function in meeting the biosynthetic need for DNA synthesis [20].

DHFR inhibition results in depletion of the tetrahydrofolates intracellular pool, leading to inhibition of de novo pyrimidine and purine biosynthesis and consequently blocking DNA and RNA synthesis, which results in cancer cell death [21]. The prototypical clinical antifolate — methotrexate — has been employed for decades in a wide variety of malignancies. As such, the design of new DHFR inhibitors – in particular with improved selectivity and reduced toxicity profiles – remains an active area of research, with benzimidazole-based candidates providing attractive strategies [21].

Protein Tyrosine Kinases (PTKs)

Protein tyrosine kinases (PTKs) are a large superfamily of enzymes that transfer the γ -phosphate group of ATP to tyrosine residues in protein substrates, which in turn affects the function and activity of proteins [22]. PTKs can be further classified into receptor tyrosine kinases (RTKs) as transmembrane proteins activated by binding of ligand at the extracellular side and non-receptor (cytoplasmic) tyrosine kinases. PTKs play central roles in normal physiology and oncogenic signaling, as the central nodes in signal transduction cascades that regulate cell growth, differentiation, migration, metabolism, and apoptosis [22, 23].

In cancer, PTK activity is often misregulated through activating mutations, gene amplification, chromosomal rearrangements generating constitutively active fusion kinases (such as BCR-ABL), or autocrine/paracrine growth factor loops. The epidermal growth factor receptor (EGFR), a classic RTK, is overexpressed or mutated in many solid tumors (e.g., NSCLC, colorectal cancer, and head and neck squamous cell carcinoma) [9]. Angiogenic receptor tyrosine kinases, VEGFR, PDGFR, FGFR, are also attractive targets since tumor neovascularization is essential for tumor growth and metastasis [23]. The availability of imatinib, gefitinib, erlotinib and sunitinib in the clinic has established PTK inhibition as the backbone of contemporary targeted cancer therapy.

Microtubules

Microtubules (MTs) are highly dynamic polymers formed by the assembly of α/β -tubulin heterodimers that constitute essential elements of the cytoskeleton and play multiple roles in

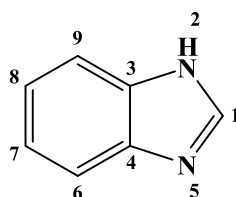
maintaining cellular architecture, transporting intracellular cargos, and dividing cells [24]. The mitotic spindle - a microtubule-based structure - is also required for accurate chromosome segregation in mitosis, and disruption of microtubule dynamics leads to mitotic arrest/apoptotic cell death.

Increased expression of β III-tubulin, a developmentally regulated tubulin isotype, has been linked to resistance to tubulin-directed agents and poor outcome in tumors of epithelial origin such as those of the lung and prostate [25]. Microtubule-targeting agents (MTAs) can also be classified as either microtubule-stabilizing agents (e.g. taxanes) or microtubule-destabilizing agents (e.g. vinca alkaloids, colchicine-site binders), both of which interfere with microtubule dynamics and spindle function. Substituted benzimidazoles that inhibit tubulin polymerization are a significant category of microtubule-destabilizing anti-cancer drugs, with nocodazole and carbendazim being examples [9,29].

Benzimidazole: Chemistry and Pharmacological Significance

Structural Overview and Physicochemical Properties

Benzimidazole (C₇H₆N₂) is a heterocyclic aromatic organic compound belonging to the group of fused-ring azoles and is a fusion of benzene and imidazole. The resultant scaffold is an amphoteric, possessing both weak acidic (pK_a ~5.5 of the conjugated base) and basic (pK_a ~12.8 of the conjugated acid) character, due to the different electronic environments of the two nitrogens. The resonance-stabilized aromatic system leads to high thermal and chemical stability of the molecule, and the capacity of the compound to serve as hydrogen bond donor/acceptor also enables multiple non-covalent interactions with biomacromolecules [8,9].



Tautomerism is a key structural aspect of benzimidazole: the 1H and 3H tautomers can interconvert through proton transfer between the two nitrogen atoms, and the N-1 substituted derivatives could also show such tautomerism. This characteristic has major consequences on molecular recognition events in biological systems [9]. The electron withdrawing effect of the fused benzene on the imidazole ring alters the electrophilic substitution reaction so that the electrophilic substitution occurs at N-1 and the nucleophilic substitution at C-2 (2. Stable carbocations derived from nucleophilic attack at C-2), and another electrophilic substitution can take place on the benzene ring [9].

