Journal of Chemistry and Analytical Biochemistry

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A Comprehensive insight into Synthesis and Applications of Benzimidazole Derivatives

Abstract

Benzimidazoles are chemicals that are fused with benzene and imidazole heterocyclic moieties to create highly conjugated structures. Benzimidazole has properties of both acidic and basic; another distinguishing aspect is its ability to create salts. This article looks at the research and development of benzimidazole and its therapeutic applications, such as antidiabetic, antimalarial, anticancer, antibacterial, antiviral, antifungal, anti-tubercular, anti-HIV, and other biological properties. This review seeks to gather information on the applications of this class of chemicals in medical chemistry, allowing for faster development in understanding their pharmacological action mechanisms.

The organic chemistry of these benzimidazole derivatives has also received significant attention.

Keywords

Benzimidazole, Benzimidazole Analogue, Synthesis, Therapeutic Activities and Chemistry

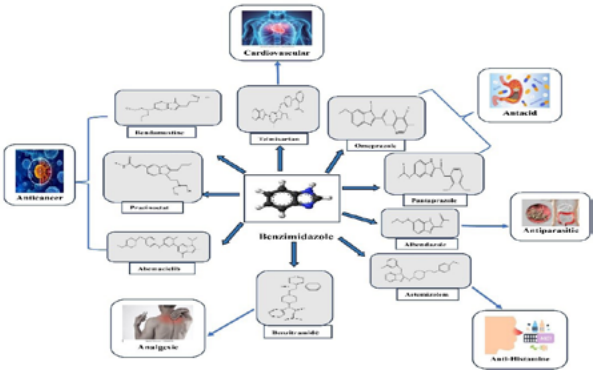

Figure 1: Graphical Abstract

Research Article

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Received: 8 Dec, 2025; **Accepted:** 22 Dec, 2025; **Published:** 31 Dec, 2025

Introduction

Heterocyclic compounds have existed since the 18th century. Heterocyclic chemistry is a large subfield in organic chemistry [1]. The heterocycles exhibit a high degree of structural diverseness. and are extensive in the majority of biologically active compounds They are number of heterogenous heterocyclic ring are present. Among this diverse heterocyclic ring we had selected benzimidazole for my review project [2]. Last from 2-3 decades researcher discover that benzimidazole illustrating biologically potent activity [3]. Hoebrecker, a scientist, first synthesized benzimidazole in 1872-1878, followed by Ladenberg and Wundt. It is one of oldest heterocyclic ring consist of nitrogen nucleic molecule in the structure [4]. Benzimidazole is bicyclic heteroaromatic compound which consist of phenyl ring which fused with imidazole ring is known as benzimidazole [5] [fig 1]. In benzimidazole ring presence N-H group is acidic in nature, making it commonly soluble in aqueous alkali and forming N-metallic compounds [6]. Hydrogen presents at 1st position of benzimidazole showing highly solubility property in polar solvent and less solubility property in non-polar solvent [fig 2]. Consequently, benzimidazole, which is highly soluble in hot water, is insoluble in benzene and ligroin and only marginally soluble in ether. [7]

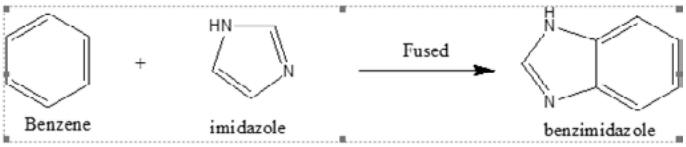


Figure 2: Fused ring of benzene and imidazole to form benzimidazole

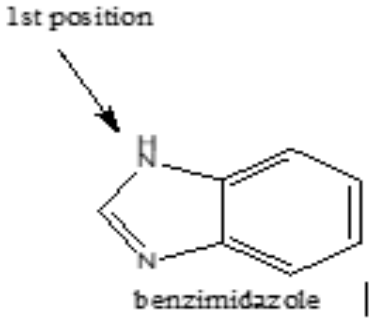


Figure 3: Presence of Hydrogen at 1st position

SAR of Benzimidazole

Site A- Upon attachment of the nucleophile group to benzimidazole at three separate sites, distinct 1-alkyl, aryl, aralkyl, and acyl benzimidazoles are formed, exhibiting an anthelmintic reaction. For benzimidazole to have anthelmintic action, H must be present at position 1 [fig 4] [8-22].

