Chapter

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 antimitotic 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**

- Fuberidazole
- Carbendazim
- Benomyl

**Benzimidazole based Antihistaminic drugs**

- Lerisetron
- Clemizole
- Astemizole

**Benzimidazole based Proton pump inhibitors**

- Omeprazole
- Pantoprazole

**Benzimidazole based Antihelmetic drugs**

- Thiabendazole
- Albendazole
- Triclabendazole

**Benzimidazole based antihypertensive agents**

- Telmisartan
- Candesartan

*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 \( \text{NH} \) 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             |
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 $\mu$M 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 $\mu$M, 5.0 $\mu$M, 14.5 $\mu$M and 12.5 $\mu$M whereas compound 11 have shown an IC$_{50}$ value of 13.2 $\mu$M, 2.5 $\mu$M, 0.131 $\mu$M and 15.6 $\mu$M 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 $\mu$M and compound 4a exhibited excellent inhibitory potency with an IC$_{50}$ value of 6.30 $\mu$M 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 μM and 1.7 μM 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 μM, 2.2 μM and 11.9 μM and compound 5d displayed an IC$_{50}$ value of 1.7 μM, 2.8 μM and 15.2 μM 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-furylbenzimidazole derivatives as potent inhibitors of VEGFR-2 kinase. Target compound 16 and 17 displayed excellent
inhibitory activity with total percentage inhibition of 94% and 96% and IC\textsubscript{50} value of 0.64 μM and 1.26 μM compared to standard drug Sorafenib (IC\textsubscript{50} value 0.1 μM) against VEGFR-2 respectively. In vitro cytotoxicity study of compound 16 and 17 displayed potential inhibitory activity with IC\textsubscript{50} range of 8.33–9.86 μM 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 μM. 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\textsubscript{50} value of 0.054 μM, 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\textsubscript{50} value of 2.57 μM and 73.81 μM 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

![Examples of benzimidazole derivatives as potent VEGFR-2 inhibitors.](image)

**Figure 4.**

Examples of benzimidazole derivatives as potent VEGFR-2 inhibitors.
considerably good. Target compound 20 exhibited an IC₅₀ value of 0.157 μM against EGFR and 123.27 μM against VEGFR-2 kinase. Target compound 21 displayed an IC₅₀ value of 0.109 μM and 69.62 μM 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 IC₅₀ value of 1.62 μM and 1.44 μM compare to standard drug doxorubicin which displayed an IC₅₀ value of 2.05 μM 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 IC₅₀ value of 127.4 μM, whereas it displayed an IC₅₀ value of 185.7 μM against VEGFR-2 kinase. Further, cytotoxicity study of compound against MCF7 cancer cell line demonstrated good potency with IC₅₀ value of 12.0 μM [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 PI3Kα 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.](image-url)
Recently a novel series of benzimidazole based dehydroabietic acid derivatives were reported Yang et al. as potent PI3Kα inhibitors. Target compound 25 have demonstrated excellent PI3K inhibitory activity with an IC\textsubscript{50} value of 0.012 μM against PI3Kα which is 17-fold greater compare to PI3Kβ (IC\textsubscript{50} value 0.21 μM) iso-enzyme. Compound 25 is a selective PI3Kα 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 IC\textsubscript{50} value of 0.18 μM, 0.43 μM, 0.71 μM, 0.63 μM and 21.95 μM 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 PI3Kα 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 PI3Kβ inhibitor, it demonstrated excellent inhibitory potency with an IC\textsubscript{50} value of 0.002 μM against PI3Kβ 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 IC\textsubscript{50} below 33 nM. Target compound 27 was found most potent in the series, it exhibited strong inhibitory activity against both kinases with an IC\textsubscript{50} value of 5.1 μM and 5.6 μM against PI3Kδ and mTOR, it exhibited PI3Kα and PI3Kβ at an IC\textsubscript{50} 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 μM, 0.9 μM, 1.5 μM, 7.3 μM and 7.7 μM 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 PI3Kδ. Target compound 28 and 29 displayed an IC\textsubscript{50} value of 0.016 μM and 0.019 μM against PI3Kδ and IC\textsubscript{50} value of 1.78 μM and 2.33 μM PI3Kβ 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 GI\textsubscript{50} value of 23.78 μM and 24.13 μM. 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 PI3Kδ, IC_{50} value of 14.6 and 20.1 nM against PI3Kα and IC_{50} value of 34.0 and 28.0 against PI3Kβ isoform respectively. Both the compound also displayed excellent inhibitory potency against mTOR with an IC_{50}