Because of its structural similarity to the purine ring system, which forms a part of both the DNA and RNA, benzimidazole can act as a bioisostere of natural purines leading to beneficial interaction with nucleic acid-binding proteins, nucleotide-dependent enzymes, and other biological components involved in cell signaling and cellular division. This analogy in structure at the base is base of a wide range of nucleic acid related biological activities of benzimidazole derivatives [26].

Historical Development and Clinical Derivatives

The benzimidazole drug history can be dated back to the 1950s when Brink et al. reported 5,6-dimethylbenzimidazole as a degradation product of vitamin B12 and later described a number of analogs having vitamin B12-like activity [9]. This finding bred interest towards the biological attributes of benzimidazole during the following years in which a great expansion to the therapeutic applications of drugs containing the benzimidazole moiety was observed [8].

Nowadays there are a lot of clinically useful drugs incorporating a benzimidazole nucleus, covering a wide range of therapeutic areas. In gastroenterology, proton pump inhibitors such as

omeprazole, pantoprazole, and lansoprazole bind covalently to and irreversibly inhibit H⁺/K⁺-ATPase, the enzyme responsible for acid secretion by parietal cells in the stomach [27]. In antiparasitic pharmacotherapy, the broad-spectrum anthelmintics albendazole and mebendazole bind to parasitic microtubules and prevent their assembly [27]. In cardiology, positive inotropic and vasodilatory actions of pimobendan are well known [27]. Most importantly for this review, a number of anticancer benzimidazole derivatives have gained regulatory approval or are undergoing late stage clinical development and are presented in the following sections.

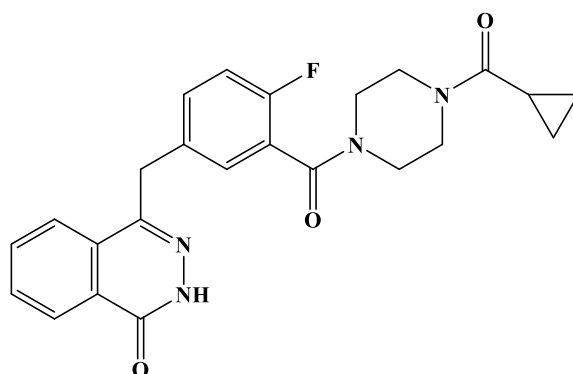
ANTICANCER ACTIVITIES OF BENZIMIDAZOLE DERIVATIVES

Clinically Approved Benzimidazole Anticancer Agents

Olaparib (Lynparza®)

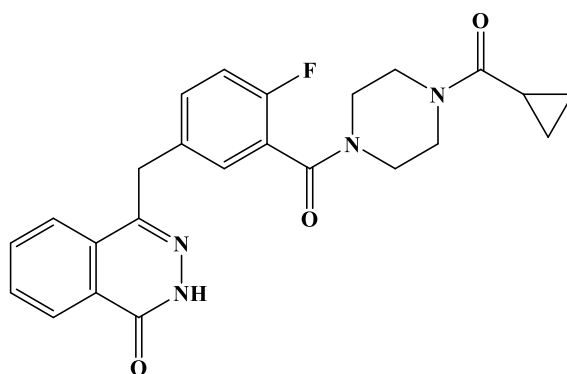
Olaparib (AZD2281), under the trade name Lynparza®, was the first PARP inhibitor that was granted approval for clinical use, the FDA approved olaparib in December 2014 as monotherapy for the maintenance treatment of adult patients with BRCA1/2-mutated advanced ovarian cancer after a response to platinum-based chemotherapy [28]. Olaparib competitively inhibits PARP-1 and PARP-2 and traps PARP-DNA complexes at sites of DNA damage, preventing resolution and inducing irreparable replication-associated double-strand breaks in HR-deficient tumor cells [19,28].

The benzimidazole ring system interacts with the distance ancillary ligand in the binding pocket and is responsible for the PARP catalytic domain selectivity. The drug has since been approved for treatment of metastatic breast cancer, pancreatic cancer, and prostate cancer in BRCA-mutated patients, helping to define a new era in precision oncology.