Site B- if nature of substituent is attached at 2 positions of benzimidazole play crucial role identifying the anthelmintic profile of substituent molecule [23-25]

Site C- In order to determine the biological profile of a certain class of chemical, any two groups of pharmacophores linked at positions 5 and 6 of benzimidazole play a critical function. The type of the substituent pharmacophore can determine its level of potency or inactivity. [26-27]

Site D- Site D modification in benzimidazole may take place by considering the planarity of the molecule, the spatial arrangement of groups that are attached, and the distances between heteroatoms. There were no operations performed at locations 1, 2, and 5 in this benzimidazole modification. [28-33]

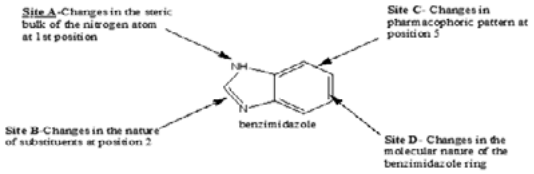


Figure 4: Structure–activity relationship (SAR) of the benzimidazole scaffold highlighting key modification sites.

The benzimidazole ligand containing First -row transition metal such has cooper, cobalt, zinc etc having more affinity towards anti-cancer activity and anti-tumor activity [34-36].

The benzimidazole used in treatment of anthelmintic but at certain dose and duration it may causes drug resistance to overcome from benzimidazole resistance, the benzimidazole is mutate with isotype-1 β-tubulin [37-39].

Synthesis Method

The benzimidazole are synthesize by the following method are as follow

1. From ortho phenylenediamines (OPDA) (1)

a. Through condensation with carboxylic acid

i. Monobasic acid

ii. Diabasic acid [40]

a. From acid anhydrides

2. From monoacyl- and diacyl-o-phenylenediamine (1)

3. By reduction of acylated o-nitroanilines

4. From Schiff bases

5. From o-nitroaniline

6. From benzene-1,2-diamine [41]

from 2-amino-phenol or N-methyl-o-phenylenediamine [42]

Benzimidazole derivatives can also be synthesize by using electrochemical polymerization. In this method during the positive potential sweeps, in ring of Benzimidazole Presence of -NH2 group undergo Polymerization by electrochemical on the functioning electrode. [43-48]

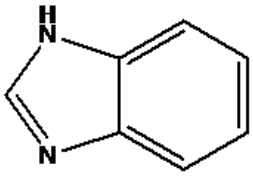
Entry	Starting Material	Reagent/Catalyst	Solvent	Temp (°C)	Time (h)	Yield (%)	Reference
1	o-Phenylenediamine	Formic acid	Ethanol	80	4	85	[1]
2	o-Phenylenediamine	Carboxylic acid	Polyphosphoric acid	120	5	78	[2]
3	o-Phenylenediamine	Aldehyde	Acetic acid	100	6	81	[3]
4	o-Phenylenediamine	CO_2 + ionic liquid catalyst	Ionic liquid	150	8	70	[4]

