RECENT ADVANCEMENT OF BENZIMIDAZOLE IN TREATMENT OF CANCER

A Project Report Submitted

In Partial Fulfillment of the Requirements

For the Degree of

BACHELOR OF PHARMACY

by

Pawan Kumar Sah

(Enrollment no. 1821020330)

Under the Supervision of

Mr. Rakesh Sahu
Assistant Professor
Galgotias University
Greater Noida.

Department of Pharmacy
GALGOTIAS UNIVERSITY
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May, 2022

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List of abbreviations

S No.	Abbreviations	Meaning
1.	Ar	aromatic ring
2.	IARC	International Agency for Research on Cancer
3.	g/cm^3	gram per cubic centimetre
4.	MRI	magnetic resonance imaging
5.	R	an abbreviation for radical
6.	MEK	methyl ethyl ketone
7.	BRAF V600E	nature and location of the mutation: V and E represent the amino acids (building blocks of protein) that mutated
8.	HCL	Hydrochloric acid
9.	TLC	Thin layer chromatography.
10.	IUPAC	International Union of Pure and Applied Chemistry

GALGOTIAS UNIVERSITY

CERTIFICATE

This is to certify that project work entitled **"RECENT ADVANCEMENT OF BENZIMIDAZOLE IN TREATMENT OF CANCER"** done by Mr. Pawan Kumar Sah submitted to Department of Pharmacy, is a bonafide research work done by Mr Pawan Kumar Sah under the supervision and guidance of Mr. Rakesh Sahu**,** Professor/Associate/Assistant Professor, School of Medical and Allied Sciences, Greater Noida. The work is completed and ready for evaluation in partial fulfillment for the award of Bachelor of Pharmacy during the academic year 2021-2022. The project report has not formed the basis for the award of any Degree/Diploma/Fellowship or other similar title to any candidate of any University.

Date: 12/05/2022

Prof. Pramod Kumar Sharma
Dean
School of Medical and Allied Sciences
Galgotias University
Greater Noida (U.P.)

BONAFIDE CERTIFICATE

This to certify that the project work **"RECENT ADVANCEMENT OF BENZIMIDAZOLE IN TREATMENT OF CANCER" is** the bonafide research work done by Mr. Pawan Kumar Sah, who carried out the research work under my supervision and guidance for the award of Bachelor of Pharmacy under Galgotias University, Greater Noida during the academic year 2018-2022. To the best of my knowledge the work reported herein is not submitted for award of any other degree or diploma of any other Institute or University.

Mr. Rakesh Sahu
Guide
Assistant Professor
School of Medical and Allied Sciences
Galgotias University
Greater Noida (U.P.)

DECLARATION

I hereby declare that the work embodied in this project report work **"RECENT ADVANCEMENT OF BENZIMIDAZOLE IN TREATMENT OF CANCER"** in Partial fulfillment of the requirements for the award of Bachelor of Pharmacy, is a record of original and independent research work done by me during the academic year 2018-22 under the supervision and guidance of Mr. Rakesh sahu, Assistant Professor, School of Medical and Allied Sciences, Galgotias University, Greater Noida. I have not submitted this project for award of any other degree or diploma of any other Institute or University.

Date: 12/05/2022 Mr. Pawan Kumar Sah

Place: Greater Noida **Name and Signature of candidate**

Acknowledgement

I cannot express enough thanks to my Guide for their continued support and encouragement: Mr. Rakesh Sahu Sir, my Subject teacher; my friends. I offer my sincere appreciation for the learning opportunities provided by my University. My completion of this project could not have been accomplished without the support of my classmates, my teachers, my class mates, and guide. To Mr. Rakesh Sahu thank you for allowing me time away from you to research and write. ! Thanks to my parents as well, Mr. and Mrs. Raj Kumar Sah. Finally, to my roommates: my deepest gratitude. Your encouragement when the times got rough are much appreciated and duly noted. It was a great comfort and relief to know that you were willing to provide management of our household activities while I completed my work. My heartfelt thanks

RECENT ADVANCEMENT OF BENZIMIDAZOLE IN TREATMENT OF CANCER

Abstract

The incidence of cancer is increasing worldwide, affecting a vast majority of the human population, therefore, new different anticancer agents are being developed now and their safety still needs to be evaluated. Among them, benignidazole based drugs are contributing a lot, as they are one of the imperative pharmacophores occurring synthetically as well as naturally in heterocyclic compounds, having a wide-range of therapeutic applications in the area of drug discovery that offers many chances for further improvement in antitumor agents via acting onto numerous receptors of extreme prominence. It also has simple synthetic procedures for the manufacture of numerous benzimidazole derivatives. There are many derivatives of benzimidazole among them few important and mostly used drugs are Albendazole, benzoyl, carbendazim, thiabenzendazole, Albendazole oxide etc. Bendamustine & Rabeprazole are benzimidazole derivatives which have anticancer properties showing promising effect on recent studies. Researcher found out that novel 2-substituted benzimidazole derivatives and 2-benzimidazoly substituted acrylonitrile, and heteroaromatic fluorenes shows antineoplastic activity of standard anticancer drug paclitaxel. Mechanism of action of benzinudazole is by binding to B-tubulin in microtubes. Thus. suppresses cell proliferation and cell division. The assembly of spindle microtubules and chromosomal alignment at metaphase plate which lead to hond at junction chromosomes and chromatid loss. Therefore, this review sheds light on the recent therapeutic expansion of benzimidazole together with synthetic schemed, availability in the market. and a summary of recently published research works that shall jointly help the scientists to produce effective drugs with the desired pharmacological activity.

Keywords: Cancer, anticancer agents, benzimidazole, broadness of cancer, advancement, resistance, target-based derivatives, synthesis, application, ADRs

CHAPTER 1

INTRODUCTION

Cancer is among the most common causes of mortality, with an expected 18.1 million people in 2018, 9.6 million persons were diagnosed with cancer globally, and 9.6 million died.. According to recent World Health Organization (WHO) figures, cancer is responsible for around one in 6 deaths worldwide. As a result, for many forms of cancer, a discovery of effective treatments with innovative mechanisms is required[1]. The top 3 cancer kinds, namely breast, lung, and colorectal cancer, account for one-third of all cancer cases and deaths globally[1-2]. The primary contributions to cancer include risk behaviours such as cigarette use and smoking,physical health conditions such as ionising radiation and asbestos, and genetic predominance factors. Despite the best efforts, the illness continues to kill millions of people throughout the world [3]. Following pie charts shows the report of most common cancers in terms of new cases (Fig. 1) and the most common cause of death by different cancer (Fig 2) by WHO.

Resistance to chemotherapeutic drugs and quasi toward targets has shifted the focus of contemporary cancer charities to the discovery of highly developing selective models for the study of prospective anticancer medicines. Because of its broad anticancer activity and many methods to suppress tumour growth, benzimidazole is recognised as an important pharmacophore in disease research. It also has simple synthetic procedures for the manufacture of numerous benzimidazole derivatives [2]. Benzimidazole has various applications such as antihypertensive antihistaminic anticancer anti-inflammatory [4-5]. The benzimidazole can be synthesized by varies procedures such as Substituting benzene-1,2diamine reacting and cylices with substituted carboxylic acid in presence of $^{H+}$ donor (acid) [6].

There are many derivatives of benzimidazole among them few important and mostly used drugs are Albendazole, benzoyl, carbendazim, thiabenzendazole, Albendazole oxide [7]. The derivatives benzimidazole has broad use such as Albendazole and Mebendazole which are used anthelmintic drug. Omeprazole and Pantoprazole which are used as antiulcer drug. Telmisartan is used as antihypertensive. Mizolastin and Asemizole used derivatives which have anti-histaminic. Bezitramide used as Opioid Analgesic. Carbendazim is fungicidal drug. Selumetinib and binimetinib are used as anticancer agent [8].

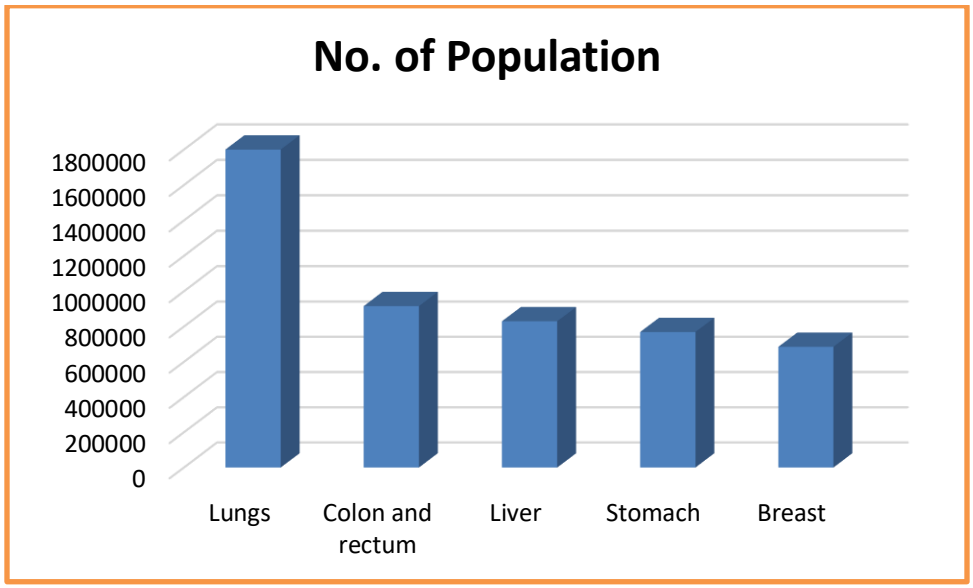


Fig1: Common causes of cancer death across the world. Lung cancer was the leading cause of cancer death among all the cancer disease .

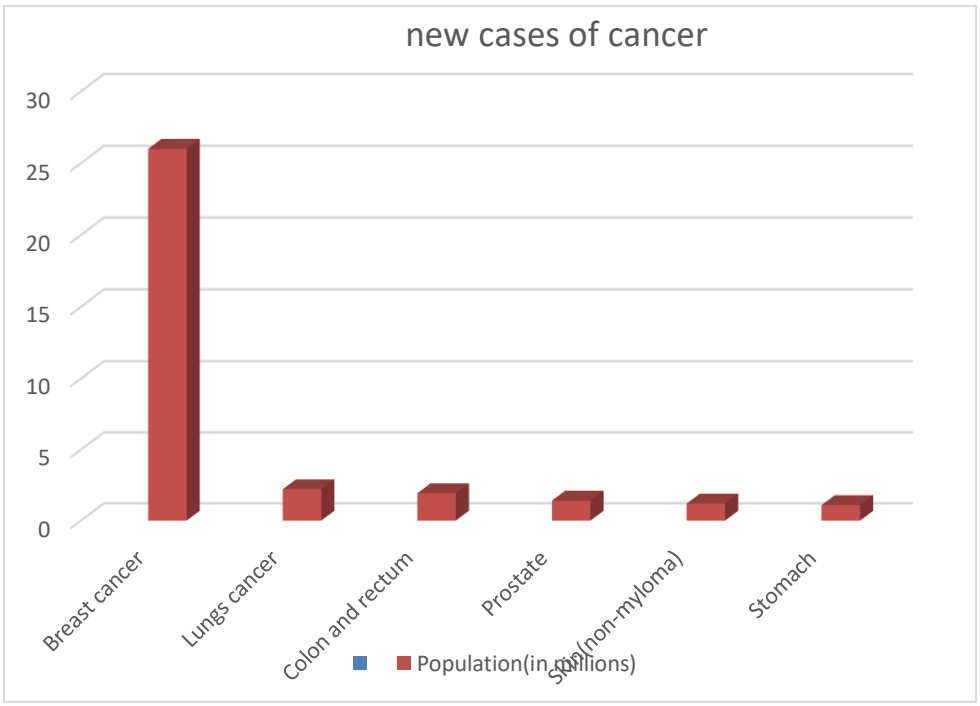


Fig 2: New cases of cancer in millions as shown . among all the cancer breast cancer is showing a large mass which are in new cases in millions across the world.

Bendamustine& Rabeprazole are benzimidazole derivatives which have anticancer properties showing promising effect on recent studies [9].Researcher found out that novel 2-substituted benzimidazole derivatives and 2-benzimidazolyl substituted acrylonitrile and heteroaromatic fluorenes shows antineoplastic activity of standard anticancer drug paclitaxel[10].Mechanism of action of benzimidazole is by binding to B-tubulin in microtubes. Thus,suppresses cell proliferation and cell division.

Current scenario about cancer

According to the (IARC) International Agency for Research on Cancer one in every five men and one in every six women will get cancer at some point in their lives, with one in every eight men and one in every eleven women dying from it [1In 2018, an expected 18.1 million new cases and 9.6 million disease deaths annually, with disease morbidity and mortality expected to reach 24.1 million and nearly 13 million by 2030.In 1975–76, India started the National Cancer Control Program. This has helped to fund the creation of Regional Cancer Centers (RCCs), oncology wings at medical schools, and teletherapy machine purchases. The District of Cancer Control Program was started;however, it did not produce any long-term or effective results.[113]

Heterocyclic contribution in cancer drug discovery [115-119]

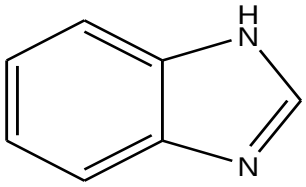
Heterocycles can be classed as oxygen, nitrogen, or sulfur-based depending on the heteroatom(s) present in the ring structures compounds are classified into classes based on the size of the ring structure, which is determined by the total number of atoms. [115].The physicochemical qualities are greatly influenced by the kind and size of ring structures, as well as the substituent groups scaffold[116-117].Heterocyclic compounds play a significant role in clinical applications of the core as antibacterial, antiviral, antifungal, anti-inflammatory, and anti-tumor drugs[118].