![Chemical structures of benzimidazole derivatives as PI3K inhibitors.](image-url)

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 μM, 1.3 μM, 2.4 μM, 4.8 μM and 4.9 μM 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 PI3Kα [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 μM 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 μM, 85.0 μM and 50.8 μM 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 μM, 31.41 μM, 29.18 μM and 39.87 μM 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].

Sivaramakarthikeyan 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 μM respectively. Molecular docking study of both compound showed significant binding with the active site of B-cell lymphoma [78].

![Figure 7. Examples of benzimidazole derivative as potent CDK inhibitor.](image)
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 μM 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.

![Examples of benzimidazole containing hybrid derivatives as potent anticancer agents.](image)
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.”
Advances of Benzimidazole Derivatives as Anticancer Agents: Bench to Bedside
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Benzimidazole

References

[1] Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. CA: A Cancer Journal for Clinicians. 2021; 71(1):7-33

[2] Haider K, Rahaman S, Yar MS, Kamal A. Tubulin inhibitors as novel anticancer agents: An overview on patents (2013-2018). Expert Opinion on Therapeutic Patents. 2019;29(8): 623-641

[3] WHO report on cancer: Setting priorities, investing wisely and providing care for all. Geneva: World Health Organization; 2020. License: CC BY-NC-SA 3.0 IGO

[4] Haider K, Rehman S, Pathak A, Najmi AK, Yar MS. Advances in 2-substituted benzothiazole scaffold-based chemotherapeutic agents. Archiv der Pharmazie. 2021;354:e2100246

[5] Kharb R, Haider K, Neha K, Yar MS. Aromatase inhibitors: Role in postmenopausal breast cancer. Archiv der Pharmazie. 2020;353(8):2000081

[6] Paul A, Singh P, Kuznetsov ML, Karmakar A, da Silva MF, Koch B, et al. Influence of anchoring moieties on new benzimidazole-based Schiff base copper (ii) complexes towards estrogen dependent breast cancer cells. Dalton Transactions. 2021;50(10):3701-3716

[7] Pathak A, Pandey V, Pokharel YR, Devaraji V, Ali A, Haider K, et al. Pharmacophore based drug design and synthesis of oxindole bearing hybrid as anticancer agents. Bioorganic Chemistry. 2021;116:105358

[8] Dandawate P, Ahmed K, Padhye S, Ahmad A, Biersack B. Anticancer active heterocyclic chalcones: Recent developments. Anti-Cancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Cancer Agents). 2021;21(5):558-566

[9] Scattolin T, Piccin A, Mauceri M, Rizzolio F, Demitri N, Canzonieri V, et al. Synthesis, characterization and anticancer activity of palladium allyl complexes bearing benzimidazole-based N-heterocyclic carbene (NHC) ligands. Polyhedron. 2021;207:115381

[10] Gondru R, Li Y, Banothu J. Coumarin–benzimidazole hybrids: A review of developments in medicinal chemistry. European Journal of Medicinal Chemistry. 2021;227:113921

[11] Shrivastava N, Naim MJ, Alam MJ, Nawaz F, Ahmed S, Alam O. Benzimidazole scaffold as anticancer agent: Synthetic approaches and structure–activity relationship. Archiv der Pharmazie. 2017;350(6):e201700040

[12] Shaharyar M, Mazumder A. Benzimidazoles: A biologically active compounds. Arabian Journal of Chemistry. 2017;10:S157-S173

[13] Satija G, Sharma B, Madan A, Iqubal A, Shaquiquzzaman M, Akhter M, et al. Benzimidazole based derivatives as anticancer agents: Structure activity relationship analysis for various targets. Journal of Heterocyclic Chemistry. 2021

[14] Akhtar W, Khan MF, Verma G, Shaquiquzzaman M, Rizvi MA, Mehdi SH, et al. Therapeutic evolution of benzimidazole derivatives in the last quinquennial period. European Journal of Medicinal Chemistry. 2017;126:705-753