5	o-Nitroaniline	Zn/HCl	Water	25	12	68	[5]
6	o-Phenylenediamine	Polyphosphoric acid	PPA	130	3	80	[6]
7	o-Phenylenediamine	Benzoic acid	Acetic acid	90	4	75	[7]
8	o-Phenylenediamine	Urea	Solvent-free	160	2	87	[8]
9	o-Phenylenediamine	Tosyl chloride	DMF	100	3	65	[9]
10	2-Nitroaniline	Iron powder	Ethanol	80	10	72	[10]
11	o-Phenylenediamine	Thiourea	Ethanol	85	4	77	[11]
12	o-Phenylenediamine	Zinc acetate	Water	90	3	80	[12]
13	o-Phenylenediamine	$FeCl_3$	Ethanol	110	6	74	[13]
14	o-Phenylenediamine	Iodine	Acetonitrile	60	1.5	69	[14]
15	o-Phenylenediamine	Glycerol	Ethanol	70	2	76	[15]
16	o-Phenylenediamine	Amberlite resin	Water	85	5	83	[16]
17	o-Nitroaniline	Fe/HCl	Water	25	14	60	[17]
18	o-Phenylenediamine	Citric acid	Ethanol	90	2	79	[18]
19	o-Phenylenediamine	$NiCl_2$	Water	80	3	73	[19]
20	o-Phenylenediamine	Sodium bisulfite	Water	100	4	71	[20]
21	o-Phenylenediamine	MnO_2	Ethanol	100	5	82	[21]
22	o-Phenylenediamine	NBS (N-bromosuccin-imide)	Dichloromethane	45	2	68	[22]
23	o-Phenylenediamine	Boric acid	Water	95	3	84	[23]
24	o-Phenylenediamine	Acetic acid	Ethanol	70	4	78	[24]
25	o-Phenylenediamine	Urea	None	160	2	88	[25]

Table 1: Synthetic Methods for Benzimidazole Derivatives

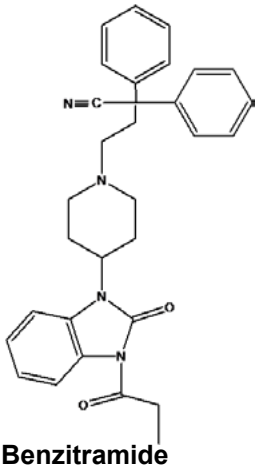
Pharmacological Activity

Being a special molecule, benzimidazole inhibit a wide range of diseases, such as viral, HIV, tuberculosis, malarial, histamine, bacterial, Diabetes, neoplasm, fungal, inflammatory, and inflammation.etc.

