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Advances of Benzimidazole Derivatives as Anticancer Agents: Bench to Bedside

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Abstract

Benzimidazole is one of the privileged nitrogen-containing scaffolds known for its versatile diversified role in insecticides, pesticides, dyes, pigments and pharmaceuticals. Due to its electron-rich environment, structural features and binding potency of various therapeutic targets, benzimidazole derivatives exhibit a broad spectrum of biological activity that majorly includes antimicrobial, antifungal, analgesics, anti-diabetic and anticancer agents. Several benzimidazole scaffolds bearing drugs are clinically approved; they are used for various indications. For example, Bilastine, Lerisetron, Maribavir and Nocodazole are the most widely used benzimidazole-based marketed drugs available as an antihistamine, antiviral and antimetabolic agent, respectively. Another example is the recently approved anticancer drug Binimetinib and Selumetinib, which are indicated for BRAF mutated melanoma and plexiform neurofibromas. Not only this, many benzimidazole-based anticancer drugs are in late phases of clinical development. Due to the vast therapeutic potential of benzimidazole scaffold in cancer research, medicinal chemists have gained a lot of attraction to explore it more and develop novel, highly effective and target-specific benzimidazole-based potential anticancer drugs.

Keywords: benzimidazole, enzyme inhibitors, anticancer agents, hybrid derivatives

1. Introduction

Cancer is a complex, severe class of diseases that involves a group of cells that exhibit abnormal and uncontrolled division and proliferation. It is one of the primary health concerns which accounts for the second major cause of death globally. As per the recent statistics of the world health organization (WHO), in 2020, around 10 million people succumbed to death due to cancer. However, every year the number of incidences is increasing day by day. According to WHO, around 0.3 million new cases are diagnosed each year among the age group of 0–19 years. Cancer can affect a person of any age; however, with age, the risk increases. Globally, steady increases in cancer cases every year are taking a toll on the health care system [1–5]. To combat cancer, identification of potential drugs and potential drugs combination is essential. Potential research has been carried out to counter such problems

by addressing novel drug design and discovery approaches. In medicinal chemistry, heterocyclic rings have played a significant role in the search for potential therapeutic agents. Various drugs are currently in use and in development that widely addresses

Benzimidazole based antifungal drugs

Benzimidazole based Antihistaminic drugs

Benzimidazole based Proton pump inhibitors

Benzimidazole based Anthelmintic drugs

Benzimidazole based antihypertensive agents

Figure 1.
Examples of benzimidazole based drugs in clinical use.

such problems. However, due to changes in cancer forms and mutations, current therapy faces challenges of poor selectivity and specificity towards certain types of cancer cells, which narrows down their effectiveness. Generally, cancer cells act by disrupting and disturbing the cell signaling pathways; therefore, it is crucial to design novel target-based heterocyclic anticancer compounds with high efficacy and fewer side effects, which will provide a solid backup to the present chemotherapeutic regime [6–10].

2. Benzimidazole

Benzimidazole is a bicyclic nitrogen bearing aromatic heterocyclic ring, structurally it consists of benzene ring fused with imidazole ring at the 4th and 5th position of the ring. Chemically it appears as white crystals, amphoteric in nature, resembles the structure of purine. It is synthesized by different reported methods. However, condensation of 1,2-diamino benzene with carbonyl compounds to give benzimidazole is the conventional method which was used widely for its preparation. In 1858, it was synthesized by Heinrich Debus, a German chemist from glyoxal, ammonia and formaldehyde, that's why it was also known as glyoxalin. Benzimidazole ring is one of bioactive heterocyclic scaffold exhibiting wide range of biological activities. The NH group present at second position of the ring is both highly acidic and weak base in nature, it also has ability to form stable salts [11–16].

With time benzimidazole ring emerged as an important multifaceted heterocyclic system due to its wide range of pharmacological activity such as antibacterial [17], antiparasitic [18], antifungal [19], anti-inflammatory [20], analgesics [21], antiviral [22], antitubercular [23], anticoagulant [24], antihistaminic [25], antioxidant [26], antiulcer [27] and anticancer [28–31]. Some of the benzimidazole based marketed drugs are listed in with their indication and marketed name in **Figure 1**. Adding to this benzimidazole scaffold have also displayed a significant role in synthesis of organic intermediates. In light of the application of benzimidazole earlier various authors have reported many review articles. Due to the diverse therapeutic potential, benzimidazole have attracted lot of researchers to explore more in the field of drug discovery to synthesize novel and potent compounds with a broad spectrum of biological activities. Owing to this, with time efforts have been made to create libraries of these potent compounds. In cancer treatment benzimidazole based drugs played a significant role, various targeted therapies are designed and developed as Kinase inhibitors such as EGFR, VEGFR and PI3K inhibitors here, in this chapter we have included some potent benzimidazole based kinase inhibitors.