About moiety (Benzimidazole)

Because of its broad biological profiles and synthetic potential in medicinal chemistry, the imidazole hetero nucleus has been dubbed "Master Key." It's one among the top 5 five-membered aromatic n heterocyclic compounds found in U.s. food and drug pharmaceuticals in the United States.. [12]. Due to the fused nitrogen nuclei, benzimidazoles are structural isosteres

of nucleobases that rapidly engage with biomolecular targets and elicit a variety of biological actions including anticancer[13], antiulcer[14], anti-hypertensive[17], anti-inflammatory[15], anthelmintic[16], and anti-inflammatory[15]. Akhtar et al. explored the quinquennial period in a recent study[18]. This nitrogen-containing heterocycle has been discovered in a variety of well-known pharmaceuticals with diverse therapeutic effects. After evaluating for their therapeutic potential in vivo biological activities such as anticonvulsant, anti-diabetic, and DNA cleavage investigations, benzimidazole scaffolds were developed. An in vivo mouse model of convulsions was used to assess the anticonvulsant effects of the produced compounds. Blood glucose tests and oral glucose tolerance tests were used to assess ant diabetic activity. Male Wister albino rats of either sex (150–200 g) were chosen. The electrophoresis approach is also used to investigate the DNA breakage of chosen substances [114].

Structure of Benzimidazole



1H Benzimidazole

Fig 3: Structure Benzimidazole

Medicines like rabeprazole and omeprazole, for example, are proton pump inhibitors that contain benzimidazole and are used to treat stomach ulcers. [19]. Albendazole as well as thiabendazole seem to be anthelmintic medicines that work by inhibiting tubulin polymerization thus impairing glucose absorption, finally causing parasite death[20].

Table 1: Physical properties of benzimidazole

Molar mass	**Formula**	**Boiling point**	**Solubility in water**	**Melting Point**	**Density**	**Appearance**
68.077 g/mol	$C_3H_4N_2$	256 °C	633 g/L	89 to 91 °C (192 to 196 °F;	1.23 g/cm^3, solid	White or pale yellow solid

				362 to 364 K)		

Diagnosis of cancer

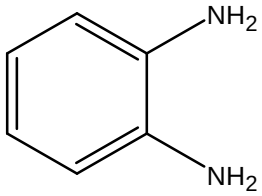
1. Physical Exam – Patients might feel bumps on his body that might signal cancer. Duringphysical examination a doctor may look for changes in skin colour or organ enlargement that could indicate the presence of cancer. [22].
2. 2. Laboratory test - tests including blood or urine tests might help your doctor spot cancer-related abnormalities. A normal blood test termed a full blood counts, for example, may detect an unusual number or type of white blood cells in persons with leukaemia. [23].
3. Imaging test- Non-invasive imaging studies allow bones and interior organs to be examined. Some imaging methods used to diagnose cancer are computed tomography, positron emission tomography, bone scan, MRI, ultrasound, and X-ray[24].
4. Biopsy - A tissue sample has been taken for laboratory testing during biopsy. A sample can be collected in a variety of ways. The sort of cancer you have and where it is located determine which biopsy method is best for you. In most cases, a biopsy seems to be the only option to confirm a cancer diagnosis[25].

The stage of cancer uses to assess options for treatment and prospects of a cure. Imaging tests, including bone scans and X-rays, may be used as part of the staging process to check if the cancer spreads to other regions of the body[26], [27]. The digits 0 through 4, which are typically represented as Numerals 0 through IV, are used to signify cancer stages. Higher figures imply that the cancer has progressed. The cancer stage is marked by letters or phrases in several kinds of cancer[28].

General synthesis for benzimidazole

Warming o-phenylene diamine (12 mmol) or phenyl glyc (36 mmol) in ml of 4N HCl for four hours and afterwards cooling to room temperature yielded benzimidazole (fig. No. 03). Tlc 3,8-10 was used to monitor the reaction's completion. Sodium hydroxide pellets were used to elevate the pH to 7.2. The black substance was then filtered, rinsed with water, and vacuum dried., and

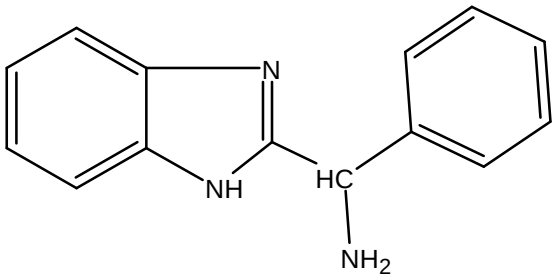
acetone recrystallized. With a melting point of 280°C, 2-(1-amino benzyl) benzimidazole yields 78.5 percent. Using the solvent system ethyl acetate, thin layer chromatography was performed to monitor the reaction's completion: Methanol: N-hexane [21].



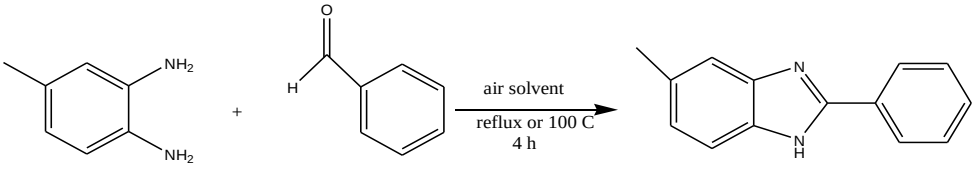
o-phenylene diamine

\+ HOOC - R
(phenyl glycine)

4 N HCL



Scheme 1: 2-phenyl-5-methylbenzimidazole synthesis In the production of 2-phenyl-5-methylbenzimidazole



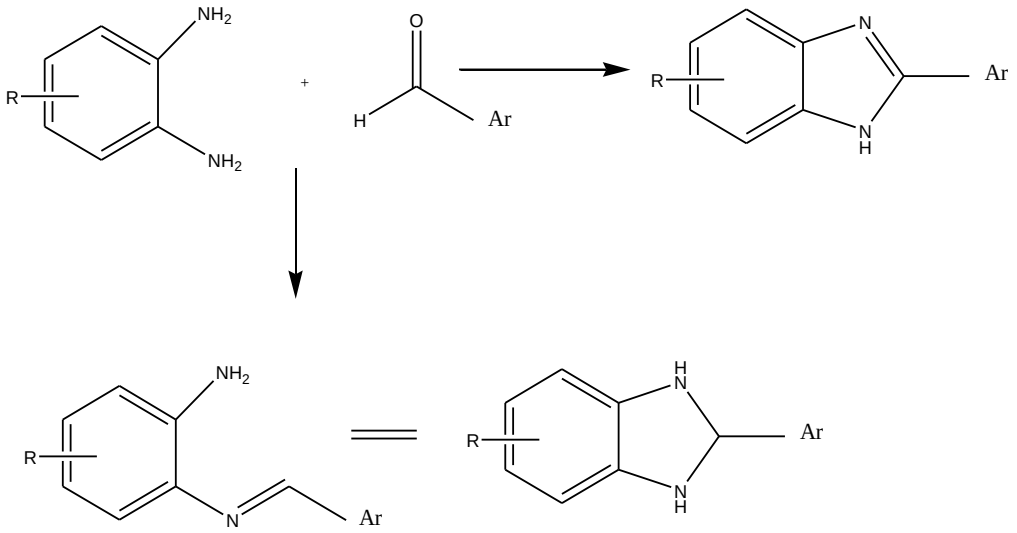
Scheme 2: Synthesis of 2-phenyl-5-methylbenzimidazole When 2-phenyl-5-methylbenzimidazole is made,

The reaction is carried out in a 50 ml sealed tube (with a screw top) using 0.25 mmol of 3,4-Diaminotoluene and 0.25 mmol of benzaldehyde in 1 ml of Solvent or neat for 4 hours at refluxing at 100 C. (see Table 1). b Consumption of 3,4-diaminotoluene.

HPLC analysis was used.

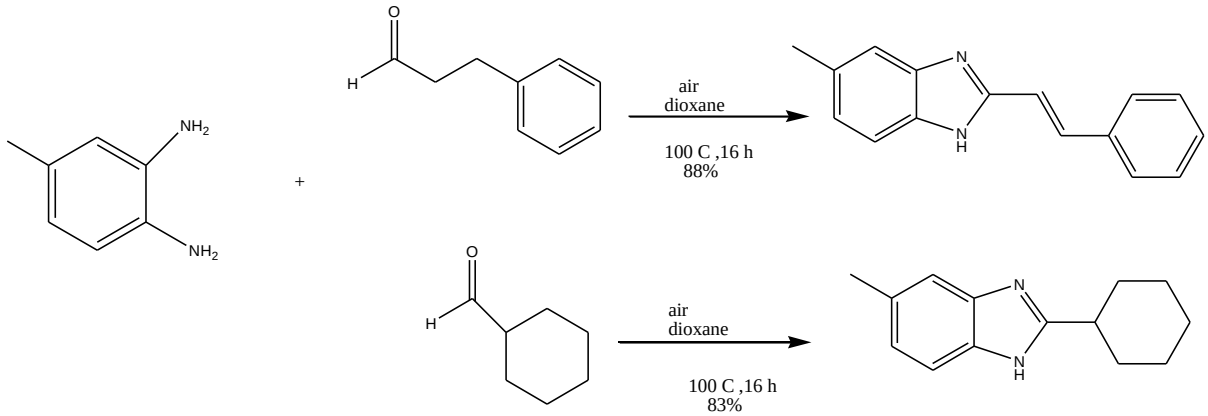
The reaction mixture was not evenly distributed.[120]

Synthesis of benzimidazoles

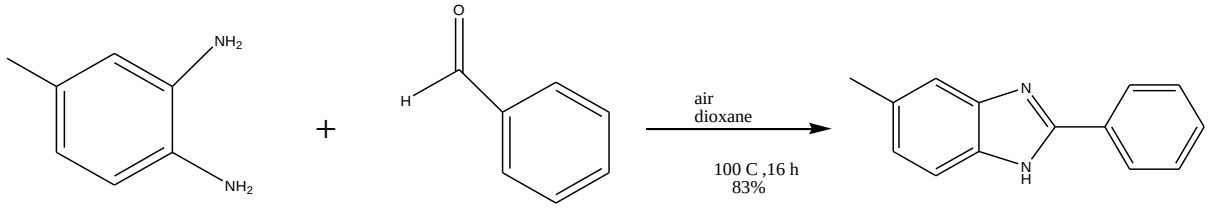


Scheme 3 : Synthesis of benzimidazoles

The reaction is carried out in a 50 mL sealed tube (with a screw top) with 0.25 m mol of phenylenediamine,0.25 m mol of aldehyde with 1 mL of Dioxane for the period indicated at 100 C. (see Table 2). b After silica gel Chromatography, the yield was isolated.[120]

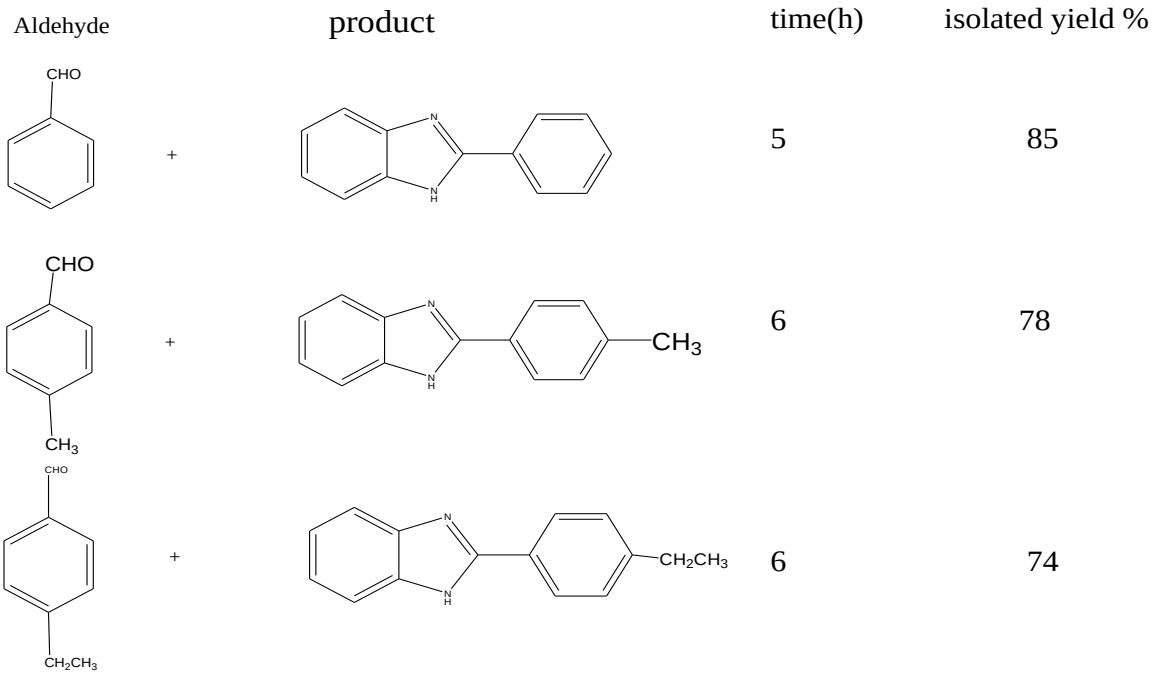


Scheme 4: Synthesis of 2-alkenyl- and 2-alkylbenzimidazoles

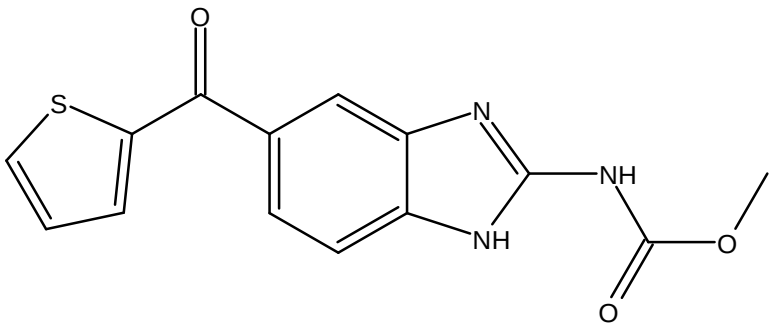


Scheme 5: Synthesis of 2-phenyl-5-methylbenzimidazole.