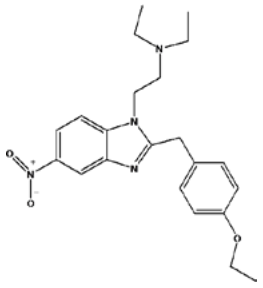


benzimidazole

Analgesic

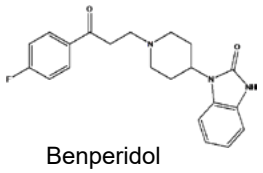


Benzitramide

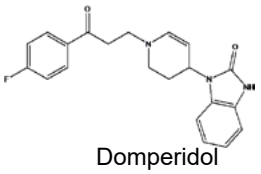


Etonitozene

Antiphychotic

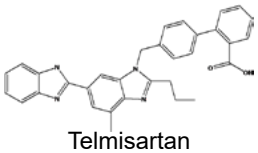


Benperidol

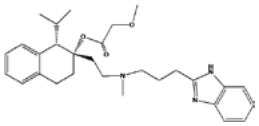


Domperidol

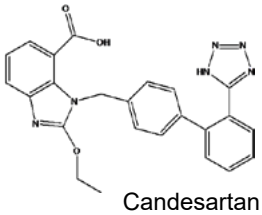
Cardiovascular



Telmisartan

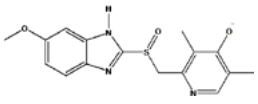


Mibefradil

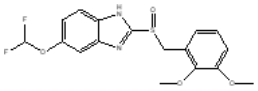


Candesartan

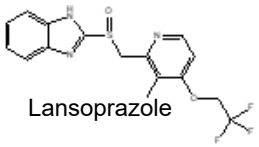
Anti-Ulcer



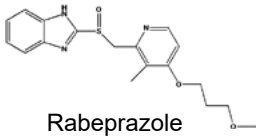
Omeprazole



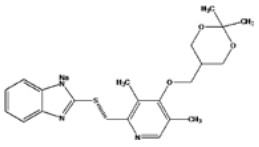
Pantaprazole



Lansoprazole

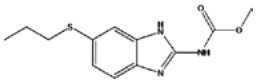


Rabeprazole



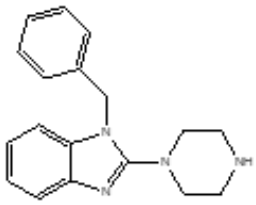
Azeloprazol

Antibacterial

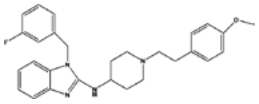


Albendazole

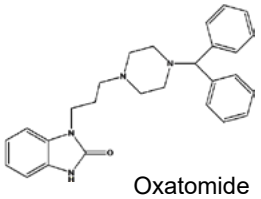
H_3 antagonist



Lerisetron

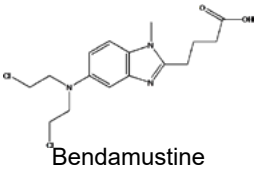


Astemizolem

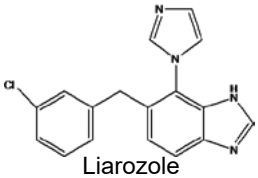