3. Advances of benzimidazole based anticancer agents

Benzimidazole based compounds have got much attention due to exhibiting significant cytotoxic activity. In last one decade a lot of benzimidazole based anticancer drugs have received status of US FDA global approval. Recently, Binimetinib, Selumetinib and Abemaciclib got approval for treatment of various mutated forms of cancer. Here, we have discussed some of benzimidazole based anticancer drugs which are recently approved, under development and in pipeline.

3.1 Benzimidazole based marketed anticancer drugs

3.1.1 Binimetinib (1)

Binimetinib (1) is chemically 5-((4-bromo-2-fluorophenyl)amino)-4-fluoro-N-(2-hydroxyethoxy)-1-methyl-1H-benzimidazole-6-carboxamide approved by US FDA recently in 2018. It is an orally available, potent selective inhibitor of mitogen activated protein kinase (MEK 1/2). Binimetinib is developed by Array Biopharma, commercially available by the name of Mektovi. It is indicated for patients having metastatic melanoma with BRAF mutation as combination therapy with BRAF inhibitors Encorafenib [32]. Presently, Binimetinib is in various phases of clinical development as monotherapy or in combination for conditions like KRAS mutated cancer, mutated non-small cell lung cancer [33, 34]. Structures of all the drugs are presented in **Figure 2**. More details of clinical trials are enlisted in **Table 1**.

3.1.2 Bendamustine (2)

Bendamustine (2) is chemically 4-(5-(bis(2-chloroethyl)amino)-1-methyl-1H-benzimidazol-2-yl)butanoic acid, it is an alkylating agent well known for its efficacy and tolerability in wide range of hematologic malignancies [35]. Bendamustine is indicated for the treatment of chronic lymphocytic leukemia and non-Hodgkin lymphoma [36]. Currently Bendamustine is further investigation as combination therapy along with Bcl-2 inhibitor Venetoclax and Rituximab for treatment of patient above 60 years of age with mantle cell lymphoma (NCT03834688).

Figure 2.
Benzimidazole based clinically approved anticancer agents.

Drug	Clinical trial number	Clinical trial study	Date of study	Current status and study phase
Binimetinib	NCT04965818	Phase 1b/2 study of Futibatinib in combination with Binimetinib in patients with advanced KRAS mutant cancer	Last update on September 27, 2021	Recruiting Phase 1b/2
	NCT03170206	Study of CDK4/6 inhibitor Palbociclib in combination with the Binimetinib for patients with advanced KRAS mutant NSCLC	Last update on June 10, 2021	Recruiting Phase 1
Bendamustine	NCT04217317	CPI-613 in combination with Bendamustine in patients with relapsed or refractory T-cell Non-Hodgkin lymphoma	Last update on August 30, 2021	Recruiting Phase 2
	NCT04510636	Study of Pembrolizumab with Bendamustine in Hodgkin lymphoma	Last update on August 30, 2021	Not yet Recruiting Phase 2
Selumetinib	NCT02768766	Intermittent Selumetinib for uveal melanoma	Last update on March 19, 2021	Recruiting Phase 1
	NCT05101148	Phase I study to assess the effect of food on the PK and gastrointestinal toxicity of Selumetinib in adolescent children with Neurofibromatosis Type 1 related plexiform neurofibromas	Last update on November 1, 2021	Recruiting Phase 1
Abemaciclib	NCT04003896	A study to evaluate Abemaciclib in advanced biliary tract carcinoma who failed prior first line therapy.	Last update on	Active, Not recruiting Phase 2
	NCT04040205	Abemaciclib for bone and soft tissue sarcoma with cyclin dependent kinase (CDK) pathway attention	February 15, 2021	Recruiting Phase 2
Veliparib	NCT02723864	Veliparib and VX-970 in combination with cisplatin in people with refractory solid tumors	Last update on February 5, 2021	Active, Not recruiting Phase 1
	NCT01434316	Veliparib and Dinaciclib in treating patients with advanced solid tumors	July 20, 2021	Recruiting Phase 1
Dovitinib	NCT01635907	Dovitinib in neuroendocrine tumors	Last update on April 14, 2020	Completed Phase 2