In a 50 ml closed chamber (with a screw cap), 0.25 mmol 3,4-Diaminotoluene and 0.25 mol benzaldehyde in 1 ml Solvent or neat are refluxed for 4 hours at 100 C. (See Figure 1). b 3,4-diaminotoluene consumption120]

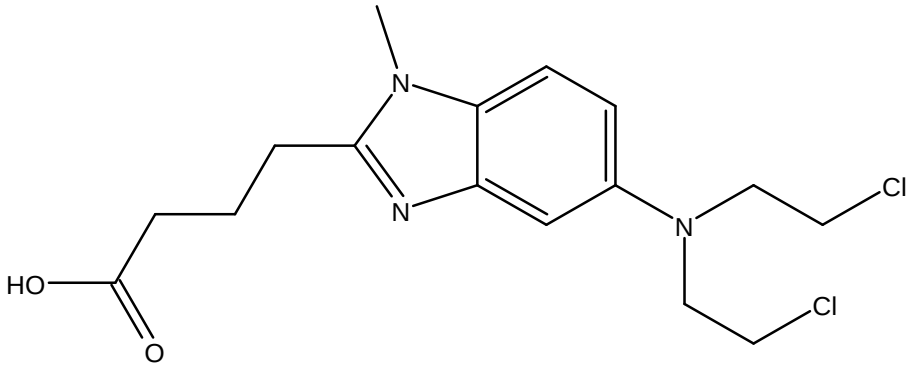


Scheme 6: Synthesis of benzimidazoles using (bromodimethyl)sulfonium bromide

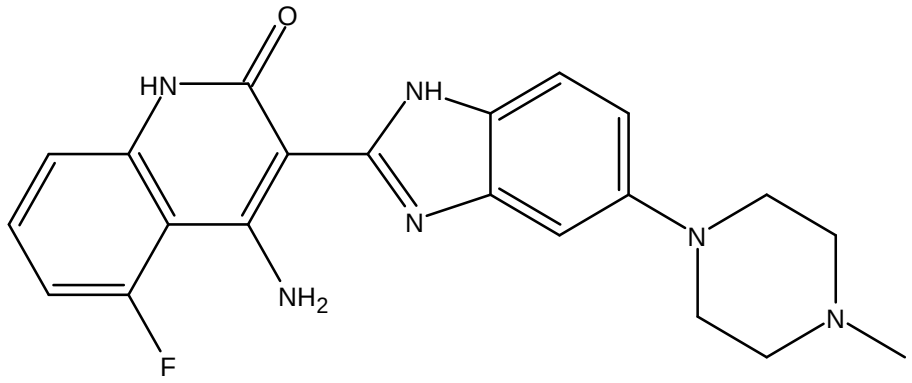


Scheme 7: Methyl [5-(2-thienylcarbonyl)-1H-benzimidazol-2-yl]carbamate

Nocodazole (Anticancer)



Scheme 8 : 4-[5-[bis(2-chloroethvi)amino]-1-methylbenzi midazol-2-y1 butanoic acid Bendamustine (Antigancer)



Scheme 9: -4-Amino-S-fluoro-3-[5-(4-methylpiperazin-1-y]) -1H-benzimidazol-2-yl] quinolin-2(1H) -a single Dovitinib (Anticancer)

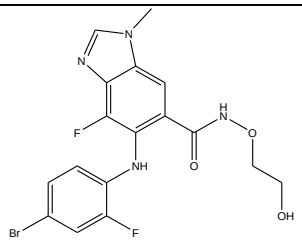
Tamm, Folkers, and colleagues published the first paper on the synthesis as well as antiviral activity of benzimidazole nucleosides that was halogenated, in 1954[32]. They discovered that 5,6-dichloro-1-D-ribofuranosyl benzimidazole (DRB) possesses a variety of biological actions, including anti-RNA and anti-DNA viral activity. DRB is more deadly than antiviral because it inhibits RNA polymerase, impacting various cellular functions. Albendazole and thiabendazole, both recognized tubulin inhibitors, interfered with and slowed Mycobacterium tuberculosis cell division processes, according to Slayden et al[33]. Kumar et al. later hypothesised that now the benzimidazole core is a new FtsZ inhibitor with action against several drug-sensitive or drug-resistant Mtb[34]. This molecular framework has a variety of biological features and is commonly seen in medication formulations. Because of its wide spectrum of biological

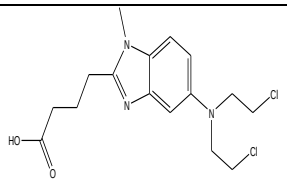
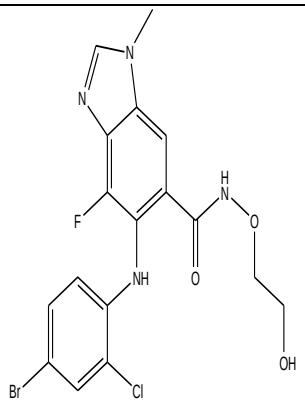
activities, benzimidazoles have revolutionized the drug discovery process, making this scaffold an essential anchor for the development of new therapeutic anticancer agents.

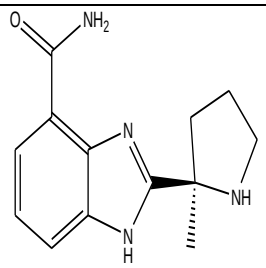
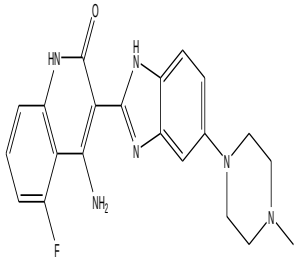
Anticancer medicines based on benzimidazoles

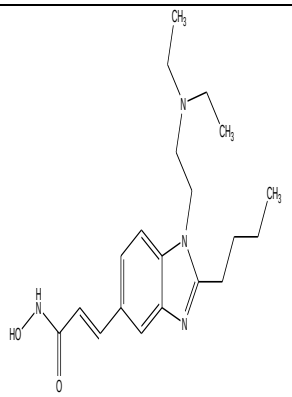
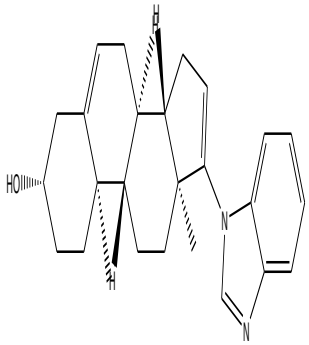
Benzimidazole-based compounds have gotten a lot of attention, because of their considerable cytotoxic action. Many benzimidazole-based anticancer medicines have acquired global clearance from the US FDA in the previous decade. Binimetinib, Selumetinib, and Abemaciclib were recently approved for the treatment of mutant cancers. Some benzimidazole-based anticancer medications that have recently been authorized, are in development, or are in the pipeline are included below.

Table 2 : Benzimidazole based marketed anticancer drugs

S.NO	**Name Of Drugs**	**IUPAC**	**USFDA**	**Target**	**Chemical Structure**
1)	Binimetinib	((4-bromo-2-fluorophenyl) amino) 5-((4-bromo-2-fluorophenyl) -4-fluoro-N-(2-hydroxyethoxy) -1-methyl -1H-benzimidazole -6-carboxamide	On June 27, 2018 For unresectable or malignant melanoma patients with a BRAF V600E , V600K mutation, the combination of encorafenib & binimetinib (BRAFTOVI & MEKTOVI,	**MEK an enzyme that regulates the** biosynthesis of the inflammatory cytokines TNF, IL-6 and IL-1. MEK	 Binimetinib

			Array Bioscience Inc.) has been authorised.	inhibitors	
2)	Bendamustine	4-(5-(bis(2-chloroethyl) amino) 4-(5-(bis(2-chloroethyl) -1-methyl -1H-benzimidazol-2-yl) butanoic acid	bendamustine hydrochloride) injection for the treatment of patients with chronic lymphocytic leukemia (CLL) and indolen	Recombinant humanized monoclonal antibody that binds to all forms of VEGF, preventing binding to its receptors	 Bendamustine
3)	Selumetinib	((4-bromo-2-chlorophenyl) amino) 5-((4-bromo-2-chlorophenyl) -4-fluoro-N-(2-hydroxyethoxy) -1-methyl -1H-benzimidazole -6-	On April 10, 2020, Selumetinib (KOSELUGO, AstraZeneca) has been authorised by the FDA for the treatment of paediatric patients.	In a Phase II study of women with recurrent low-grade serous carcinoma, MEK1 and	 Selumetinib

		carboxamide		MEK2 were found to be effective.	
4)	Veliparib	(R)-2-(2-methylpyrrolidin-2-yl)-1H-benzimidazole-4-carboxamide	Veliparib has been designated as an orphan medication by the Available for tr eatment of progressed epithelial non–small carcinoma.	BRCA breast cancer and ovarian cancer, PARP-1 and PARP-2	 Veliparib
5)	Dovitinib	4-amino-5-fluoro-3-(5-(4-methylpiperazin-1-yl)-1H-benzoimidazol-2-yl) quinolin-2(1H)-one	Dovitinib for Third-Line Renal Cell Carcinoma is awaiting FDA approval in the third-line treatment of patients with renal cell carcinoma.	metastatic renal cell carcinoma on a vascular endothelial growth factor (VEGF)	 Dovitinib

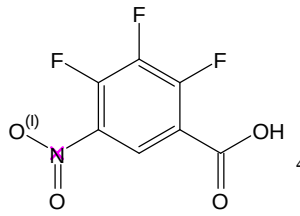
6)	Pracinostat	(2E) -3-(2-butyl-1-(2-(diethyl amino) ethyl)-1H-benzoimidazol-5-yl)-1H-benzoimidazol-5-yl) -N-hydroxyacrylamideay	Pracinostat in combination with azacytidine has been given Orphan Drug Designation by the US (FDA) and the (EMA) for newly ,diagnosed at AML patients who are equal to or older than 75 years of age and are not suitable for aggressive chemotherapy.	HDAC10 as the primary	 Pracinostat
7)	Galeterone	(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	No	androgen pathway suppression	 Galeterone

SYNTHETIC REACTION OF MARKETED DRUGS

Binimetinib is a chemical compound that is5-((4-bromo-2-fluorophenyl)amino) -4-fluoro-N-(2-hydroxyethoxy) -1-methyl -1H-benzimidazole -6-carboxamide, which was recently authorized by the US Food and Drug Administration. It's a strong, selective inhibitor of mitogen-activated protein kinase that may be taken orally. Binimetinib is a drug created by Array Biopharma and sold under the brand name Mektovi. It's used in conjunction with BRAF inhibitors like Encorafenib for individuals with metastatic melanoma who have the BRAF mutation[35]. Binimetinib is now being studied as a combination therapy for disorders such as KRAS-mutated cancer and mutated quasi cell lung cancer[36,37].