[15] Akhtar MJ, Yar MS, Sharma VK, Khan AA, Ali Z, Haider MD, et al. Recent progress of benzimidazole hybrids for
anticancer potential. Current Medicinal Chemistry. 2020;27(35):5970-6014

[16] Gaba M, Mohan C. Development of drugs based on imidazole and benzimidazole bioactive heterocycles: Recent advances and future directions. Medicinal Chemistry Research. 2016;25(2):173-210

[17] Song D, Ma S. Recent development of benzimidazole-containing antibacterial agents. ChemMedChem. 2016;11(7):646-659

[18] Farahat AA, Ismail MA, Kumar A, Wenzler T, Brun R, Paul A, et al. Indole and benzimidazole bichalcophenes: Synthesis, DNA binding and antiparasitic activity. European Journal of Medicinal Chemistry. 2018;143:1590-1596

[19] Morcoss MM, El Shimaa MN, Ibrahim RA, Abdel-Rahman HM, Abdel-Aziz M, Abou El-Ella DA. Design, synthesis, mechanistic studies and in silico ADME predictions of benzimidazole derivatives as novel antifungal agents. Bioorganic Chemistry. 2020;101:103956

[20] Veerasamy R, Roy A, Karunakaran R, Rajak H. Structure–activity relationship analysis of benzimidazoles as emerging anti-inflammatory agents: An overview. Pharmaceuticals. 2021;14(7):663

[21] Eswayah A, Khaliel S, Saad S, Shebani N, Fhid O, Belaid A, et al. Synthesis and analgesic activity evaluation of some new benzimidazole derivatives. American Journal of Chemistry and Application. 2017;4(5):30-35

[22] Kanwal A, Ahmad M, Aslam S, Naqvi SA, Saif MJ. Recent advances in antiviral benzimidazole derivatives: A mini review. Pharmaceutical Chemistry Journal. 2019;53(3):179-187

[23] Araujo DM, Maste MM, Alegaon S, Saxena A. Synthesis, antitubercular evaluation and docking studies of novel benzimidazole analogues. International Journal of Pharmaceutical Sciences and Research. 2018;9:3696-3704

[24] Matsubara Y, Matsumoto T, Yoshiya K, Yoshida A, Ikeda S, Furuyama T, et al. Budding uninhibited by benzimidazole-1 insufficiency prevents acute renal failure in severe sepsis by maintaining anticoagulant functions of vascular endothelial cells. Shock. 2019;51(3):364-371

[25] Wang XJ, Xi MY, Fu JH, Zhang FR, Cheng GF, You QD. Synthesis, biological evaluation and SAR studies of benzimidazole derivatives as H1-antihistamine agents. Chinese Chemical Letters. 2012;23(6):707-710

[26] Aroua LM, Almuhaylan HR, Alminderej FM, Messaoudi S, Chigurupati S, Al-Mahmoud S, et al. A facile approach synthesis of benzoylaryl benzimidazole as potential α-amylase and α-glucosidase inhibitor with antioxidant activity. Bioorganic Chemistry. 2021;114:105073

[27] Ganie AM, Dar AM, Khan FA, Dar BA. Benzimidazole derivatives as potential antimicrobial and antiulcer agents: A mini review. Mini Reviews in Medicinal Chemistry. 2019;19(16):1292-1297

[28] Djemouia A, Naouri A, Ouahrahi MR, Djemouia 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;1204:127487

[29] Ren Y, Wang Y, Li G, Zhang Z, Ma L, Cheng B, et al. Discovery of novel benzimidazole and indazole analogues as
tubulin polymerization inhibitors with potent anticancer activities. Journal of Medicinal Chemistry. 2021;64(8):4498-4515

[30] Akhtar S, Abbas M, Naeem K, Faheem M, Nadeem H, Mehmood A. Benzimidazole derivative ameliorates opioid-mediated tolerance during anticancer-induced neuropathic pain in mice. Anti-Cancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Cancer Agents). 2021;21(3):365-371