Bendamustine (Treanda®)

Bendamustine is a bifunctional alkylating agent with a purine analog structure that contains an N-methylbenzimidazole ring connected to a nitrogen mustard group. Initially developed in East Germany in the 1960s, it received FDA approval in 2008 (under the trade name Treanda(R)) for the treatment of chronic lymphocytic leukemia (CLL), as well as for relapsing indolent non-Hodgkin's lymphoma [30]. The drug was rationally designed via a structure-activity relationship (SAR) campaign to obtain more potent and water-soluble derivatives of chlorambucil replacing the benzene ring with a purine-like N-methylbenzimidazole moiety with the idea of integrating DNA-alkylating and antimetabolite actions into a single compound [30].

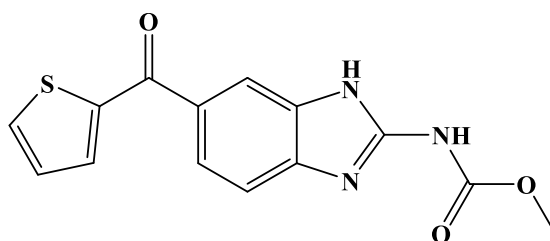


Bendamustine-mediated DNA cross-links also induce both intra-strand and inter-strand DNA cross-link breaks, with greater and more sustained DNA lesions than other traditional alkylating agents like cyclophosphamide, carmustine or chlorambucil [30]. These unusual DNA lesions seem to partially evade the cross-resistance associated with traditional alkylating agents, making bendamustine effective in certain tumors resistant to other alkylating-based therapies.

Benzimidazoles as Microtubule-Targeting Agents

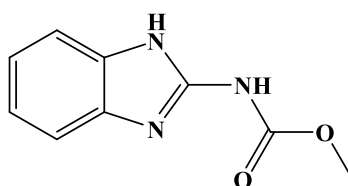
Nocodazole

Nocodazole is a benzimidazole derivative which has a 2-(methoxycarbonyl)amino group at the position 2 and a 2-thienoyl moiety at the position 5. It is a powerful antineoplastic drug whose cytotoxicity is mediated mainly by depolymerization of microtubules, thus binding to β -tubulin at the site of colchicine binding and inhibiting the assembly of the mitotic spindle [9]. This disturbance stops dividing cells at G2/M of the cell cycle and induces apoptosis. Nocodazole is commonly used in cell biology to arrest cells in mitosis and has been extensively used as a chemical probe in studies of microtubule biology and spindle assembly checkpoint mechanisms.



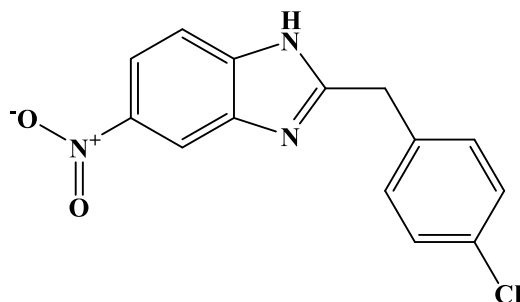
Carbendazim

Carbendazim (methyl 2-benzimidazolecarbamate) is a benzimidazole fungicide that is widely used and is also considered to have antineoplastic potency. Investigation of carbendazim in MCF7 human breast cancer cells revealed that it blocks cell growth with an IC₅₀ of around 10 μ M [29]. While the detailed mechanism of its antineoplastic effect is not yet fully known, carbendazim seems to inhibit the microtubule dynamic instability via interaction with an unknown tubulin site, culminating in metaphase/anaphase spindle checkpoint arrest [29]. The compound has shown encouraging antitumor activity in preclinical tests against both the murine B16 melanoma and the human HT-29 colorectal carcinoma, suggesting that further exploration of its therapeutic application is warranted [29].