Drug	Clinical trial number	Clinical trial study	Date of study	Current status and study phase
Pracinostat	NCT03848754	Pracinostat and Gemtuzumab ozogamicin in patients with relapsed or refractory acute myeloid leukemia	Last update on October 18, 2021	Active, not recruiting Phase 1
Galeterone	NCT04098081	Galeterone with Gemcitabine for patients with metastatic pancreatic adenocarcinoma	Last update on March 10, 2021	Recruiting Phase 2
Nazartinib	NCT02335944	Study and safety and efficacy of Nazartinib in combination with cMET inhibitor INC280 in NSCLC patients with EGFR mutation	Last update on October 4, 2021	Active, not recruiting Phase 1/2
	NCT02108964	A phase I/II, multicentre, open label study of Nazartinib, administered orally in adult patients with EGFR mutated solid malignancies	Last update on August 13, 2021	Active, Not recruiting Phase 1/2

Table 1.
Benzimidazole based anticancer drugs in clinical development.

3.1.3 Selumetinib (3)

Selumetinib (3) is chemically 5-((4-bromo-2-chlorophenyl)amino)-4-fluoro-N-(2-hydroxyethoxy)-1-methyl-1H-benzimidazole-6-carboxamide recently approved by US FDA in on April 10, 2020 for the treatment of plexiform neurofibromas and neurofibromatosis in pediatric patients [37, 38]. Selumetinib is an orally available MEK 1/2 kinase inhibitor developed by AstraZeneca commercially available by the name of Koselugo. It is also received status of orphan drug in USA as adjuvant drug for treatment of thyroid cancer [39, 40].

3.1.4 Abemaciclib (4)

Abemaciclib (4) is chemically N-(5-((4-ethylpiperazin-1-yl)methyl)pyridin-2-yl)-5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzimidazol-6-yl)pyrimidin-2-amine, approved by US FDA on 28 September 2017, for the treatment of patients with hormone receptor (HR) positive, human epidermal growth factor receptor (HER-2) advanced/negative metastatic breast cancer as a combination therapy with estrogen receptor antagonist fulvestrant in female patients and as monotherapy in adult patient with diseases progression following chemotherapy. Abemaciclib is commercially available by the name of Verzenio, developed by Eli Lilly as cyclin dependent kinase-4 (CDK4) and CDK6 inhibitor [41]. Furthermore, Abemaciclib is currently in various phase of clinical development as monotherapy or in combination therapy for treatment of various types of cancer and mutated forms [42, 43].

3.1.5 Veliparib (5)

Veliparib (5) is chemically (R)-2-(2-methylpyrrolidin-2-yl)-1H-benzimidazole-4-carboxamide, it is an oral PARP inhibitor. Veliparib is investigational drug showed promising results in preclinical and clinical studies when treated for ovarian cancer and for mutated form BRCA-mutated ovarian cancer [44]. Further development of Veliparib is ongoing as monotherapy and combination therapy for treatment of different forms of ovarian cancer [45, 46].

3.1.6 Dovitinib (6)

Dovitinib (6) is chemically 4-amino-5-fluoro-3-(5-(4-methylpiperazin-1-yl)-1H-benzoimidazol-2-yl) quinolin-2(1H)-one, it is a potent orally available pan tyrosine kinase inhibitor targeting VEGFR, FGFR) and other tyrosine kinases [47]. It is a pipeline drug under development, for treatment of gastrointestinal stromal tumor, metastatic breast cancer and renal cell carcinomas. Recently on April 2, 2021 Dovitinib has received acceptance from US FDA for premarket approval (PMA) which was filed by Allarity therapeutics (details can be found on Allarity therapeutics website). Dovitinib is also explored for different typed of mutated forms of cancer, currently it is under phase II clinical trial study for patient with castration resistant prostate cancer [48].

3.1.7 Pracinostat (7)

Pracinostat (7) is chemically (E)-3-(2-butyl-1-(2-(diethyl amino) ethyl)-1H-benzoimidazol-5-yl)-N-hydroxyacrylamide, it is orally available, investigational drug exhibiting potential antitumor activity [49, 50]. Pracinostat is a small molecule next generation histone diacetylases (HDAC) inhibitor indicated acute myeloid leukemia [51]. In some recent study Pracinostat was found to suppresses growth and metastasis of breast cancer by inactivating the IL-6/STAT3 signaling pathway [52].