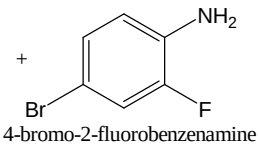
Binimetinib synthesis

Binimetinib : Synthesis route 1

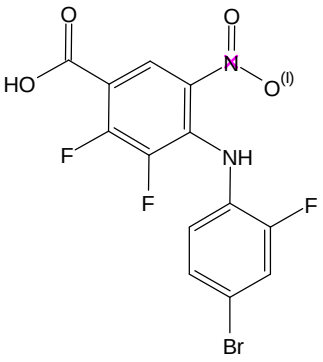


2,3,4-trifluoro-5-nitrobenzoic acid

+

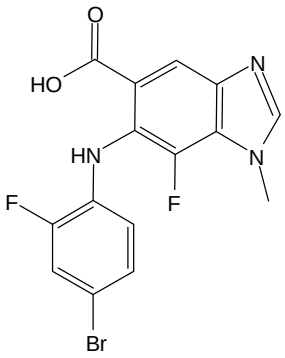


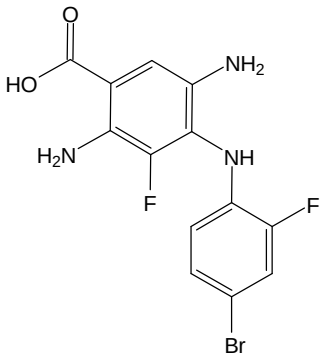
4-bromo-2-fluorobenzenamine



4-(4-bromo-2-fluorophenylamino)-2,3-difluoro-5-nitrobenzoic acid

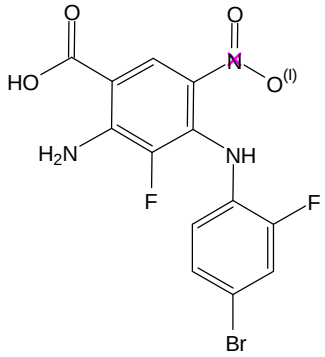
R: NH 4OH



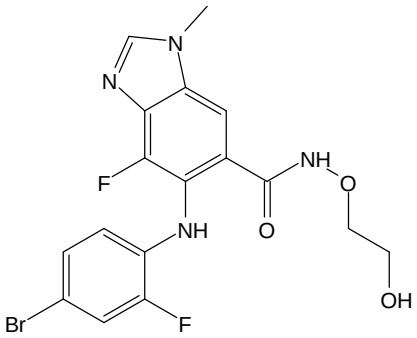


2,5-diamino-4-(4-bromo-2-fluorophenylamino)-3-fluorobenzoic acid

R : H2



2-amino-4-(4-bromo-2-fluorophenylamino)-3-fluoro-5-nitrobenzoic acid

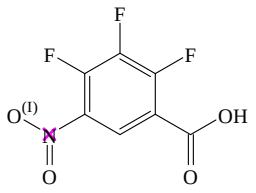


6-(4-bromo-2-fluorophenylamino)-7-fluoro-*N*-(2-hydroxyethoxy)-3-methyl-3*H*-benzo[*d*]imidazole-5-carboxamide

(Binimetinib)

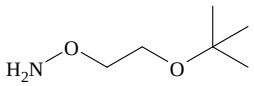
Scheme 10: Binimetinib synthesis

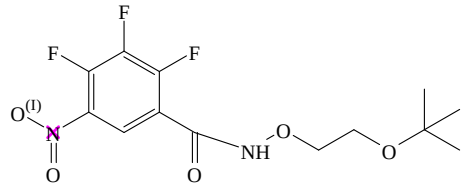
Binimetinib : Synthetic route 2



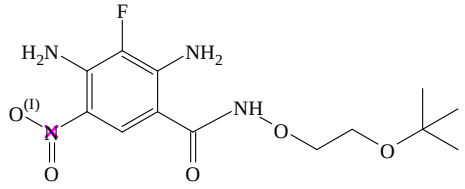
2,3,4-trifluoro-5-nitrobenzoic acid

+



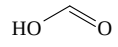


N-(2-*tert*-butoxyethoxy)-2,3,4-trifluoro-5-nitrobenzamide

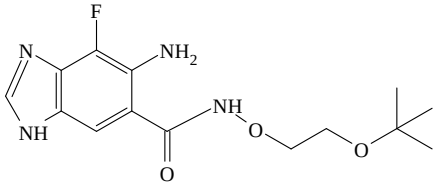


2,4-diamino-*N*-(2-*tert*-butoxyethoxy)-3-fluoro-5-nitrobenzamide

+

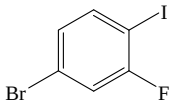


formic acid

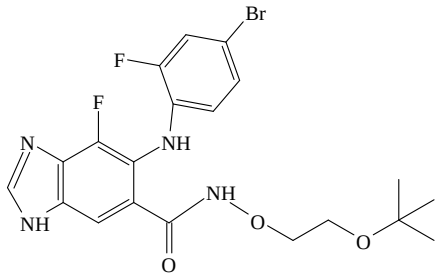


6-amino-*N*-(2-*tert*-butoxyethoxy)-7-fluoro-3*H*-benzo[*d*]imidazole-5-carboxamide

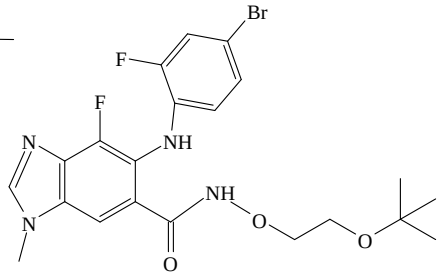
+



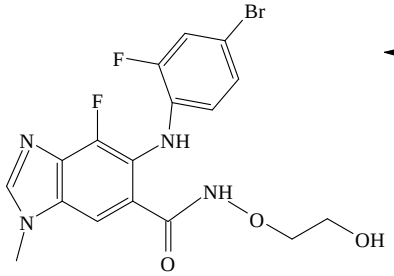
4-bromo-2-fluoro-1-iodobenzene



6-(4-bromo-2-fluorophenylamino)-*N*-(2-*tert*-butoxyethoxy)-7-fluoro-3*H*-benzo[*d*]imidazole-5-carboxamide



6-(4-bromo-2-fluorophenylamino)-*N*-(2-*tert*-butoxyethoxy)-7-fluoro-3-methyl-3*H*-benzo[*d*]imidazole-5-carboxamide

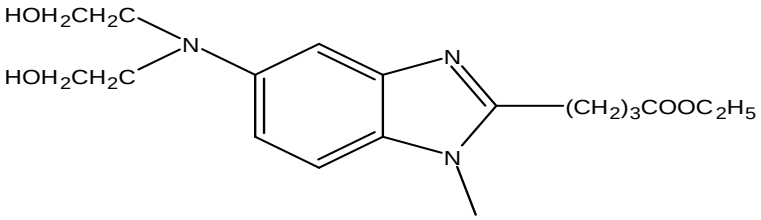


6-(4-bromo-2-fluorophenylamino)-7-fluoro-*N*-(2-hydroxyethoxy)-3-methyl-3*H*-benzo[*d*]imidazole-5-carboxamide

(Binimetinib)

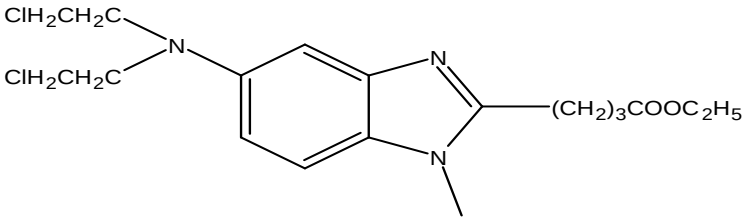
Scheme 11: Binimetinib synthesis

1. Bendamustine



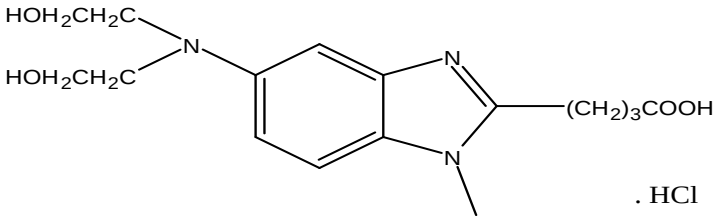
ethyl 4-(5-(bis(2-hydroxyethyl)amino)-1-methyl-1*H*-benzo[*d*]imidazol-2-yl)butanoate

Thionyl Chloride
Chloroform



ethyl 4-(5-(bis(2-chloroethyl)amino)-1-methyl-1*H*-benzo[*d*]imidazol-2-yl)butanoate

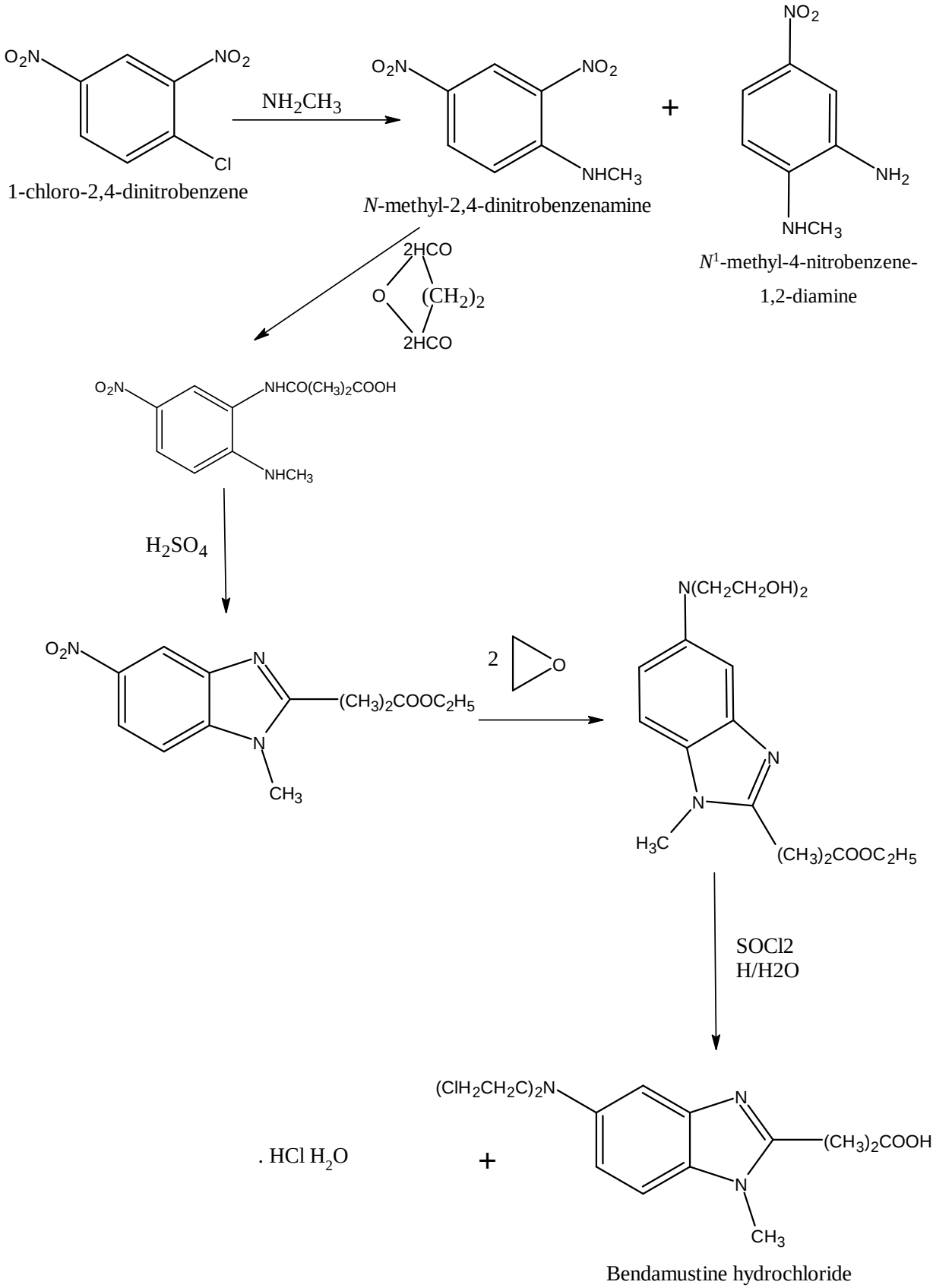
Conc. HCl,
Water



4-(5-(bis(2-hydroxyethyl)amino)-1-methyl-1*H*-benzo[*d*]imidazol-2-yl)butanoic acid

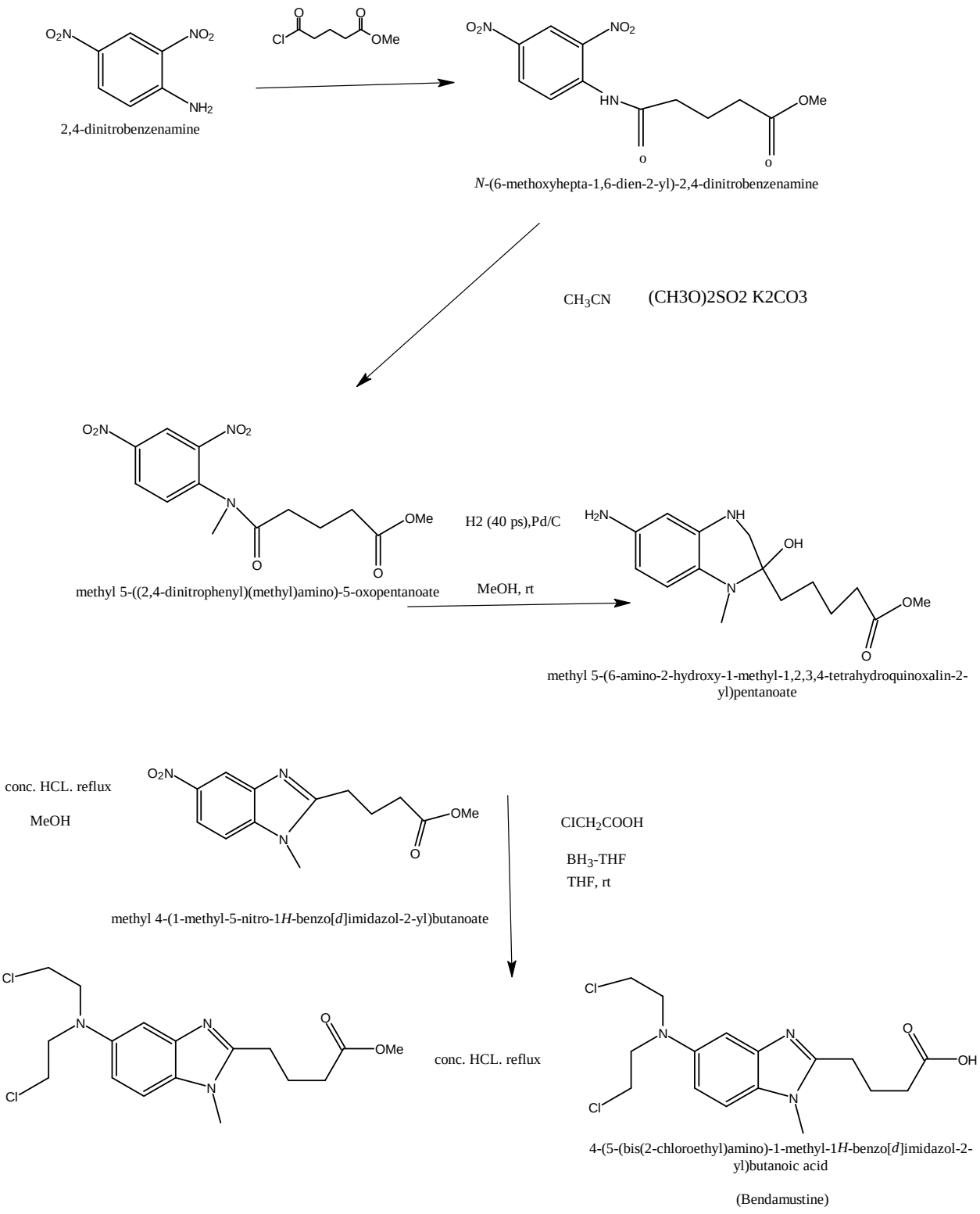
(Bendamustine)