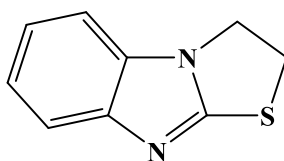


Benzimidazoles as CDK Inhibitors

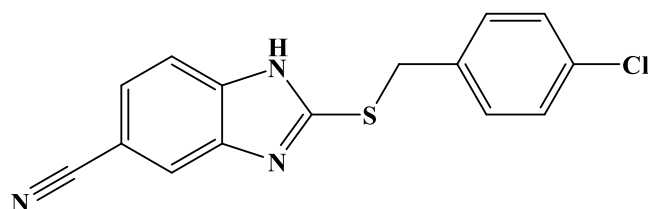
The development of benzimidazole-based CDK inhibitors has been the subject of continuous active investigation with multiple potential candidates being reported. Tahlan et al. described the *in silico* molecular design and the biological assessment of heterocyclic benzimidazole framework against human colorectal carcinoma and human breast adenocarcinoma cell lines using NCI cancer screening panel and recognized compound 12 ($IC_{50} = 9.53 \mu M$) and compound 16 ($IC_{50} = 11.97 \mu M$) as good antiproliferative agents endowed with promising CDK-8 inhibitory action, and compared well to the reference drug 5-fluorouracil ($IC_{50} 9.99 \mu M$) [6].



In a very original strategy, Eldehnaa and El-Haggarg synthesized a new series of isatin-thiazolo[3,2-a]benzimidazole (TBI) hybrids linked via a cleavable hydrazide moiety in the role of dual anticancer/CDK2 inhibitors [7]. The top-ranked compound in the series, hybrid 7d showed best CDK2 inhibitory activity, obtained the best docking score in the CDK2 ATP binding site and formed the most thermodynamically stable protein-ligand complex in molecular dynamic simulation. The compound 7d was considered as a promising lead for further development as a breast cancer tumor suppressing agent and selective CDK2 inhibitor [7].



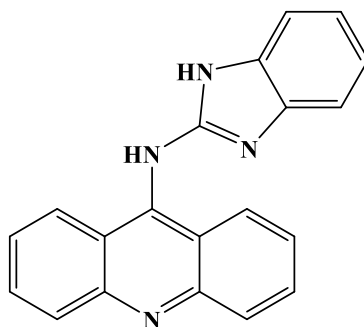
Abd El-Hameed et al. disclosed a class of 2-thiobenzimidazole analogs active against 60 cancer cell lines [35,36]. From the tested compounds, 3c and 3l exhibited the most notable anticancer potential against colon (HCT-116) and renal (TK-10) cancer cell lines, respectively. Docking investigations revealed that they adopt a necessary binding mode into the CDK2-ATP binding site and both compounds 3c and 3l showed significant CDK2/CyclinA2 kinase inhibitions in enzyme-based assays with positive control as imatinib [36,37].



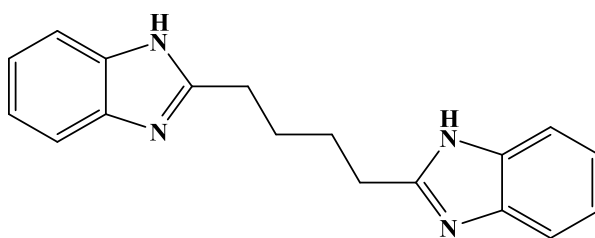
Benzimidazoles as Topoisomerase Inhibitors

Gao et al. developed a new series of benzimidazole-acridine hybrid derivatives as DNA targeted agents and tested their antiproliferative activity over various cancer cell lines [9]. The compound 21l, which contains a benzimidazole-acridine pharmacophore, exhibited strong Topoisomerase I (Topo I) inhibition with $IC_{50} = 8.11 \text{ mM}$ and a selective antiproliferative activity. The DNA-intercalating ability of this molecule was ascribed to the planar aromatic acridine moiety being sandwiched between

DNA base pairs and the benzimidazole moiety interacting further with DNA or to the Topo I enzyme active site.

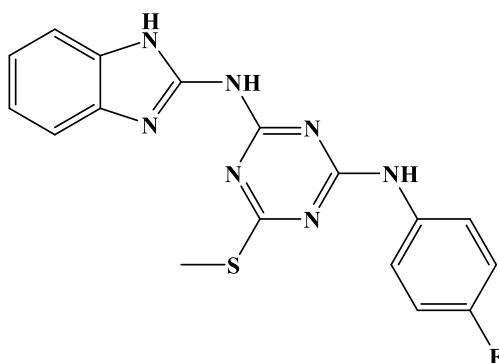


Huang et al described the synthesis and biological evaluation of a series of congeners of bis(benzimidazole)s as potent Topo II inhibitors. The most potent agent of the series, 44, underwent Topo II inhibition better than that of known clinical agents and showed remarkable antiproliferative activity on the human lung carcinoma (A-549) and human cervix epithelioid carcinoma (HeLa) cell lines [9]. The bis(benzimidazole) scaffold was hypothesized to possess bidentate interaction with the Topo II enzyme-DNA complex, providing more potency than the corresponding mono-benzimidazole counterparts.