3.1.8 Galeterone (8)

Galeterone (8) is chemically (3S,8R,9S,10R,13S,14S)-17-(1H-benzimidazol-1-yl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1H-cyclopenta[a]phenanthren-3-ol, it is an orally available, small molecule investigational drug. Galeterone is developed by Tokai pharmaceutical as potent androgen receptor antagonist, indicated for treatment of prostate cancer [53]. Some in vivo studies revealed that Galeterone monotherapy inhibited breast cancer growth, also when administered in combination with cisplatin the results where promising and much better compare to monotherapy of cisplatin [54].

3.1.9 Nazartinib (9)

Nazartinib (9) is chemically (R,E)-N-(7-chloro-1-(1-(4-(dimethylamino) but-2-enoyl)azepan-3-yl)-1H-benzo[d]imidazol-2-yl)-2-methylisonicotinamide, it is an orally available third generation EGFR kinase inhibitor under development for treatment of conditions like non-small cell lung cancer (NSCLC) and EGFR mutated NSCLC [55]. Nazartinib have demonstrated favorable safety profile and efficacy in a Phase-I study when administered to adult patients with

EGFR mutated lung carcinoma [56]. However, clinical development of Nazartinib is progress for different forms of mutated carcinomas as monotherapy or in combination [57, 58].

3.2 Benzimidazole based derivatives as potent kinase inhibitors

Commonly the mechanism behind action of anticancer agents involve DNA intercalation, gene regulation, microtubule inhibition, transcription regulation, DNA synthesis inhibition, enzyme inhibition and so on. Nowadays in cancer treatment, target therapy emerged as one of the acknowledged strategies. Most of the available anticancer drugs acts by targeting structural proteins, tyrosine kinases, phosphoinositide 3 kinase and protein kinases for example Binimetinib acts by inhibiting mitogen activated kinase as discussed in earlier section. In this section we have included some recent examples of benzimidazole based enzyme inhibitors as potent anticancer agents.

3.2.1 EGFR inhibitors

Akhter et al. have reported a novel series of benzimidazole based oxadiazole derivatives as potential EGFR inhibitors. The target compound **10** and **11** demonstrated significant binding to EGFR with an IC_{50} value of 0.081 and 0.098 μM respectively. Cytotoxicity of both derivatives against selected human cancer cell line A549, MDA-MB231, MCF7 and HepG2 was found promising. Compound **10** exhibited excellent inhibitory potency with an IC_{50} value of 15.2 μM , 5.0 μM , 14.5 μM and 12.5 μM whereas compound **11** have shown an IC_{50} value of 13.2 μM , 2.5 μM , 0.131 μM and 15.6 μM against cancer cell line A549, MCF7, MDA-MB231 and HepG2 respectively. Further findings of these derivatives showed that compound **10** cause cell cycle arrest of MCF7 cells in a dose dependent manner at G2/M phase. Docking analysis of target compound **10** and **11** showed that both the compound made strong interactions within the active site of protein kinase, the binding pattern of target compounds resembles as that of standard drug erlotinib, which is a potent EGFR inhibitor. In vivo acute toxicity of target compound showed that both compounds **10** and **11** are nontoxic and safe with oral LD_{50} value $>500 < 2000$ mg/kg which is recommended by OECD guidelines [59].

Srour et al. have reported a novel series of thiazole benzimidazole derivatives as potent inhibitor of EGFR tyrosine kinase. Target compound **12** and **13** displayed significant activity against EGFR kinase with an IC_{50} value of 71.67 nM and 109.71 nM. Both target compounds are evaluated for cytotoxicity against MCF7 cancer cell lines, compound **4n** displayed an IC_{50} value of 11.91 μM and compound **4a** exhibited excellent inhibitory potency with an IC_{50} value of 6.30 μM against MCF7 cancer cell line respectively. Furthermore, both compound **12** and **13** have shown good inhibition when tested against normal hTERT-RPE1 normal cells with 65 and 11.9% inhibition. Due to balanced bioactivity of target compound **13**, it is further studied for cell cycle analysis against MCF7 cell line, it displayed the cell cycle arrest at G2/M phase. Compound **13** also displayed increase in the expression of p53, Bax/Bcl-2 and caspase-3 expression and remarkable decrease in levels of PARP-1 enzyme. Molecular docking analysis of compound **12** and **13** showed that both the compounds embedded tightly by hydrogen bond formed between the Nitrogen of benzimidazole with amino acid residue Lys721 and Phe699 respectively [60].