Scheme 12: 4-(5-(bis(2-chloroethyl)amino)-1-methyl-1H-benzimidazol-2-yl)butanoic acid


NH2CH3
1-chloro-2,4-dinitrobenzene
N-methyl-2,4-dinitrobenzenamine
N1-methyl-4-nitrobenzene-1,2-diamine
2HCO
(CH2)2
2HCO
H2SO4
2
SOCl2
H/H2O
. HCl H2O
+
Bendamustine hydrochloride

Scheme 13: Synthesis Bendamustine

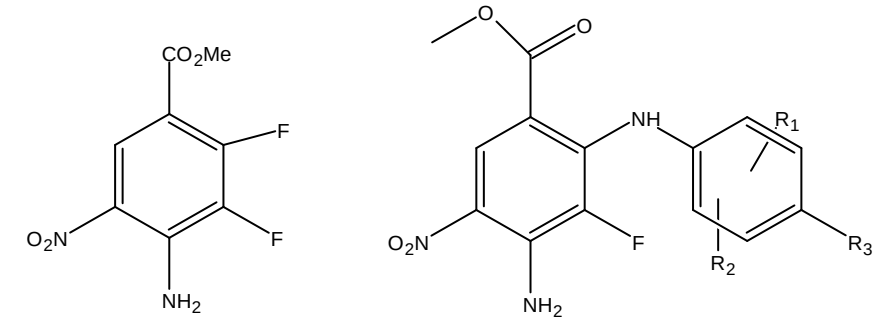
The reaction of l-methyl-2-(4'-ethyl butyrate)-5- amino] is important. -lH-benzimidazole 6 in the presence of water, sodium acetate, and acetic acid at 5°C for 5 hours and overnight at 20°C gives 4-5-[bis-(2-hydroxy-ethyl)-amino] -l-methyl-lH-benzimidazol-2-yl-butyric acid ethyl ester (dihydroxy ester) 7 as a jelly mass, which was chlorinated with thionyl chloride in chloroform and then hydrolyzed in situ with concentrated HCI to provide method for recrystallizing bendamustine hydrochloride from water, with the resultant monohydrate having a melting point of 148-151°C. Butyrate (4'-ethyl) -5-amino] -



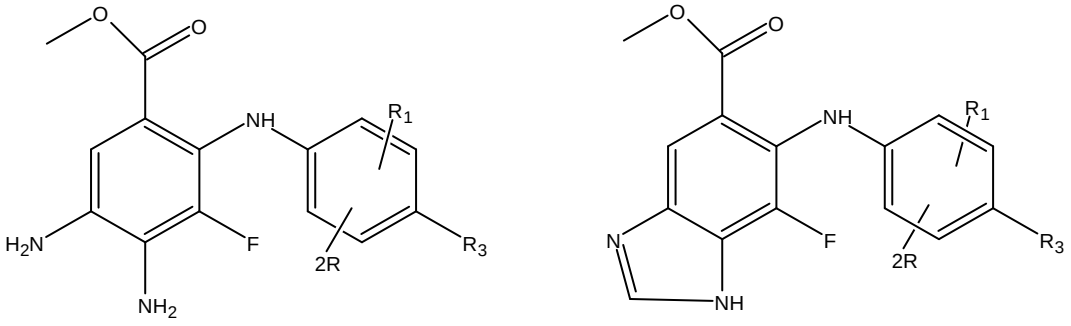
Scheme 14 : Bendamustine hydrochloride

The synthesis of Bendamustine hydrochloride as outlined in schem-3, commencing from 2,4-dintroaniline in six stages, as disclosed in Cephalon's PCT application WO 2010/042568. The essential step is the reductive alkylation of Il-a at room temperature with borane-tetrahydrofuran and chloroacetic acid, yielding the chemical of formula I-a. Bendamustine hydrochloride, which has a purity of 99.1%, was synthesised by acid mediated hydrolysis of I-a using strong hydrochloric acid at reflux. The same PCT Patent application also describes a process for purifying Bendamustine hydrochloride that involves swirling the substance in a combination of DMF and THF at 75°C for about 30 minutes, then cooling to room temperature and filtering of the solid.

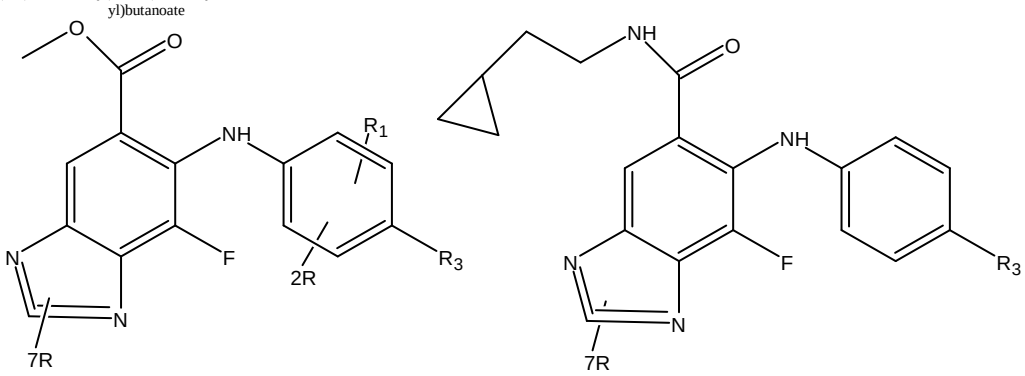
2. Selumetinib



methyl 4-amino-2,3-difluoro-5-nitrobenzoate



methyl 4-(5-(bis(2-chloroethyl)amino)-1-methyl-1*H*-benzo[*d*]imidazol-2-yl)butanoate



Scheme 16 : Synthesis Selumetinib,

3. Veliparib

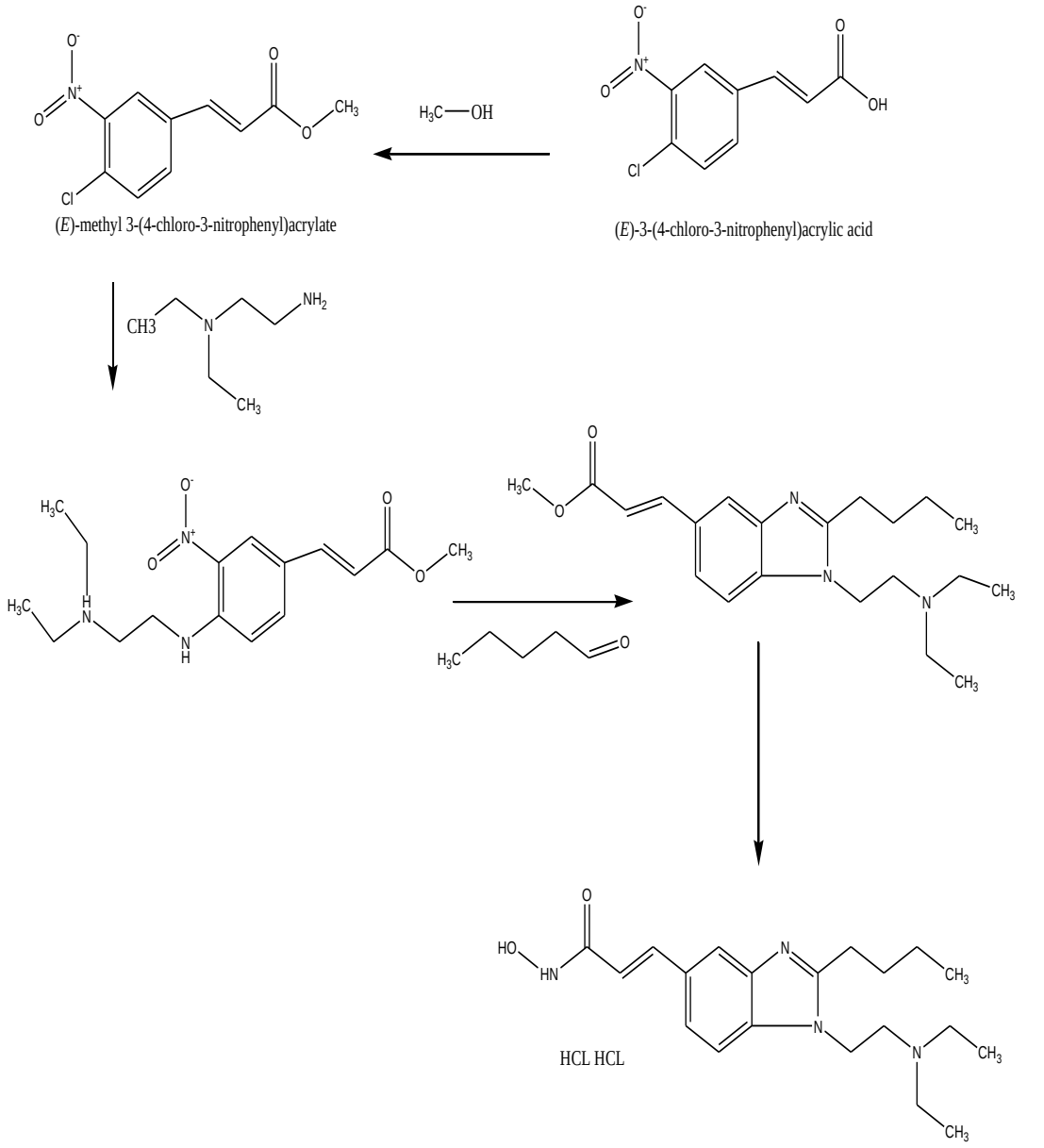
Veliparib is an oral PARP inhibitor that is chemically (R)-2-(2-methylpyrrolidin-2-yl)-1H-benzimidazole-4-carboxamide. Veliparib is an experimental medicine that has shown promise in pre - clinical and clinical tests when used to treat ovarian cancer and ovarian cancer with a mutant version of BRCA[50]. Veliparib is still being developed as a monotherapy as well as combination therapy for the management of of ovarian cancer of several types[51, 52].

4. **Dovitinib**

   Dovitinib, IUPAC named as4-amino-5-fluoro-3-(5-(4-methylpiperazin-1-yl)-1H-benzoimidazol-2-yl) quinolin-2(1H) -one, for example, is a potent pan-tyrosine kinase inhibitor that targets VEGFR, FGFR, and other Tyr kinases[53]. It's a treatment under development for gastrointestinal stromal tumours, metastatic breast cancer, and renal cell carcinomas.. On April 2, 2021, the US FDA approved Dovitinib's premarket approval (PMA) application, which has been submitted by Allarity Therapeutics. Dovitinib is also being investigated for many types of mutant cancers; it is now being studied in a phase II clinical trial for patients with castration-resistant prostate cancer[54].

5. **Pracinostat**

   Pracinostat, IUPAC named as(E2-bu) -3-(tyl-1-(2-(diethyl amino) ethyl)-1H-benzoimidazol-5-yl)-1H-benzoimidazol-5-yl) -N-hydroxyacrylamideay, is an experimental anticancer medicine that is used orally[55], [56]. Pracinostat is a small molecule inhibitor of next-generation histone diacetylases (HDACs) that has been shown to be effective in the treatment of acute myeloid leukemia[57]. Pracinostat inhibits breast cancer development and metastasis by inhibiting the IL-6/STAT3 signaling pathway, according to recent research[58].



scheme : 17 (E2-bu)-3-(tyl-1-(2-(diethyl amino) ethyl) E2-bu)-3-(tyl-1-(2-(diethyl amino -1H-benzoimidazol-5-yl) -N-hydroxyacrylamideay

Synthesis of Pracinostat

6. Galeterone

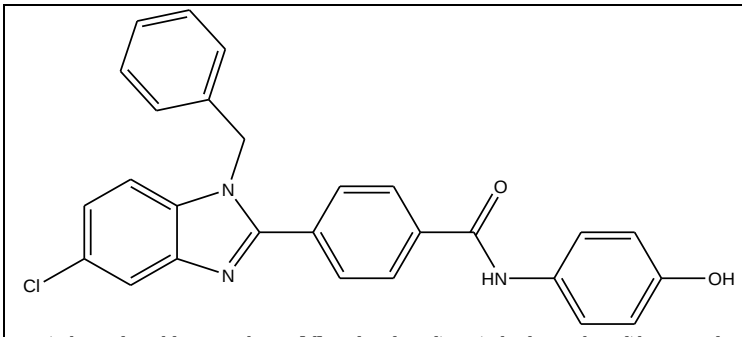
Galeterone, often named by IUPAC as (3S,8R,9S,10R,13S,14S) -17-(1H-benzimidazol-1-yl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1H cyclopenta[a]phenanthren-3-ol, is a small molecule experimental medicine that may be taken orally. Tokai Pharmaceuticals is developing galeterone as a powerful androgen receptor antagonist for the management of prostate cancer[59]. Galeterone monotherapy suppressed breast cancer development in several in vivo tests, and when used in conjunction with cisplatin, the findings were encouraging and far superior to cisplatin monotherapy[60].