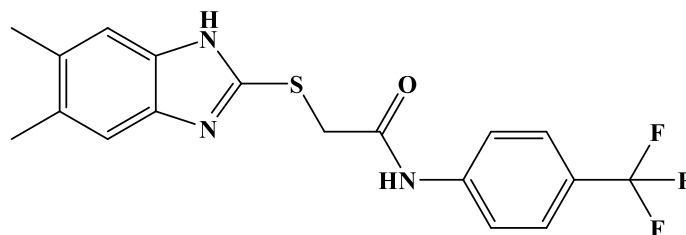
Benzimidazoles as DHFR Inhibitors

Singla and co-workers disclosed the preparation of a novel series of triazine-benzimidazole hybrids substituted with a 4-fluoroaniline group and their anticancer and pyrimidine antagonist dihydrofolate reductase (DHFR) inhibitory activities [21]. All of the compounds exhibited significant DNA intercalation with calf thymus DNA (ct-DNA) in fluorescence displacement assay and potent DHFR inhibition (IC₅₀ ranges 0.11–42.4 μ M). The SAR studies illustrated that the substituents at the C2 and C6 positions of the triazine ring greatly affected the DHFR inhibition ability, and the electron-withdrawing substituents at C6 combined with small lipophilic substituents at the C2 position exhibited the best anti-DHFR activity [21]. These results highlight the capability of triazine-benzimidazole hybrids as dual-acting anticancer agents possessing DHFR inhibitory and DNA-intercalative activity.

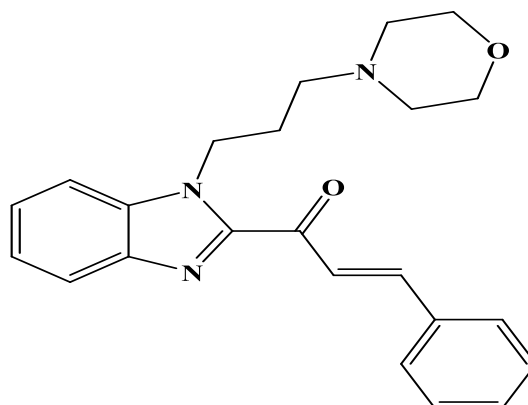


Benzimidazoles as PTK Inhibitors

Yadav et al. have reported the synthesis of new benzimidazole derivatives and have tested the EGFR-tyrosine kinase inhibitory activity [9]. Compound 247 was found to be the strongest EGFR inhibitor amongst the series having IC₅₀ values in the range of 0.049–0.005 μ M and a high potent inhibitory profile for the first generation EGFR inhibitors. The benzimidazole core was thought to represent the purine ring of ATP in the adenine pocket of the EGFR kinase domain and the substituents reached into two other nearby hydrophobic or solvent accessible areas that provide the selectivity [9].

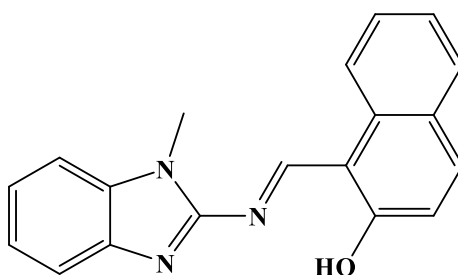


Hsieh et al. synthesized and evaluated a novel series of 24 benzimidazole-chalcone hybrids with alkyl chain-bearing cyclic moieties for their cytotoxicity towards OVCAR-3 (ovarian carcinoma) and MCF-7 (breast adenocarcinoma) cell lines [33,34]. Out of the 24 compounds the most active antiproliferative agent was 23a, with a morpholinopropyl substituent as N-1 of the benzimidazole ring, with a cell growth inhibition superior to cisplatin for both cell lines tested, which is bearing a cinnamoyl pharmacophore as C-2 substituent. Structure-activity investigations showed that a terminal N-containing heterocyclic ring in the N-substituted alkyl chain could improve the cytotoxic activity when compared to the counterparts without the group.