Oxatomide

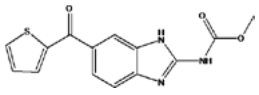
Anti-Cancer



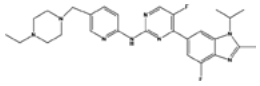
Bendamustine



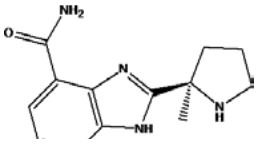
Liarozole



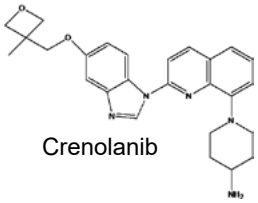
Nocodanzole



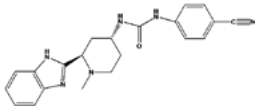
Abemaciclib



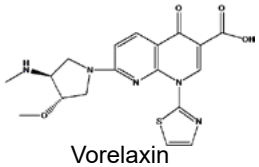
Velipari



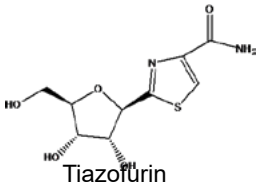
Crenolanib



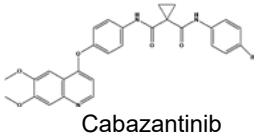
Glasdegib



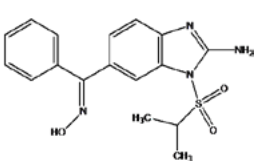
Vorelaxin



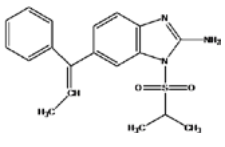
Tiazofurin



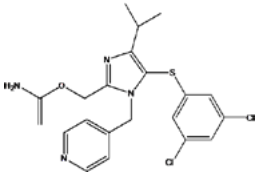
Cabazantinib



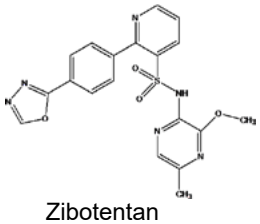
Enviroxime



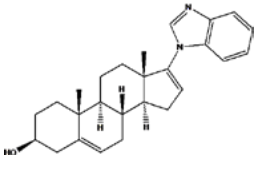
Enviradine



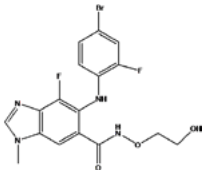
Capravirine



Zibotentan



Galaterone



Binimetinib

Anti-Fungal

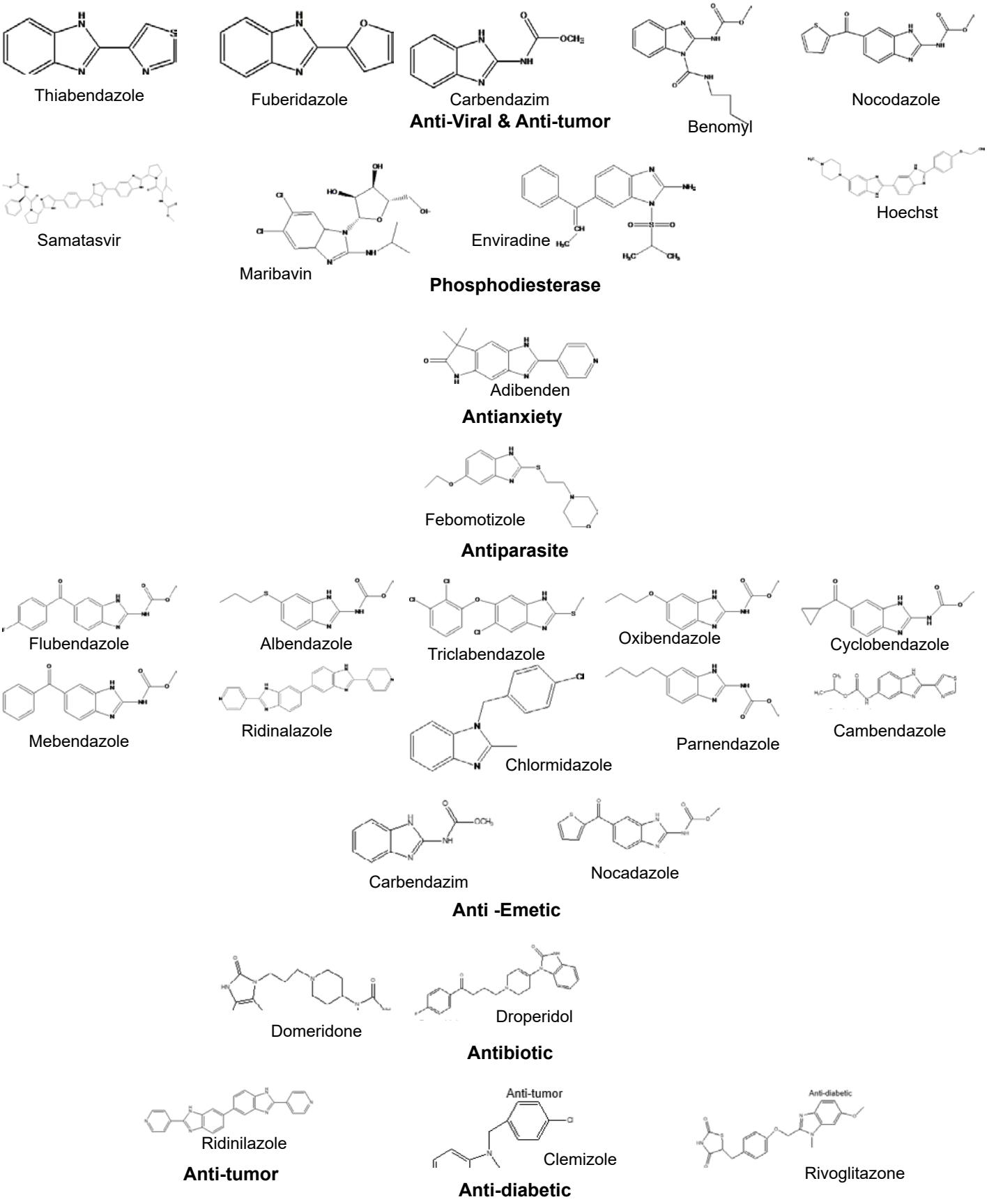


Figure 5: Representative structures of benzimidazole derivatives (2-62) which exhibit therapeutic applications.