CHAPTER- 2

POTENTIAL BENZIMIDAZOLE BASED DERIVATIVES FOR TREATMENT OF CANCER TUMOR

3.1 Galectin-1 inhibitors

Galectin-1 has a wide spectrum of biological activities and is expressed in a variety of normal and pathological circumstances. Gal-1, a 14-kilodalton human homodimeric lectin protein, has been linked to a variety of signalling pathways, immunological responses linked to cancer growth, neurological diseases, and immune disorders[61]. The carbohydrate recognition domain of Gal-1 is specific for -galactosides in the body. Human Gal-1 inhibition has been proposed as a viable therapeutic method for cancer treatment because it plays a key role in tumour formation and spread by influencing a variety of biological activities such as angiogenesis, apoptosis, migration, and cell immune evasion[62]Gal-1 overexpression has been observed in malignancies of the brain, breast, osteosarcoma, lung, prostate, and melanoma[63]. Gal-1 interacts with oncogenes like H-Ras to boost Ras-mediated signal transduction via RAF1 and external signal-regulated kinase and promote the deformation process (ERK). Gal-1 promotes tumour cell attachment at the primary site by linking cell surface glycoproteins such as integrins to glycosylated ECM proteins such as laminin and fibronectin [64]. As a result, Gal-1 is being considered as a potential target molecule for the development of new cancer therapies. RP-HPLC assays demonstrated 85.44 percent binding to Gal-1, confirming the target compound's affinity to Gal-1. Significant amino acid interactions with the target molecule, such as ARG48, TRP68, and ASP125supported up the molecular docking tests. [65,66],



4-(1-benzyl-5-chloro-1*H*-benzo[*d*]imidazol-2-yl)-*N*-(4-hydroxyphenyl)benzamide

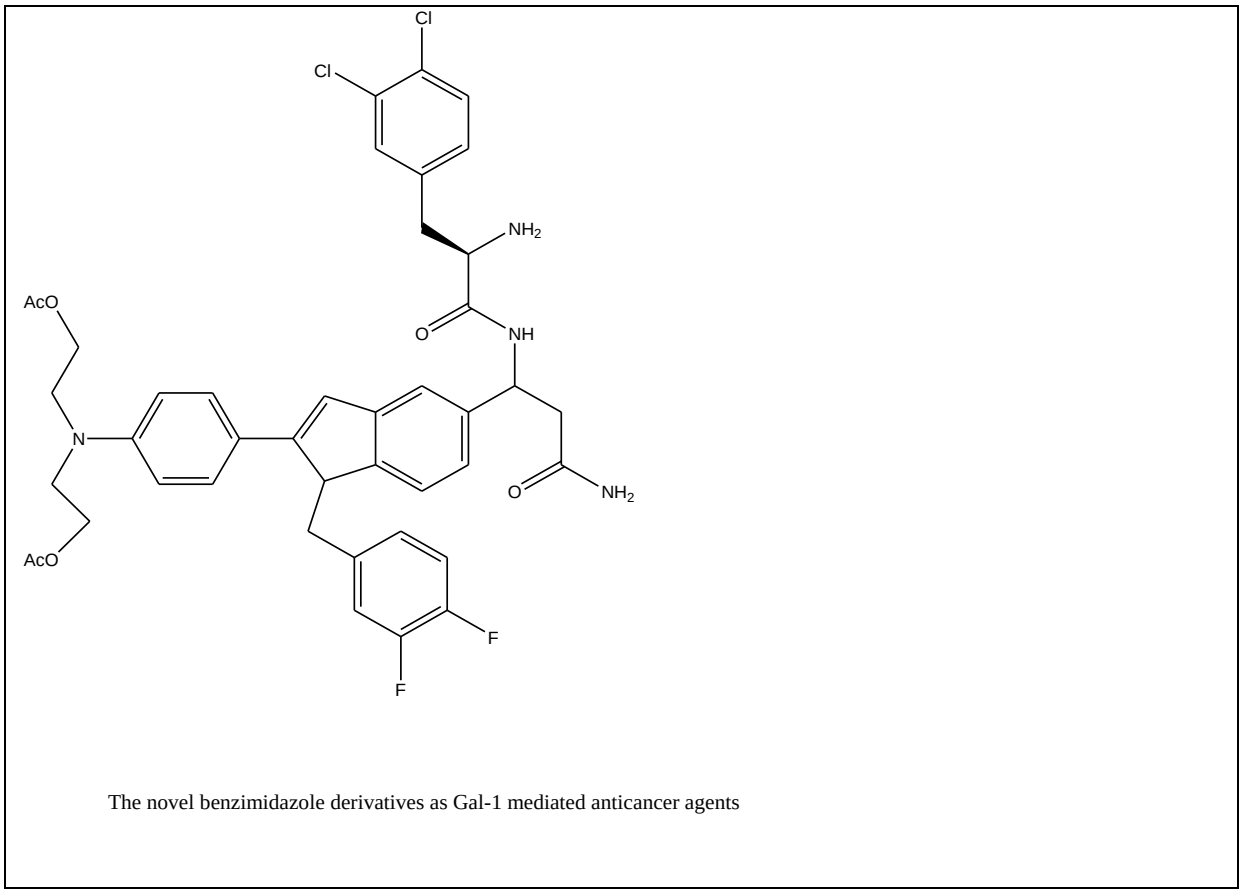


Fig 4: The novel benzimidazole derivatives as G-l-1 mediated anticancer

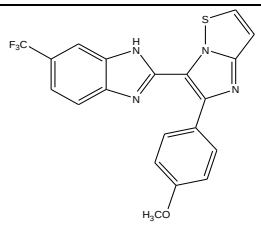
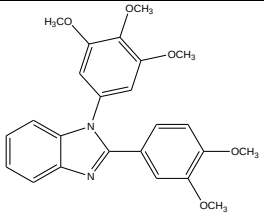
Tsung-Chieh Shih et al. recently released LLS3, a more powerful Gal-1 inhibitor that slows the development and invasion of castration-resistant prostate cancer. As an allosteric inhibitor, LLS3 decreases Gal-1 binding energy toward its binding partners, suppressing the Akt and AR signalling pathways in the process. In both androgen receptor-positive or -negative xenograft models, LLS3 exhibited in vivo effectiveness. It effectively slows the progression of the prostate cancer cells in vivo, in addition to stimulating the anticancer action of docetaxel to promote tumour suppression [67,68].

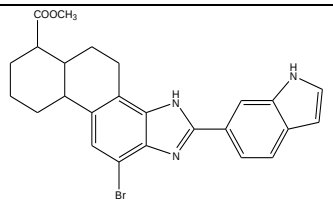
3.2 Tubulin protein inhibitors

Tubulin is a globular protein that belongs to a tiny family. Tubulin comes in a variety of isoforms, the most prevalent of which are - and -tubulins. Tubulin, a cellular protein, plays a crucial role in replication. Microtubules were hallowing filaments made up of - and -tubulins arranged in a head and tail polar pattern as component subunits. Microtubules have 13 active

protofilaments that run along to the microtubule cylinder's entire axis. This might allow motor proteins to carry cellular components across long distances in a continuous manner. Microtubules are also a They are an important component of the cytoskeleton for maintaining cell shape, motility, and intracellular transport of vesicles, mitochondria, and other components. [69,70]. Tubulin is a globular protein that belongs to a tiny family. Tubulin comes in a variety of isoforms, the most prevalent of which are - and -tubulins. Tubulin, a cellular protein, plays a crucial role in replication. Furthermore, cell division necessitates DNA duplication and the division of duplicated chromosomes in two daughter nuclei. Microtubules are responsible for the separation of these chromosomes during the mitotic phase. The positive end of the microtubule is ended by -tubulin, whereas the minus end is ended by tubulin during its creation. They're either polymerizing or depolymerizing all of the time.Tubulin is a globular protein that belongs to a tiny family. Tubulin comes in a variety of isoforms, the most prevalent of which are - and -tubulins. Microtubules in cells can shrink or lengthen in a scholastic manner by removing or adding tubulin heterodimers from the terminals of microtubules. "Dynamic instability" is the name given to this characteristic [71], [72].

Table 3: Targeting tubulin polymerization with benzimidazole derivatives as a selective anticancer agent.

S.r	**Name**	**Structure**
1	2-[2-(4-methoxyphenyl)imidazo[1,2-*b*][1,2]thiazol-3-yl]-6-(trifluoromethyl)-1*H*-benzimidazole	
2	2-[2-(4-methoxyphenyl)imidazo[1,2-*b*][1,2]thiazol-3-yl]-6-(trifluoromethyl)-1*H*-benzimidazole	

3	2-[2-(4-methoxyphenyl)imidazo[1,2-*b*][1,2]thiazol-3-yl]-6-(trifluoromethyl)-1*H*-benzimidazole	

Scheme 18 : Tubulin protein inhibitors

Zhang et al. developed a variety of 1,2-diarylbenzimidazole compounds that might be used as anticancer drugs. The target drug's binding to the microtubule protein was confirmed using molecular docking simulations, which revealed that the target molecule exhibits significant interactions with the protein [73].

Miao et al. proposed a new family of 2-aryl-benzimidazole-based dehydroabietic acid derivatives as tubulin polymerization-targeting cytotoxic medicines. The chemicals were characterised using analytical and elemental techniques. The target compound reduced microtubule polymerization strongly with an IC50 of 5 M. Molecular docking investigations backed by strong electrical interactions between the target molecule and tubulin[74] proved the target compound's selectivity for tubulin protein.

Wang et al. described a new benzimidazole family. derivatives with pyrazole-benzsulfamide ring molecules as tubulin polymerization inhibitors that show promise. Target chemical produced apoptosis in A549 cells, according to experiments employing annexin V/propidium iodide dual labelling assays and cell cycle analysis. Significant amino acid interactions with the target molecule, such as LYS 352, LYS 254, ASN 258, and CYS 241, supported the molecular docking investigations.[75].

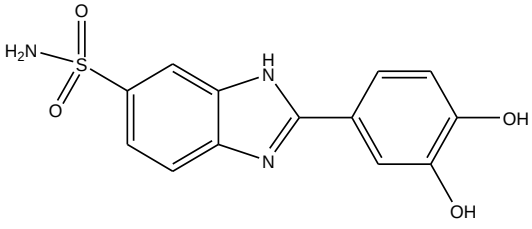
Baig et al. discovered a family of imidazo [2,1-b] thiazole-benzimidazole compounds that inhibit tubulin polymerization and so act as antiproliferative agents. With an IC50 value of 1.08 M, the target chemical has exhibited considerable cytotoxicity towards human lung (A549) cancer. upon on apoptosis studies including such Hoechst staining, mitochondrial The target chemical triggered apoptosis, as evidenced by morphological alterations in A549-treated cell such as kinds of stories, cell wall deformation, or cell shrinkage, as well as membrane current and positive

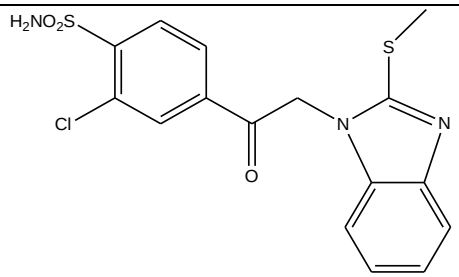
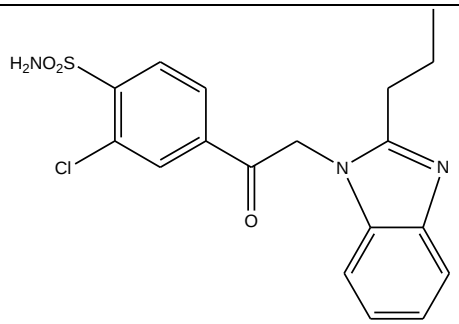
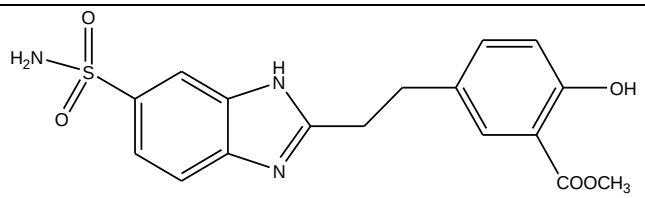
Cells iodide dual staining assays.The target chemical can easily occupy the protein's colchicine binding site, according to computer calculations[76].

3.3 Carbonic anhydrase inhibitors

There are 16 different isoforms of human carbonic anhydrases (hCAs), which belongs to a -family of carbonic anhydrase [77]. CA I, CA II, CA III, CA VII, and CA XIII are cytosol hCAs; CA IV, CA IX, CA XII, CA XIV, and CA XV are membrane hCAs; CA Va & Vb are mitochondria hCAs; CA VI is secreted hCA; ; CA VIII, CA X, & CA XII are catalytic domain isoforms.. [78]. The hCA isoforms IX and XII, which are tumor-associated transmembrane bound enzymes, are overexpressed in numerous cancer types, primarily hypoxic tumours, and are recognised as developing prospective targets for diverse tumour types[79]. Overexpression of hCA isoforms IX and XII promotes tumour growth, angiogenesis, metastasis, and proliferation in a wide range of tumour cells[80]. To show potential cytotoxicity without adverse effects, an anticancer medication should selectively decrease tumor-associated hCAs IX and XII over other hCAs. As a consequence, present medical science focuses on developing heterocycles that target specific tumor-linked hCA isoform IX and XII in order to develop effective cancer therapy techniques. [81]. Another version of the hCA gene, isoform II, has been discovered to overexpress in cancer and other diseases such as edoema, glaucoma, and epilepsy.