4.7. Benzimidazole-Based Metal Complexes

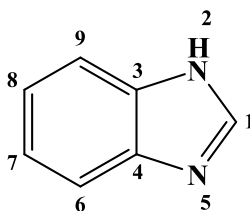
A new aspect of the benzimidazole anticancer chemistry is represented by the complexation of the benzimidazole-based ligands with transition metals resulting in metal-organic complexes with improved cytotoxic characteristics. Hussain et al. synthesized three transition metal complexes—Cu(II), Co(II), and Zn(II) with the bidentate ligand “bimnap” based on 1-methyl-2-aminobenzimidazole and 2-hydroxynaphthaldehyde as the substrate, and tested their in vitro cytotoxicity against five human cancer cell lines (HeLa, SK-MEL-1, HepG2, HT108, and MDA-MB-231) [31].



Lim et al. All three complexes exhibited marked antiproliferative activities in vitro, and studies of cell adhesion, migration and cell death pathways showed activation of apoptotic as well as necrotic signaling pathways. In vivo evaluation of the toxicity and tolerability of the drugs in murine models revealed good safety profiles, with acute and chronic toxicity studies demonstrating minimal systemic toxicity [31,32]. These results indicate that benzimidazole-metal complexes are worth exploring as potential or supplemental anticancer metallodrugs based on the clinical paradigm of platinum compounds.

STRUCTURE-ACTIVITY RELATIONSHIPS (SAR) OF ANTICANCER BENZIMIDAZOLES

The rational design of drugs within this class of compounds based on systematic SAR studies of benzimidazoles has at present found significant application. From the combined literatures, the following general rules have been concluded:



C-2 Substitution: The C-2 position of the benzimidazole nucleus is extensively exploited in structural diversity and plays an indispensable role in biological activities in many classes of targets. Lipophilic, electron-withdrawing or pharmacophoric substituents at C-2 positions are known to influence positively the anticancer efficacy by interacting with hydrophobic pocket of the enzyme active sites.

N-1 Substitution: Alkylation at N-1 removes tautomerism and may substantially influence physicochemical and target properties like lipophilicity and solubility. Polar or ionizable substituents at N-1 (e.g. aminoalkyl, morpholinopropyl chains) have been reported to increase cellular uptake as well as antiproliferative activity analogous to Hsieh and co-workers [33,34].

Substitution of benzene ring (C-5/C-6): Electron withdrawing substituents (e.g. halogen, nitro) can be introduced at 5- or 6-position of the benzene ring and can influence the electron density on the nitrogen atoms of the imidazole ring also affect the biological activity. Halogen substituents also allow halogen bonding with biomolecular targets, improving the strength of binding. **Hybrid/Conjugate Pharmacophores:** The conjugation of benzimidazole with other pharmacophoric groups, i.e., chalcone, acridine, triazine, isatin, or thiazole groups, is found to be the best approach in the synthesis of multitargeted or selective capable anticancer drugs. This kind of molecular hybridization benefits from the complementary interaction of the component pharmacophores in achieving synergistic effects [7, 34].

CONCLUSIONS AND FUTURE PERSPECTIVES

The benzimidazole framework holds a prime position among privileged pharmacophores in the war on cancer, presenting an unparalleled integration of structural diversity, synthetic convenience and target promiscuity toward multiple biologically significant oncological targets. One reviewed in this paper, the derivatives of benzimidazole produce antiproliferative effects via multiple mechanisms, such as blocking CDKs, DNA topoisomerases, PARP, DHFR, tyrosine protein kinases, and microtubule dynamics. The clinical efficacy of olaparib, bendamustine and nocodazole as successful anticancer agents derived from the benzimidazole scaffold highlights the potential of this class of compounds and emphasizes the translational value of the significant volume of preclinical investigation.

Looking ahead, a number of forthcoming strategies, are particularly promising to benzimidazole-based anticancer drug development. One attractive approach in this regard is the molecular hybridization strategy – the conjugation of benzimidazole with other pharmacophoric fragments to give multitargeted molecules – which holds considerable promise in overcoming the resistance mechanisms that often restrict properties clinical of single-target drugs. 2) The utilization of benzimidazole-transition metal coordination chemistry is another interesting field to explore for enhancing diversification of the structural repertoire of novel metallodrug leads with novel mode of actions. (Three) Recent advances in structure-based drug design and computational applications based on high-resolution crystal structures of benzimidazole-targets complexes have facilitated the rational hypothesis-driven optimization of benzimidazole derivatives to be specifically used for particular oncological pathologies.