Akhter et al. have reported a series of pyrazole benzimidazole derivatives as potential inhibitors of EGFR. Target compound **14** and **15** displayed potent activity against EGFR kinase with IC_{50} value of $0.97 \mu M$ and $1.7 \mu M$ respectively. In vitro cytotoxicity of both compound showed excellent inhibitory activity against selected cell line, compound **14** displayed an IC_{50} value of $0.97 \mu M$, $2.2 \mu M$ and $11.9 \mu M$ and compound **5d** displayed an IC_{50} value of $1.7 \mu M$, $2.8 \mu M$ and $15.2 \mu M$ against MCF7, A549 and MDA-MB-231 cancer cell lines respectively. Target compound **14** also shown cell cycle arrest at G2/M phase of MCF7 cells by inducing apoptosis. Docking analysis of **14** displayed ability of the respective compound to fit into the active site of EGFR by forming strong hydrogen and hydrophobic within the domain (**Figure 3**) [61].

3.2.2 VEGFR 2 inhibitors

Abdullaziz et al. have reported a novel series of 2-furybenzimidazole derivatives as potent inhibitors of VEGFR-2 kinase. Target compound **16** and **17** displayed excellent

Figure 3.
Examples of benzimidazole derivatives as potent EGFR inhibitors.

inhibitory activity with total percentage inhibition of 94% and 96% and IC_{50} value of 0.64 μ M and 1.26 μ M compared to standard drug Sorafenib (IC_{50} value 0.1 μ M) against VEGFR-2 respectively. In vitro cytotoxicity study of compound **16** and **17** displayed potential inhibitory activity with IC_{50} range of 8.33–9.86 μ M against HepG2 and MCF7 cancer cell lines respectively. Molecular docking analysis of target compound showed a strong binding interaction of 2-furylbenzimidazole moiety within the active site of VEGFR-2 by involving hydrogen bond formation with key amino acid residue Glu885 and Asp1046 [62].

Lien et al. have reported novel 2-aminobenzimidazole derivative **18** as potential inhibitor of VEGFR-2. Target compound **18** exhibited 30% inhibition of kinase activity of VEGFR-2 when treated at a concentration of 10 μ M. **18** displayed inhibitions of VEGF-A angiogenic action along with it also suppress MDA-MB-231 cell lines when studied in vivo. Compound **18** displayed anti-angiogenic properties by targeting VEGFR-2 signaling. Target compound **18** also found to reduce lung metastasis of B16F10 melanoma cells in mice models. Molecular docking studies of target compound showed strong binding with in the active site of VEGFR-2 by forming hydrogen bond between nitrogen of benzimidazole with amino acid residue His1026 [63].

Recently Yuan et al. have designed and synthesized a new series of benzimidazole derivatives as potent and selective inhibitor of VEGFR-2 kinase. Target compound **19** displayed excellent inhibitory activity against with VEGFR-2 kinase with an IC_{50} value of 0.054 μ M, it also displayed significant anti-angiogenesis activity. In vitro cytotoxicity study of compound **19** against HepG2 and A549 cancer cell line were found promising with an IC_{50} value of 2.57 μ M and 73.81 μ M respectively. Cell cycle analysis of target compound **19** shows that it arrests the HepG2 cells in G0/G1 phase in a dose dependent pattern. Molecular docking analysis of compound **19** demonstrated strong interactions within the ATP binding active site of VEGFR-2 kinase [64] (**Figure 4**).

3.2.3 EGFR/VEGFR-2 dual inhibitors

Meguid et al. have reported a novel series of benzimidazole derivatives as potent dual inhibitors of EGFR and VEGFR-2 kinases. Target compound **20** and **21** displayed strong inhibitory activity against EGFR kinases, however activity against VEGFR-2 is

Figure 4.
Examples of benzimidazole derivatives as potent VEGFR-2 inhibitors.

considerably good. Target compound **20** exhibited an IC_{50} value of 0.157 μ M against EGFR and 123.27 μ M against VEGFR-2 kinase. Target compound **21** displayed an IC_{50} value of 0.109 μ M and 69.62 μ M against EGFR and VEGFR-2 kinases respectively. Cytotoxicity activity of both compound **9** and **21** was also found excellent against HeLa cancer cell line with IC_{50} value of 1.62 μ M and 1.44 μ M compare to standard drug doxorubicin which displayed an IC_{50} value of 2.05 μ M respectively. Cell cycle analysis study revealed that both compounds arrest cell cycle of HeLa cells at G0/G1 phase. Furthermore, docking analysis showed that target compound **20** and **21** demonstrated strong binding within the active site of HER2 kinase with dock score of -9.4 and -9.7 kcal/mol respectively [65].