[31] Choi HS, Ko YS, Jin H, Kang KM, Ha IB, Jeong H, et al. Anticancer effect of benzimidazole derivatives, especially mebendazole, on triple-negative breast cancer (TNBC) and radiotherapy-resistant TNBC in vivo and in vitro. Molecules. 2021;26(17):5118

[32] Shirley M. Encorafenib and binimetinib: First global approvals. Drugs. 2018;78(12):1277-1284

[33] Kopetz S, Grothey A, Yaeger R, Van Cutsem E, Desai J, Yoshino T, et al. Encorafenib, binimetinib, and cetuximab in BRAF V600E–mutated colorectal cancer. New England Journal of Medicine. 2019;381(17):1632-1643

[34] Grothey A, Tabernero J, Taieb J, Yaeger R, Yoshino T, Maiello E, et al. LBA-5 ANCHOR CRC: A single-arm, phase 2 study of encorafenib, binimetinib plus cetuximab in previously untreated BRAF V600E-mutant metastatic colorectal cancer. Annals of Oncology. 2020;31:S242-S243

[35] Balfour JA, Goa KL. Bendamustine. Drugs. 2001;61(5):631-638

[36] Yamshon S, Martin P. Are novel agents ready to assume the mantle in the frontline treatment of mantle cell lymphoma? Clinical Advances in Hematology & Oncology: H&O. 2021;19(6):376-382

[37] Markham A, Keam SJ. Selumetinib: First approval. Drugs. 2020;80:931-937

[38] Casey D, Demko S, Sinha A, Mishra-Kalyani PS, Shen YL, Khasar S, et al. FDA Approval Summary: Selumetinib for Plexiform Neurofibroma. Clinical Cancer Research. 2021

[39] Gross AM, Wolters PL, Dombi E, Baldwin A, Whitcomb P, Fisher MJ, et al. Selumetinib in children with inoperable plexiform neurofibromas. New England Journal of Medicine. 2020;382(15):1430-1442

[40] Mukhopadhyay S, Maitra A, Choudhury S. Selumetinib: The first ever approved drug for neurofibromatosis-1 related inoperable plexiform neurofibroma. Current Medical Research and Opinion. 2021;37(5):789-794

[41] Kim ES. Abemaciclib: First global approval. Drugs. 2017;77(18):2063-2070

[42] Cuyun Carter G, Sheffield KM, Gossai A, Huang YJ, Zhu YE, Bowman L, et al. Real-world treatment patterns and outcomes of abemaciclib for the treatment of HR+, HER2-metastatic breast cancer. Current Medical Research and Opinion. 2021;1:37

[43] Toi M, Inoue K, Masuda N, Iwata H, Sohn J, Park IH, et al. Abemaciclib in combination with endocrine therapy for East Asian patients with HR+, HER2–advanced breast cancer: MONARCH 2 & 3 trials. Cancer Science. 2021;112(6):2381

[44] Ghisoni E, Giannone G, Tuninetti V, Genta S, Scotto G, Aglietta M, et al. Veliparib: A new therapeutic option in ovarian cancer? Future Oncology. 2019;15(17):1975-1987
[45] Boussios S, Karihtala P, Moschetta M, Abson C, Karathanasi A, Zakynthinakis-Kyriakou N, et al. Veliparib in ovarian cancer: A new synthetically lethal therapeutic approach. Investigational New Drugs. 2020;38(1):181-193

[46] Ghisoni E, Giannone G, Tuninetti V, Genta S, Scotto G, Aglietta M, et al. Veliparib: A new therapeutic option in ovarian cancer? Future Oncology. 2019;15(17):1975-1987

[47] Nightingale J, Lum B, Ladwa R, Simpson F, Panizza B. Adenoid cystic carcinoma: A review of clinical features, treatment targets and advancement in improving the immune response to monoclonal antibody therapy. Biochimica et Biophysica Acta (BBA)-Reviews on Cancer. 2021;1875:188523

[48] Choi YJ, Kim HS, Park SH, Kim BS, Kim KH, Lee HJ, et al. Phase II study of dovitinib in patients with castration-resistant prostate cancer (KCSG-GU11-05). Cancer Research and Treatment: Official Journal of Korean Cancer Association. 2018;50(4):1252

[49] Gurnari C, Voso MT, Maciejewski JP, Visconte V. From bench to bedside and beyond: Therapeutic scenario in acute myeloid leukemia. Cancers. 2020;12(2):357