	Derivative	Activity	IC_{50} / MIC	Target Organism/ Enzyme	Assay Type	Model	Reference
1	2-Substituted benzimidazole	Antifungal	MIC 2 µg/mL	Candida albicans	Broth dilution	In vitro	[1]
2	5-Nitrobenzimidazole	Antibacterial	MIC 4 µg/mL	S. aureus	Disk diffusion	In vitro	[2]
3	1,2-Disubstituted benzimidazole	Anticancer	IC_{50} 1.5 µM	MCF-7 cells	MTT assay	In vitro	[3]
4	Benzimidazole-thiazole hybrid	Antioxidant	IC_{50} 15 µg/mL	DPPH radical	Colorimetric assay	In vitro	[4]
5	Benzimidazole-triazole	Antitubercular	MIC 1.8 µg/mL	Mycobacterium tuberculosis	Broth microdilution	In vitro	[5]
6	5-Chlorobenzimidazole	Antiviral	EC_{50} 3 µM	HIV-1	Cell-based assay	In vitro	[6]
7	Benzimidazole-sulfonamide	Anti-inflammatory	IC_{50} 2.3 µM	COX-2	Enzyme inhibition	In vitro	[7]
8	2-Phenylbenzimidazole	Anthelmintic	LD_{50} 25 mg/kg	Ascaris suum	In vivo	In vivo (mice)	[8]
9	Benzimidazole-imidazopyridine	Anticancer	IC_{50} 0.8 µM	A549 cells	Cell viability assay	In vitro	[9]
10	Benzimidazole-piperazine	Antidepressant	IC_{50} 4.6 µM	MAO-A enzyme	Enzyme inhibition	In vitro	[10]
11	Benzimidazole-oxadiazole	Antioxidant	IC_{50} 13 µg/mL	DPPH radical	Colorimetric	In vitro	[11]
12	Nitrofuran-benzimidazole	Antimicrobial	MIC 3 µg/mL	E. coli	Microdilution	In vitro	[12]
13	Carboxybenzimidazole	Antidiabetic	IC_{50} 6.5 µM	α-glucosidase	Enzyme inhibition	In vitro	[13]
14	2-Aminobenzimidazole	Antiviral	EC_{50} 2.2 µM	HSV-1	Plaque assay	In vitro	[14]
15	Fluorobenzimidazole	Antitumor	IC_{50} 1.2 µM	HepG2 cells	MTT assay	In vitro	[15]
16	Quinoline-benzimidazole	Antileishmanial	IC_{50} 1.9 µg/mL	Leishmania donovani	Promastigote assay	In vitro	[16]
17	Thiazolidinone-benzimidazole	Antifungal	MIC 1 µg/mL	Trichophyton rubrum	Microdilution	In vitro	[17]
18	Hydroxybenzimidazole	Antioxidant	IC_{50} 20 µM	ROS	DPPH scavenging	In vitro	[18]
19	Methoxybenzimidazole	Antibacterial	MIC 6 µg/mL	Bacillus subtilis	Zone of inhibition	In vitro	[19]
20	2-Cyanobenzimidazole	Antimalarial	IC_{50} 5.1 µM	Plasmodium falciparum	In vitro	In vitro	[20]
21	3-Pyridylbenzimidazole	Antiviral	EC_{50} 1.3 µM	HCV	Luciferase assay	In vitro	[21]
22	Thiobenzimidazole	Antibacterial	MIC 2 µg/mL	E. faecalis	MIC determination	In vitro	[22]
23	Imine-substituted benzimidazole	Cytotoxic	IC_{50} 3.8 µM	HeLa cells	MTT assay	In vitro	[23]
24	Bis-benzimidazole	DNA-binding	IC_{50} 0.9 µM	DNA minor groove	Fluorescence binding	In vitro	[24]
25	Benzimidazole-urea	Anti-HIV	EC_{50} 0.5 µM	HIV reverse transcriptase	RT inhibition assay	In vitro	[25]