Kassab et al. have reported novel quinazoline bearing benzimidazole derivatives as potential inhibitors of EGFR and VEGFR-2 kinases. Target compound **22** displayed excellent inhibitory activity against EGFR kinase with an IC_{50} value of 127.4 μ M, whereas it displayed an IC_{50} value of 185.7 μ M against VEGFR-2 kinase. Further, cytotoxicity study of compound against MCF7 cancer cell line demonstrated good potency with IC_{50} value of 12.0 μ M [66] (**Figure 5**).

3.2.4 PI3K inhibitors

GSK2636771 (**23**) is a novel, potent, orally available benzimidazole derivatives. It demonstrated selective PI3K beta inhibitor with antineoplastic activity. Preclinical study of GSK2636771 demonstrated selective inhibition of PTEN-deficient cancer cell growth along with inhibition of protein kinase B in a dose and time dependent manner. First in human trial study of GSK2636771 in patients of advanced solid tumors on oral administration as monotherapy demonstrated significant exposure, inhibition of target and excellent safety profile [67, 68].

Jin et al. have reported novel benzimidazole derivatives as potent PI3K inhibitor. Target compound **24** was found most potent against PI3K α with 36% and 86% inhibition compare to reference drug Alpelisib, which showed an inhibition of 110% and 109% at 50 nM and 500 nM respectively. Further, molecular docking analysis of target compound **24** demonstrated strong binding with six strong hydrogen bond with GLN-859, SER-854 and VAL-851 amino acid residues. Further, HUMO-LUMO calculation which is studied by using Gaussian 09 software target compound **24** showed presence of thiazole core and amide bonds which played an important role in its biological activity [69].

Figure 5.
Examples of benzimidazole derivatives as potent EGFR/VEGFR dual inhibitors.

Recently a novel series of benzimidazole based dehydroabietic acid derivatives were reported Yang et al. as potent PI3K α inhibitors. Target compound **25** have demonstrated excellent PI3K inhibitory activity with an IC₅₀ value of 0.012 μ M against PI3K α which is 17-fold greater compare to PI3K β (IC₅₀ value 0.21 μ M) iso-enzyme. Compound **25** is a selective PI3K α inhibitor, it also displayed suppression of phosphorylated Akt level in HCT-116 cancer cells in a dose dependent pattern. In vitro cytotoxic activity of compound **25** showed its potent inhibitory activity against selected cancer cell line namely HCT-116, MCF-7, HeLa, HepG2 and Ges-1 cancer cell lines with an IC₅₀ value of 0.18 μ M, 0.43 μ M, 0.71 μ M, 0.63 μ M and 21.95 μ M respectively. Further cell apoptosis study of target compound **25** showed that it induces also apoptosis in HCT-116 when treated in a concentration dependent manner, Compound **25** comes out as potent PI3K α inhibitor, it can be a promising agent for further development in discovery of novel anticancer agent [70].

Chanrasekhar et al. have reported a novel series of benzimidazole derivatives as potent PI3K inhibitors Target compound **26** was found to exhibit potential inhibitory activity against PI3K β inhibitor, it demonstrated excellent inhibitory potency with an IC₅₀ value of 0.002 μ M against PI3K β with good selectivity against all three isoforms of class I PI3Ks. Further pharmacokinetic profile of compound was evaluated in four different preclinical species (Sprague-Dawley rat, Beagle dog, Cynomolgus monkey, Rhesus monkey). Target compound **26** has shown low to intermediate clearance compare to hepatic flow of blood, whereas in rat model consistent high oral availability and high permeability was observed [71].