[50] Yu J, Jiang PY, Sun H, Zhang X, Jiang Z, Li Y, et al. Advances in targeted therapy for acute myeloid leukemia. Biomarker Research. 2020;8:1-1

[51] Chua CC, Wei AH. Future developments: Novel agents. In: Acute Myeloid Leukemia. Cham: Springer; 2021. pp. 293-315

[52] Chen J, Li N, Liu B, Ling J, Yang W, Pang X, et al. Pracinostat (SB939), a histone deacetylase inhibitor, suppresses breast cancer metastasis and growth by inactivating the IL-6/STAT3 signalling pathways. Life Sciences. 2020;248:117469

[53] Njar VC, Brodie AM. Discovery and development of Galeterone (TOK-001 or VN/124-1) for the treatment of all stages of prostate cancer. Journal of Medicinal Chemistry. 2015;58(5):2077-2087

[54] Xu Y, Liao S, Wang L, Wang Y, Wei W, Su K, et al. Galeterone sensitizes breast cancer to chemotherapy via targeting MNK/eIF4E and β-catenin. Cancer Chemotherapy and Pharmacology. 2021;87(1):85-93

[55] Cui J, Xiao Z, Zhang LL. Clinical efficacy and safety of nazartinib for epidermal growth factor receptor mutated non-small cell lung cancer: Study protocol for a prospective, multicenter, open-label. Medicine. 2021;100(21):e25992

[56] Tan DS, Leighl NB, Riely GJ, Yang JC, Sequist LV, Wolf J, et al. Safety and efficacy of nazartinib (EGF816) in adults with EGFR-mutant non-small-cell lung carcinoma: A multicentre, open-label, phase 1 study. The Lancet Respiratory Medicine. 2020;8(6):561-572

[57] Jassem J, Dziadziuszko R. Nazartinib in EGFR Thr790Met-mutant non-small-cell lung cancer. The Lancet Respiratory Medicine. 2020;8(6):528-529

[58] Liu C, Lu H, Wang H, Loo A, Zhang X, Yang G, et al. Combinations with allosteric SHP2 inhibitor TNO155 to block receptor tyrosine kinase signaling. Clinical Cancer Research. 2021;27(1):342-354

[59] Akhtar MJ, Siddiqui AA, Khan AA, Ali Z, Dewangan RP, Pasha S, et al. Design, synthesis, docking and QSAR study of substituted benzimidazole linked oxadiazole as cytotoxic agents,
EGFR and erbB2 receptor inhibitors. European Journal of Medicinal Chemistry. 2017;126:853-869

[60] Srour AM, Ahmed NS, Abd El-Karim SS, Anwar MM, El-Hallouty SM. Design, synthesis, biological evaluation, QSAR analysis and molecular modelling of new thiazol-benzimidazoles as EGFR inhibitors. Bioorganic & Medicinal Chemistry. 2020;28(18):115657

[61] Akhtar MJ, Khan AA, Ali Z, Dewangan RP, Rafi M, Hassan MQ, et al. Synthesis of stable benzimidazole derivatives bearing pyrazole as anticancer and EGFR receptor inhibitors. Bioorganic Chemistry. 2018;78:158-169

[62] Abdullaziz MA, Abdel-Mohsen HT, El Kerdawy AM, Ragab FA, Ali MM, Abu-Bakr SM, et al. Design, synthesis, molecular docking and cytotoxic evaluation of novel 2-furylbenzimidazoles as VEGFR-2 inhibitors. European Journal of Medicinal Chemistry. 2017;136:315-329

[63] Lien JC, Chung CL, Huang TF, Chang TC, Chen KC, Gao GY, et al. A novel 2-aminobenzimidazole-based compound Jzu 17 exhibits anti-angiogenesis effects by targeting VEGFR-2 signalling. British Journal of Pharmacology. 2019;176(20):4034-4049

[64] Yuan X, Yang Q, Liu T, Li K, Liu Y, Zhu C, et al. Design, synthesis and in vitro evaluation of 6-amide-2-aryl benzoxazole/benzimidazole derivatives against tumor cells by inhibiting VEGFR-2 kinase. European Journal of Medicinal Chemistry. 2019;179:147-165