To sum up, benzimidazole is a structure privileged, mechanistically diverse and clinically validated anticancer pharmacophore with a large unrealized potential. Further interdisciplinary studies involving synthetic organic chemistry, molecular pharmacology, computational modeling, and translational oncology are required to exploit the full therapeutic potential of this unique chemical scaffold.

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البنزيميدازول: بنية واعدة كموامل مضادة للسرطان متعددة الأهداف - مراجعة للكيمياء والآليات والآفاق العلاجية

الملخص

لا يزال السرطان أحد أكبر التحديات التي تواجه الصحة العامة العالمية، ويتسبب في ثاني أكبر عدد من الوفيات على مستوى العالم. ولذلك، يُعد تصميم واكتشاف وتطوير عوامل فعالة مضادة للسرطان، بما في ذلك العوامل المضادة للأورام، والمضادة للتكاثر، والمضادة للأورام الخبيثة، هدفاً هاماً لأبحاث الأدوية الحالية. ومن العقبات التي لطالما واجهت أنظمة العلاج التقليدية السامة للخلايا ضعف انتقائيتها للخلايا السرطانية، مما يؤدي إلى آثار جانبية ضارة في الأنسجة السليمة. نظراً لأهمية البيورينات في علم الأحياء، أجريت أبحاث مكثفة حول استبدال بنية نيوكليوزيد البيورين بنظائر حيوية مختلفة، مثل البنزيميدازول، الذي يُعد نظيراً حيوياً لبنية نيوكليوزيد البيورين، ويُمثل مجموعة دوائية مميزة في الكيمياء الطبية نظراً لنطاقه الواسع من الأنشطة البيولوجية، كمضاد للقرحة، ومضاد للأكسدة، ومثبط لإنزيم النسخ العكسي لفيروس نقص المناعة البشرية (HIV-RT)، ومضاد للسرطان، ومضاد للديدان، ومضاد للميكروبات، ومضاد للهيستامين. وقد خضعت بنية البنزيميدازول لدراسة مستفيضة كنموذج في تطوير أدوية لعلاج السرطان والأورام. وقد تم الحصول على تحولات متنوعة في مواقع مختلفة من نواة البنزيميدازول، مما أدى إلى تطوير مجموعة واسعة من المركبات النشطة التي تُظهر فعالية قوية مضادة للتكاثر. تقدم هذه المراجعة نظرة شاملة على الكيمياء الطبية لمشتقات البنزيميدازول المُستبدلة، مع التركيز بشكل خاص على تفسيرات علاقة التركيب بالنشاط (SAR) التي تؤثر على فعاليتها السامة للخلايا ضد أنواع مختلفة من خلايا الأورام البشرية. تشمل الأهداف الآلية الرئيسية التي تم بحثها تثبيط كينازات السيكلين المعتمدة (CDK)، وتثبيط توبوزوميراز الحمض النووي، وتثبيط بوليميراز عديد (أدينوزين ثنائي الفوسفات-ريبوز) (PARP)، وتثبيط مختزلة ثنائي هيدروفولات (DHFR)، وتثبيط كيناز بروتين التيروسين (PTK)، وتعطيل الأنابيب الدقيقة. كما يركز النقاش على عوامل مضادة للسرطان تعتمد على البنزيميدازول والتي تمت الموافقة عليها سريرياً، بالإضافة إلى المركبات الرائدة المحتملة قيد البحث، مما يُظهر الأهمية المستمرة لهذا الهيكل في اكتشاف أدوية الأورام.

الكلمات المفتاحية: بنزيميدازول؛ عوامل مضادة للسرطان؛ مثبطات كينازات السيكلين المعتمدة (CDK)؛ مثبطات توبوزوميراز؛ مثبطات بوليميراز عديد (أدينوزين ثنائي الفوسفات-ريبوز)؛ مثبطات مختزلة ثنائي هيدروفولات (DHFR)؛ مثبطات كيناز التيروسين