Wu et al. have reported a novel series of triazine substituted benzimidazole derivatives a potent dual inhibitor of PI3K and mTOR, most of the compounds from the series displayed potent inhibitory activity with IC₅₀ below 33 nM. Target compound **27** was found most potent in the series, it exhibited strong inhibitory activity against both kinases with an IC₅₀ value of 5.1 μ M and 5.6 μ M against PI3K δ and mTOR, it exhibited PI3K α and PI3K β at an IC₅₀ of 7.3 nM and 21.3 nM respectively. Further, western blot analysis of compound **27** shown inhibition of phosphorylation of Akt and p70S6K, confirming dual inhibitory activity of the presenting compound. Target compound **27** displayed potent antiproliferative activity against selected cell lines, exhibited an IC₅₀ of 0.4 μ M, 0.9 μ M, 1.5 μ M, 7.3 μ M and 7.7 μ M against MCF-7, HCT116, MDA-MB-231, CNE2 and HeLa respectively. Compound **27** displayed promising PI3K/mTOR dual inhibitory activity, further development can add a potent dual inhibitor in the regimen of cancer therapy [72].

Shin et al. have reported a novel series of benzimidazole derivatives a potent inhibitor of PI3K δ . Target compound **28** and **29** displayed an IC₅₀ value of 0.016 μ M and 0.019 μ M against PI3K δ and IC₅₀ value of 1.78 μ M and 2.33 μ M PI3K β respectively. In vivo pharmacokinetic profile of target compound was found good with oral bioavailability of 45% and 41% respectively. In vivo studied of compound **28** and **29** suggested that both the compounds can inhibit KLH-specific antibodies [73].

He et al. has reported benzimidazole-isoquinolinone derivatives which inhibits the cell growth via inhibiting PI3K/mTOR/Akt pathway. Target compound **30** demonstrated excellent inhibitory activity against SW620 and HT29 cancer cell line with an GI₅₀ value of 23.78 μ M and 24.13 μ M. Target compound **30** also decreases the levels of phosphorylated Akt and mTOR levels. Compound **30** also demonstrated cell cycle arrest of human colorectal cancer cells at G2/M phase by decreasing the levels of cyclin B1 and CDK1 [74].

Wu et al. have reported triazine bearing benzimidazole derivatives a potent inhibitor of PI3K and mTOR. Target compound **31** and **32** displayed potent activity with

and IC_{50} value of 2.3 nM and 13.0 nM against PI3K δ , IC_{50} value of 14.6 and 20.1 nM against PI3K α and IC_{50} value of 34.0 and 28.0 against PI3K β isoform respectively. Both the compound also displayed excellent inhibitory potency against mTOR with an IC_{50}

Figure 6.
Examples of benzimidazole derivatives as potent PI₃K inhibitors.

value of 12.9 nM and 15.4 nM respectively. Further, compound **32** was evaluated for antiproliferative activity where it demonstrated moderate activities against selected cancer cell line HCT116, HepG2, HeLa, MDA-MB-231 and MCF7 with an IC_{50} value of 0.3 μ M, 1.3 μ M, 2.4 μ M, 4.8 μ M and 4.9 μ M respectively. Further western blot analysis study of compound **32** confirmed that it completely prevented the phosphorylation of Akt and p70S6K in HCT116 cells, thus target compound was determined as potential dual inhibitor of PI3K and mTOR kinase. Molecular docking analysis of compound **32** displayed that good binding interaction within the active site of PI3K α [75] (**Figure 6**).

3.2.5 CDK inhibitors

Ibrahim et al. have reported a novel series of flavopiridol-benzimidazole as potent inhibitor potent inhibitor of CDK2 and CDK9 kinase. Target compound **33** exhibits potential inhibitory activity with an IC_{50} value of 0.064 and 1.725 μ M against CDK2 and CDK9 kinases respectively. Furthermore, compound **33** also displayed potential antiproliferative activity against selected cancer cell line SKOV3, PC3 and K562 with an IC_{50} value of 94.0 μ M, 85.0 μ M and 50.8 μ M respectively. Cell cycle analysis study of target compound revealed that it arrests the cell cycle of K562 cancer cell at G1 and G2 phase in a dose dependent manner [76] (**Figure 7**).

3.3 Benzimidazole based hybrid derivatives as potent anticancer agents

Pankaj et al. have reported a novel hybrid derivatives of benzimidazole-thiazolidinedione as potent cytotoxic agents. Target compound **34** demonstrated potent inhibitory activity against A549, DU-145, MDA-MB-231 and PC-3 cancer cell line with an IC_{50} value of 11.46 μ M, 31.41 μ M, 29.18 μ M and 39.87 μ M respectively. Compound **34** have shown cell cycle arrest in G2/M phase of A549 cells in a dose dependent manner. Furthermore, compound **34** also demonstrated cell shrinkage of A549 cells along with chromatin condensation and horse shoe shaped nuclei formation [77].