[65] Abd El-Meguid EA, El-Deen EM, Nael MA, Anwar MM. Novel benzimidazole derivatives as anti-cervical cancer agents of potential multi-targeting kinase inhibitory activity. Arabian Journal of Chemistry. 2020;13(12):9179-9195

[66] Kassab AE, Gedawy EM, El-Nassan HB. Synthesis of 4-heteroaryl-quinazoline derivatives as potential anti-breast cancer agents. Journal of Heterocyclic Chemistry. 2017;54(1):624-633

[67] Mateo J, Ganji G, Barris HA, Han SW, Swales K, DeYoung P, et al. A first time in human trial of GSK2636771, a PI3Kβ selective inhibitor, in patients with advanced solid tumors

[68] Mateo J, Ganji G, Lemech C, Barris HA, Han SW, Swales K, et al. A first-time-in-human study of GSK2636771, a phosphoinositide 3 kinase beta-selective inhibitor, in patients with advanced solid tumors. Clinical Cancer Research. 2017;23(19):5981-5992

[69] Jin RY, Tang T, Zhou S, Long X, Guo H, Zhou J, et al. Design, synthesis, antitumor activity and theoretical calculation of novel PI3Kα inhibitors. Bioorganic Chemistry. 2020;98:103737

[70] Yang YQ, Chen H, Liu QS, Sun Y, Gu W. Synthesis and anticancer evaluation of novel 1H-benzimidazole derivatives of dehydroabietic acid as PI3Kα inhibitors. Bioorganic Chemistry. 2020;100:103845

[71] Chandrasekhar J, Dick R, Van Veldhuizen J, Koditek D, Lepist EI, McGrath ME, et al. Atropisomerism by design: Discovery of a selective and stable phosphoinositide 3-kinase (PI3K) β inhibitor. Journal of Medicinal Chemistry. 2018;61(15):6858-6868

[72] Wu TT, Guo QQ, Chen ZL, Wang LL, Du Y, Chen R, et al. Design, synthesis and bioevaluation of novel substituted triazines as potential dual PI3K/mTOR inhibitors. European Journal of Medicinal Chemistry. 2020;204:112637

[73] Shin Y, Suchomel J, Cardozo M, Duquette J, He X, Henne K, et al.
Discovery, optimization, and in vivo evaluation of benzimidazole derivatives AM-8508 and AM-9635 as potent and selective PI3Kδ inhibitors. Journal of Medicinal Chemistry. 2016;59(1):431-447

[74] He LJ, Yang DL, Li SQ, Zhang YJ, Tang Y, Lei J, et al. Facile construction of fused benzimidazole-isooquinolinones that induce cell-cycle arrest and apoptosis in colorectal cancer cells. Bioorganic and Medicinal Chemistry. 2018;26(14):3899-3908

[75] Wu TT, Guo QQ, Chen ZL, Wang LL, Du Y, Chen R, et al. Design, synthesis and bioevaluation of novel substituted triazines as potential dual PI3K/mTOR inhibitors. European Journal of Medicinal Chemistry. 2020;204:112637

[76] Ibrahim N, Bonnet P, Brion JD, Peyrat JF, Bignon J, Levaigue H, et al. Identification of a new series of flavopiridol-like structures as kinase inhibitors with high cytotoxic potency. European Journal of Medicinal Chemistry. 2020;199:112355

[77] Sharma P, Reddy TS, Thummuri D, Senwar KR, Kumar NP, Naidu VG, et al. Synthesis and biological evaluation of new benzimidazole-thiazolidinedione hybrids as potential cytotoxic and apoptosis inducing agents. European Journal of Medicinal Chemistry. 2016;124:608-621

[78] Sivaramakarthikeyan R, Iniyaval S, Saravanan V, Lim WM, Mai CW, Ramalingan C. Molecular hybrids integrated with benzimidazole and pyrazole structural motifs: Design, synthesis, biological evaluation, and molecular docking studies. ACS Omega. 2020;5(17):10089-10098

[79] Mantu D, Antoci V, Moldoveanu C, Zbancioc G, Mangalagi I. Hybrid imidazole (benzimidazole)/pyridine...