Table 4 : Targeting carbonic anhydrase with benzimidazole as effective anticancer agents [77-81]

S No.	Name of compound	Chemical structure
1	2-(3,4-dihydroxyphenyl)-1*H*-benzimidazole-6-sulfonamide	

2	2-chloro-4-{[2-(methylsulfanyl)-1*H*-benzimidazol-1-yl]acetyl}benzene-1-sulfonamide	
3	2-chloro-4-[(2-propyl-1*H*-benzimidazol-1-yl)acetyl]benzene-1-sulfonamide	
4	methyl 2-hydroxy-5-[2-(6-sulfamoyl-1*H*-benzimidazol-2-yl)ethyl]benzoate	

Upon test with 4 biologically relevant hCAs, like CA I, CA II, CA IX, and CA XII, a novel family of 2-substituted-benzimidazole-6-sulfonamides was recently described as having anticancer potential. novel class of structural sulfonamide compounds displayed specific inhibition of tumor-associated genes such as CA IX and CA XII, as according hCA inhibition data [82].

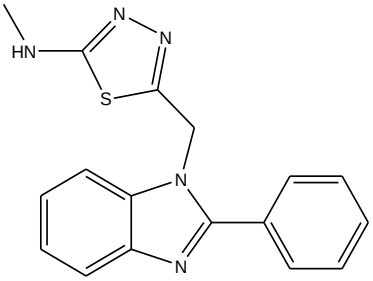
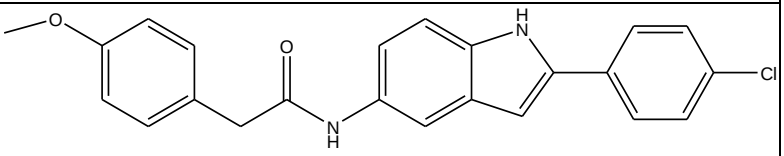
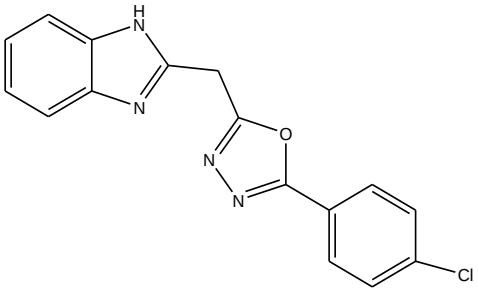
AstaZubriene et al. developed a novel family of benzenesulfonamides with benzimidazole derivatives that are effective inhibitor of human carbonic I, II, 7, XII, and XIII are anhydrases. Various phenacyl bromides were used to make the target compounds from the parent benzimidazole derivative. CA I, CA Iii, CA 7, CA 12, or CA XIII is a classification.that are physiologically significant hCA isoforms, were compared to the protein targets (18, 19). (EC 4.2.1.1). The target compound demonstrated potential inhibitory activity against chosen hCAs at a lower micromolar level, with an inhibitory constant range value of 1.67–66.7 M. Another target

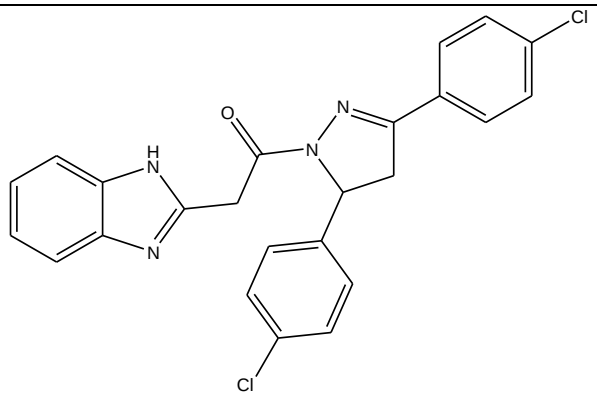
chemical, with an inhibitory constant range value of 2.86–62.5 M, has shown inhibitory activity of particular hCAs at lower micromolar levels. [83].

3.4 EGFR inhibitors

Epidermal Growth Factor Receptor (ErbB-1) is a kinase receptor that belongs to the ErbB family, which also contains the HER2/neu (ErbB-2), Her 3 (ErbB-3), and Her 4 (ErbB-4) subfamilies. [84]. Internal ligands such EGF & TGF engage with EGFR receptors to provide a development signal to cells and regulate epithelial tissue development and homeostasis. [85, 86]. Overproduction of the EGFR ligands in tumour microenvironment promotes continuous mutations of the EGFR receptors, resulting in enhanced epithelial tumour development, metastasis, and invasion in cancer, particularly epithelial malignancies [87,88].

Table 5: Targeting EGFR with benzimidazole derivatives as a selective anticancer agent[88-89]

S.No	Name of Compound	Structure
1	*N*-methyl-5-[(2-phenyl-1*H*-benzimidazol-1-yl)methyl]-1,3,4-thiadiazol-2-amine	
2	*N*-[2-(4-chlorophenyl)-1*H*-indol-5-yl]-2-(4-methoxyphenyl)acetamide	
3	2-{[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]methyl}-1*H*-benzimidazole	

4	2-(1*H*-benzimidazol-2-yl)-1-[3,5-bis(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl]ethan-1-one	

A novel family of benzimidazole-based triazole and thiadiazol compounds was produced and tested as selective EGFR inhibitors in recent research. The molecular structure of the target chemical was confirmed using single-crystal X-ray crystallographic analysis. With erlotinib as that of the reference standard, the synthesised compounds were tested for potential EGFR kinase inhibitory potencies, and the majority of the compounds exhibited promising activity. The target chemical displayed two-hydrogen bonding interactions between residues of LYS721 and THR830 in the binding site for EGFR tyrosine kinase, according to molecular docking experiments[89]. The benzimidazole-oxadiazole hybrids were discovered to be selective EGFR as well as erbB2 receptor inhibitors by Akhtar et al. The target molecule inhibited breast cancer (MCF-7) cells significantly in in-vitro cell inhibition tests, with an IC50 of 5.0 M. At 0.081 and 0.098 M, the target molecule showed substantial inhibition of the EGFR and erbB2 receptors, respectively. Against a number of human cancer cell lines, the majority of the produced compounds showed good cytotoxic activity. The target drug preferentially stopped MCF-7 cell growth just at G2/M phase in cell cycle study. The target chemical has high interactions with the EGFR enzyme's Asp831, Met769, and Thr830, according to computational and 3D-QSAR analyses[90].

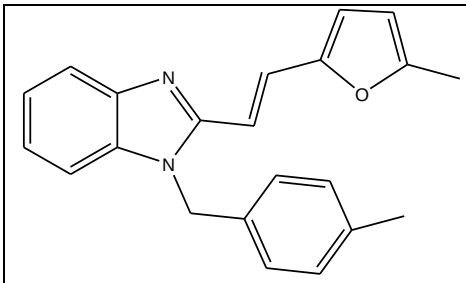
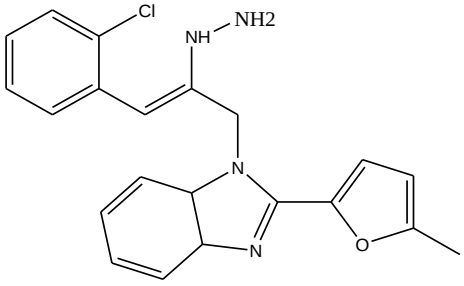
Akhtar et al. used a one-pot multicomponent synthesis to synthesise benzimidazole-based pyrazole derivatives and tested them for possible anticancer activity. The synthesised compounds were tested against MCF-7, MDA-MB231, A549, HepG2, and HaCaT human cancer cell lines. All of the produced compounds were tested for their EGFR inhibitory activity. It inhibited lung cancer cell proliferation by triggering apoptosis. Tests of molecular docking, the target molecule

showed substantial electronic contacts with Met769, The amino acids Thr830, Lys721, and Phe699 of the EGFR receptor's functional pocket[91]. Yuan et al. developed a series of benzimidazole, 6-amide-2-aryl and investigated their ability to specifically inhibit VEGFR-2. The targeted drug decreased vasculature in chick chorioallantois barrier (CAM) experiments (79 percent reduction at 10 nM/eggs) and reduced IC50 of VEGFR-2 kinase is 0.051 mM. According the inquiry using computers, the target chemical formed strong connections with the VEGFR-2 kinase active site. The 6-amide-2-aryl benzimidazole compounds have been discovered to be important inhibitors of VEGFR-2 kinases for anti-angiogenesis treatment.[92].

3.5 VEGFR 2 inhibitors

Abdullaziz et al. discovered a new class of 2-furybenzimidazole compounds that are effective inhibitors of the VEGFR-2 kinase. When compared to the conventional medicine Sorafenib, target compounds 16 and 17 showed good inhibitory efficacy against VEGFR-2, with overall percentage inhibition of 94 percent and 96 percent, respectively, and IC50 values of 0.64 M and 1.26 M. In vitro cytotoxicity testing of compound inhibitory activity against HepG2 and MCF7 cancer cell lines with IC50 values of 8.33–9.86 M. Molecular docking studies of the target chemical revealed a significant binding relationship between the 2-furylbenzimidazole moiety and critical amino acid residues Glu885 and Asp1046 inside the active region of VEGFR-2[93].

Table 6: Targeting VEGFR 2 with benzimidazole as selective anticancer drugs[93]

 % inhibition (VEGFR-2)=30%	 % inhibition (VEGFR-2)=96%

Novel 2-aminobenzimidazole compound has been identified by Lien et al. as a potential inhibitor of the VEGFR-2. When administered at a dose of 10 M, target compound 18 inhibited the kinase

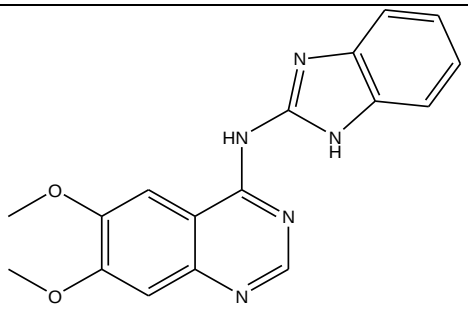
activity for VEGFR-2 by 30%. When investigated in vivo, they showed suppression of VEGF-A angiogenic function as well as suppressing MDA-MB-231 cell lines. The compound has anti-angiogenic effects because it inhibited VEGFR-2 signalling. In animal models, the target chemical was also demonstrated to inhibit lung metastasis of the B16F10 melanoma cells. By creating a hydrogen bond between the nitrogen of benzimidazole and the amino acid residues His1026 in the active region of VEGFR-2, molecular docking tests of the target chemical revealed significant binding[94].

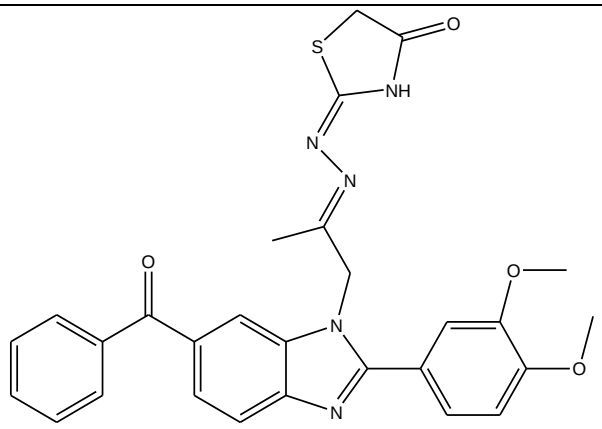
Yuan et al. recently developed and synthesised a novel class of benzimidazole compounds that inhibit VEGFR-2 kinase in a powerful and specific manner. With an IC50 value of 0.054 M, target compound 19 showed good inhibitory efficacy against VEGFR-2 kinase, as well as substantial anti-angiogenesis activity. Compound 19 showed promising in vitro cytotoxicity against HepG2 and A549 cancer cell lines, to IC50 values of 2.57 M and 73.81 M, respectively. The target chemical arrests In a dose-dependent manner, HepG2 cell with in G0/G1 phase fashion, according to cell cycle analyses. A molecular docking investigation of the chemical revealed robust contacts inside the VEGFR-2 kinase's ATP binding active region[95]

3.6 EGFR/VEGFR dual inhibitors

Meguid et al. discovered a new class of benzimidazole compounds that are both EGFR and VEGFR-2 kinase inhibitors.

Table 7: The t Targeting EGFR with benzimidazole derivatives as a selective anticancer agent [95]

S No.	Name of Compound	Chemical structure
1	*N*-(1*H*-benzimidazol-2-yl)-6,7-dimethoxyquinazolin-4-amine	 IC 50 (EGFR)=127.4 mM IC 50 (VEGFR-2)=185.7 mM

2	*N*-(1*H*-benzimidazol -{[2-(methylsulfanyl)-1*H*-benzimidazol-1-dimethoxyquinazolin-4-amine	 IC 50 (EGFR)=0.109 mM IC 50 (VEGFR-2)=69.62 mM

The inhibitory effect of target compounds 20 and 21 against EGFR kinases was significant, although action against VEGFR-2 was excellent. The IC50 value of target compound 20 was 0.157 M for EGFR and 123.27 M for VEGFR-2 kinase. Against the EGFR and VEGFR-2 kinases, target compound 21 had IC50 values of 0.109 M and 69.62 M, respectively. Compounds have remarkable cytotoxicity action against In comparison to the traditional drug doxorubicin, which has an IC50 value of 2.05 M, the HeLa cancer cell line showed IC50 values of 1.62 M & 1.44 M, respectively. As according cell cycle analysis studies, these drugs stop the HeLa cells from entering the G0/G1 phase. Additionally, docking investigations demonstrated that targeted compounds 20 and 21 bind strongly to the active area with the HER2 kinase docking values of kcal/mol are 9.4 and 9.7, respectively.