Sivaramakarthykeyan et al. have reported novel hybrid derivatives of benzimidazole and pyrazole as potent anticancer agents. Compound **35** and **36** have demonstrated potent anticancer activity against selected human pancreatic cancer cell lines namely SW1990 and AsPC1 with an IC_{50} value in range of 30.9–61.8 μ M respectively. Molecular docking study of both compound showed significant binding with the active site of B-cell lymphoma [78].

33

IC_{50} (CDK2) = 0.064 μ M

IC_{50} (CDK9) = 1.725 μ M

Figure 7.
Examples of benzimidazole derivative as potent CDK inhibitor.

Mantu et al. have reported a novel series of benzimidazole-quinoline hybrid derivatives as potent anticancer agent. Target compound 37 exhibited potent antitumor activity against renal cancer cell line A498 and breast cancer cell line MDA-MB-468 with percentage growth inhibition of 52.92% and 56.54% respectively. Compound 37 also exhibited potent antitumor activity against leukemia cell line RPMI-8226 and non-small cell lung cancer cell line NCI-H23 with total growth inhibition of 35% [79].

Sharma et al. have reported benzimidazole-thiazolidinedione hybrid derivatives as potent anticancer agents. Target compound 38 and 39 displayed potent anticancer activity against cancer cell line with an IC₅₀ value of in range of 0.13-10.24 μ M against prostate cancer cell line PC-3, breast cancer (MDAMB-231), cervical cancer (HeLa), lung cancer (A549), and bone cancer (HT1080) cell lines. Both hybrid derivative 38 and 39 demonstrated significant inhibition of A549 cells migration

Figure 8.
Examples of benzimidazole containing hybrid derivatives as potent anticancer agents.

through disruption of F-actin assembly, further treatment with 38 and 39 also showed increase in level of ROS in A549 cells by collapsing the mitochondrial membrane potential [80].

Bistrovic et al. have reported novel hybrid derivatives of benzimidazole-1,2,3-triazole as potent anticancer agents. Target compound 40 and 41 demonstrated excellent inhibitory activity with IC₅₀ value of 0.05 and 6.18 against A549 cancer cell line and an IC₅₀ value of 17.53 and 8.80 against HeLa cancer cell line respectively. Furthermore, apoptosis detection study by annexin assay of compound **40** showed significant reduction of viable cell population by 70.59%, with increase in early necrotic cell population by 27.81% and late apoptotic cells by 40%. Similarly compound 41 also displayed markable decrease in cell population by 49.77%. Molecular docking analysis of compound 40 and 41 demonstrated that both the compound bind to the active site of p38 complex strongly [81] (**Figure 8**).

4. Conclusion

Many benzimidazole-containing compounds as anticancer agents are studied and available, involving various mechanisms in inhibiting mutated cancerous cells, in which kinases inhibitors play a significant role. However, in targeted therapy, benzimidazole-based derivatives are still widely explored. Due to the challenge of target specificity and poor selectivity, very few compounds have been approved to treat mutated cancers. The search for a novel benzimidazole-based next generation kinase inhibitor is going to subside such challenges. Benzimidazole-based target therapies such as enzyme inhibitors have gained a lot of attraction; owing to this, recently US FDA has approved EGFR inhibitor Abemaciclib and MEK inhibitor Binimetinib and Selumetinib as potent anticancer compounds against mutated forms of cancer. Apart from this, many benzimidazole-containing compounds are in the developmental phase as EGFR, VEGFR-2, CDK and PI3K inhibitors. However, some of the compounds demonstrated excellent kinase inhibitory activity but failed to provide a strong safety profile; these compounds will pave a path as lead compounds; further modifications, designing, and developing such compounds will give potent compounds with maximum efficiency and minimal side effects. The presented chapter mainly focuses on benzimidazole-based kinase inhibitors and their advances; the pivotal information catered here can be regarded as noteworthy and crucial by medicinal chemists for drug design, discovery and development of novel, potent and safe, target-based anticancer agents.

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Conflict of interest

Authors declare “no conflict of interest.”

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