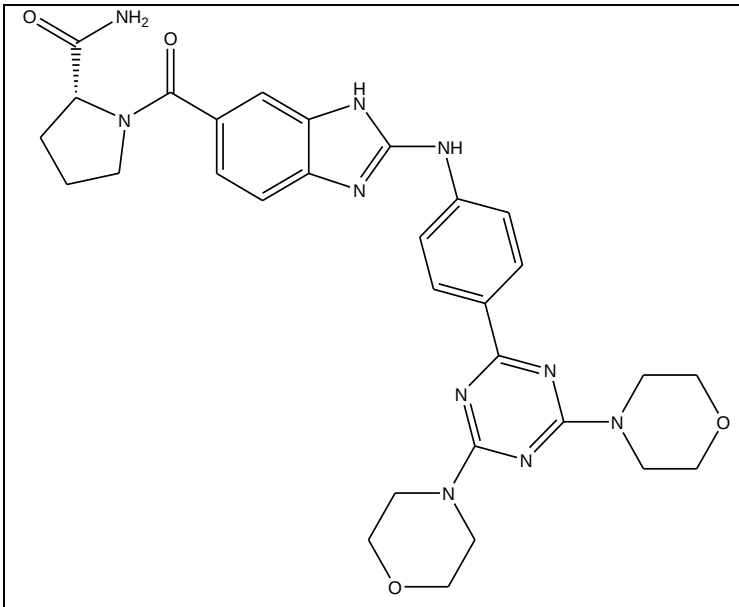
Kassab et al. discovered benzimidazole with quinazoline compounds as potential kinase inhibitor for EGFR ,VEGFR-2. The target compound demonstrated substantial inhibitory effect towards EGFR kinase and VEGFR-2 kinase, with IC50 values of 127.4 M and 185.7 M, respectively. The reactor's cytotoxic against by the MCF7 tumor cell lines was very impressive, with an IC50 of 12.0 M. [97].

3.7 PI3K inhibitors

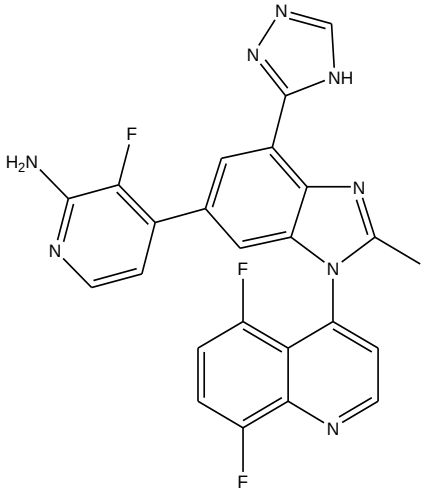
GSK2636771 is a benzimidazole derivative that is new, powerful, and orally accessible. It showed antineoplastic effect as a selective PI3K beta inhibitor. GSK2636771 showed selective suppression of PTEN-deficient tumor growth as well as inhibition of cell kinase B in a dosage

and duration dependent manner in preclinical studies. The first human trial of GSK2636771 in patients with advanced solid tumours showed considerable exposure, target inhibition, and a favourable safety profile when given orally as a monotherapy[98,99].

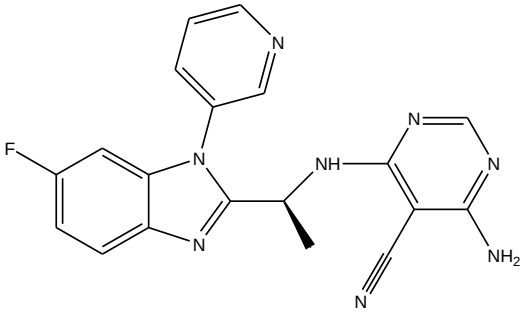
Table 8: Benzimidazole derivatives as anticancer medicines that target PI3K. [98,99].



IC 50 (PI3KI)=5.1



IC 50 (PI3KI)=0.002 M



IC 50 (PI3KI)=0.016 mM

Jin et al. discovered new benzimidazole compounds that are effective PI3K inhibitors. In comparison to standard drug Alpelisib, which exhibited inhibition of 110 percent and 109 percent at 50 nM and 500 nM, the target molecule was shown to be the most powerful against PI3K, with 36 percent and 86 percent inhibition. Furthermore, molecular docking studies of target compound revealed robust binding including six strong h-bonds with the amino acid residues GLN-859, SER-854, and VAL-851. Furthermore, the target compound's HUMO-LUMO calculation, which was performed using Gaussian 09 software, revealed the existence of thiazole cores and amide bonds, which were crucial in its biological activity[100].

Chanrasekhar and colleagues developed a novel family of benzimidazole compounds PI3K. The possible inhibitory effect of target chemical 26 on PI3K was found. With an IC50 value of 0.002 M, it exhibited significant inhibitory activity against PI3K and great specificity on any and all three isoform in class I PI3Ks. The pharmacokinetics characteristics of the drug was also investigated in four different preclinical species. Target chemical 26 had low to medium clearance as compared to hepatic blood flow, but it had persistently high bioavailability and permeability in a rat model[102].

Wu et al. discovered a novel class of triazine-swapped benzimidazole derivatives that are potent dual inhibitor of PI3K and mTOR, with IC50 levels as low as 33 nM for the bulk of the compounds. On Western blots, Compound 27 reduced Akt and p70S6K phosphorylation, demonstrating the present compound's dual inhibitory effect. MCF-7, HCT116, MDA-MB-231, CNE2, and HeLa cell lines showed substantial antiproliferative action, with IC50 values of 0.4 M, 0.9 M, 1.5 M, 7.3 M, and 7.7 M, respectively, against target compound 27. Further study might lead to the addition of a strong dual antagonist to cancer therapy regimens, since compound 27 exhibited potential PI3K/mTOR dual inhibitory action.Shin et al. discovered a new class of benzimidazole compounds that are effective PI3K inhibitors. The target chemical has an IC50 value of 0.016 M and 0.019 M against PI3K, respectively, and an IC50 value of 1.78 M and 2.33 M PI3K. The target compound's in vivo pharmacokinetic profile was determined to be favourable, with oral bioavailability of 45 percent and 41 percent, respectively. In vivo testing of the compounds revealed that both can suppress KLH-specific antibodies[104].

He et al. discovered benzimidazole-isoquinolinone compounds that stop cells from growing by blocking the PI3K/mTOR/Akt pathway. With GI50 values of 23.78 M and 24.13 M, target compound 30 showed good inhibitory action against the SW620 as well as HT29 cancer cell lines, respectively. Phosphorylated Akt as well as mTOR levels are likewise reduced by target compound 30. By reducing levels of cyclin B1 and CDK1, compound was also able to stop human colorectal cancer cells from entering the G2/M phase[105].

Wu et al. discovered that triazine containing benzimidazole derivatives are effective PI3K and mTOR inhibitors. With IC50 values of 2.3 nM and 13.0 nM against PI3K, 14.6 and 20.1 nM against PI3K, and IC50 values against PI3K isoform, target compounds showed strong action. Further western blot analysis of compound 32 revealed that it totally blocked Akt and p70S6K phosphorylation in HCT116 cells, indicating that the target chemical is a potential dual inhibitor of PI3K and mTOR kinase. The chemical has an excellent binding contact inside the active region of PI3K, according to a molecular docking investigation[106].

3.8 CDK inhibitors

Ibrahim et al. described a new flavopiridol-benzimidazole series as a powerful inhibitor of CDK2 and CDK9 kinase. The target chemical has potential inhibitory action against CDK2 and CDK9 kinases, with IC50 values of 0.064 and 1.725 M, respectively. Furthermore, the chemical showed potential antiproliferative action against SKOV3, PC3, and K562 cancer cell lines, with IC50 values of 94.0 M, 85.0 M, and 50.8 M, respectively. The target chemical, according to a cell cycle analysis research, arrests cell cycle of the K562 cancer cells in the G1 and G2 phases in a dose-dependent manner [107].

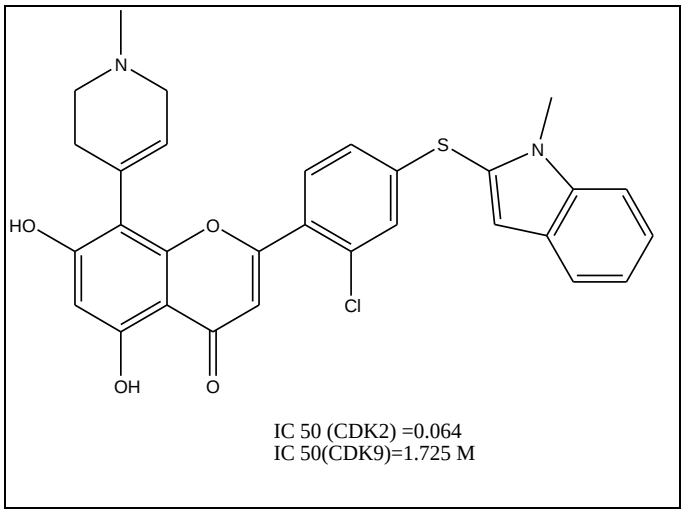


Fig 5: CDK inhibitors

Benzimidazole based hybrid derivatives as potent anticancer agent

Pankaj et al. discovered new benzimidazole -thiazolidinedione hybrid compounds that are effective cytotoxic agents. With IC50 values of 11.46 M, 31.41 M, 29.18 M, and 39.87 M, respectively, the target chemical showed substantial inhibitory action against the Tumor cells A549, DU-145, MDA-MB-231, and PC-3 lines. In A549 cells, compound caused growth arrest in the G2/M phase in a dose-reliant approach. Furthermore, the chemical caused cell shrinkage in A549 cells, as well as chromatin condensation and the creation of horseshoe-shaped nuclei[108].

Novel hybrid compounds of benzimidazole and also pyrazole have been identified as powerful anticancer drugs by Sivaramakarthikeyan et al. Compounds showed strong anticancer activity against SW1990 and AsPC1 human pancreatic cancer cell lines, with IC50 values ranging from 30.9 to 61.8 M, respectively. Both compounds demonstrated strong interaction with the active center of B-cell lymphoma in a molecular docking investigation[109].

Mantu et al. discovered a new class of benzimidazole-quinoline hybrid compounds that are effective anticancer agents. With a growth inhibition percentage of 52.92, this is a good start.

percent and 56.54 percent, respectively, the target chemical showed significant anticancer activity towards renal tumor cell lines A498 and breast tumor cell lines MDA-MB-468. Compound was also shown to have substantial anticancer action against the leukaemia cell line RPMI-8226 and the non-small cells cancerous cell line NCI-H23, inhibiting development by 35%[110].According to Benzimidazole-thiazolidinedione hybrid, Sharma et al. compounds are effective anticancer agents. The target chemical showed substantial anticancer activity against

prostate tumor cell lines PC-3, Carcinoma (MDAMB-231), cervix (HeLa), lung disease (A549), & bone carcinoma (HT1080) cell lines had IC50 values ranging from 0.13 to 0.24 M. Both hybrid derivatives inhibited A549 cell migration by disrupting F-actin assembly, and subsequent treatment resulted in a rise in ROS levels in A549 cells by collapsing the mitochondrial membrane potential[111].Novel hybrid compounds of benzimidazole-1,2,3-triazole have been identified as powerful anticancer agents by Bistrovic et al. The inhibitory action of target compounds was outstanding, with IC50 values of 0.05 and 6.18 against the A549 tumor cell lines and 17.53 and 8.80 against the HeLa cancer cell line, respectively. Furthermore, apoptosis detection using the compound's annexin test revealed a 70.59 percent drop in viable cell population, with a 27.81 percent rise in early necrotic population of cells and a 40 percent increase in late apoptotic cells. Similarly, compound showed a significant reduction in cell population of 49.77 percent. Both compounds attach firmly to active site of the p38 complex, according to a molecular docking investigation[112].

CHAPTER 3

CONCLUSION

Many benzimidazole-containing compounds have been researched and are accessible as anticancer treatments, with varied methods for suppressing mutated malignant cells, including kinase inhibitors. However, benzimidazole-based compounds are still being investigated in targeted treatment. Only a few medicines have been approved to treat mutant tumours due to the difficulty of target specificity and low selectivity. Such difficulties will be alleviated by the hunt for a new benzimidazole-based next-generation kinase inhibitor. The FDA has approved the EGFR inhibitor Abemaciclib, as well as the MEK inhibitors Binimetinib and Selumetinib, as effective anticancer drugs against mutant cancers., owing to the growing popularity of benzimidazole-based target treatments such as enzyme inhibitors. EGFR, VEGFR-2,CDK and PI3K inhibitors and other benzimidazole-containing drugs are also in the development stage.Many benzimidazole-containing compounds have been researched and are accessible as anticancer treatments, with varied methods for suppressing mutated malignant cells, including kinase inhibitors. However, benzimidazole-based compounds are still being investigated in targeted treatment. Few compounds have been developed due to the difficulty of target specificity and low selectivity. However, several of the compound showed great However, kinase inhibitory activity lacked a strong safety profile; all the compound will serve as lead compound, with additional modifications, design, and development resulting in powerful compounds with maximum efficiency and lowest side effects.The material offered in this chapter is primarily focused on benzimidazole-based kinase inhibitors and their advancements; medicinal chemists will find it useful in medication development, discovery, and design innovative, powerful, target-based anticancer therapy that is both effective and safe medicines.

CHAPTER 4

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