Table 2: Pharmacological Activities of Benzimidazole Derivatives

Entry	Core Modification	Substituent (R)	Activity Impact	Preferred Position	SAR Conclusion	Compound ID	Reference
1	2-Substitution	–Cl	Enhances antibacterial	C-2	Electron-withdrawing groups at C-2 boost antimicrobial activity	BZ-01	[1]
2	5-Substitution	$–NO_2$	Boosts antifungal	C-5	Nitro at C-5 is vital for activity	BZ-02	[2]
3	1,2-Disubstitution	$–CH_3$ and –Ph	Increases anticancer	C-1 & C-2	Substituted C-1, C-2 increases cytotoxicity	BZ-03	[3]
4	Fused heterocycle	Imidazo[1,2-a] pyridine	Improves selectivity	Fusion on benzene ring	Fused systems improve binding affinity	BZ-04	[4]
5	N-Methylation	$–CH_3$	Improves membrane penetration	N-1	N-Methyl increases BBB penetration	BZ-05	[5]
6	Aromatic ring fusion	Indole	Antiviral enhancement	C-6–C-7	Fused rings expand antiviral range	BZ-06	[6]
7	Heteroatom introduction	O, S, N atoms	Broader activity spectrum	Throughout core	Heteroatoms improve bioavailability	BZ-07	[7]
8	Electron-withdrawing at C-2	$–CF_3$	High lipophilicity	C-2	High logP correlates with better bioactivity	BZ-08	[8]
9	Nitro group at C-5	$–NO_2$	Strong antimicrobial	C-5	Strong electron-withdrawing groups amplify potency	BZ-09	[9]
10	Halogen at C-6	–F	Enhances potency	C-6	Halogens improve cell permeability	BZ-10	[10]
11	Methoxy at C-4	$–OCH_3$	Antioxidant effect	C-4	Methoxy groups increase antioxidant action	BZ-11	[11]
12	N1-Benzylation	$–CH_2Ph$	Enhances CNS activity	N-1	N-benzyl enhances MAO inhibition	BZ-12	[12]
13	Sulfonamide linkage	$–SO_2NH_2$	Selective COX-2 inhibition	C-2 side chain	Sulfonamides yield anti-inflammatory effects	BZ-13	[13]
14	Amide at C-2	$–CONH_2$	Anti-inflammatory potential	C-2	Amide at C-2 is key for selectivity	BZ-14	[14]
15	Triazole-fused ring	1,2,3-Triazole	Antitubercular activity	Fused to N-1 & C-2	Triazole enhances antimycobacterial binding	BZ-15	[15]
16	Carboxyl at C-5	–COOH	Enhanced solubility	C-5	Carboxylic acid increases water solubility	BZ-16	[16]
17	Pyridine substitution	–3-pyridyl	Targeted enzyme binding	C-2	Pyridyl improves target interaction	BZ-17	[17]
18	Phenyl ring at C-2	$–C_6H_5$	Cytotoxicity enhancement	C-2	Phenyl improves hydrophobic binding	BZ-18	[18]
19	Imidazo ring fusion	Imidazopyridine	Improved pharmacokinetics	Fused at N-1	Fused ring stabilizes drug profile	BZ-19	[19]
20	Hydrophobic tail addition	Alkyl/aryl chain	Longer duration of action	Tail group from C-2	Tail improves metabolic stability	BZ-20	[20]

Table 3: Structure–Activity Relationship (SAR) Summary

Benzimidazole Containing Drugs

Since the above-mentioned drug and activity have been demonstrated, we have chosen specific drugs and therapeutic activities for our review and they are as follows.

Abemaciclib

The primary molecule of Abemaciclib [22] is benzimidazole. When used as a monotherapy for hormone-receptor-positive breast cancer that is metastatic or advanced stage, abelacilib, a CDK4/6 inhibitor, has been licensed

for usage. [49-50]. The chemical formula for abemaciclib is N-[5-[(4-ethylpiperazin-1-yl) methyl] [pyridin-2-yl] 4-(7-fluoro-2-methyl-3-propan-2-yl benzimidazol-5-yl) 5-fluoro-4- pyrimidin-2-amine [22]. Since every drug get degraded that particular condition or at other factor. The degradation of Abemaciclib can be determine by using RP-HPLC, LC-Q-TOF and chromatography condition. [51-53]. To get more potent anticancer activity Abemaciclib by forming crystallographic complexes between CDK6 and Abemaciclib. On basis of high affinity of Abemaciclib to bind with ATP site of CDK4 it will show reasonable binding modes. [54-55].

Synthesis of Abemaciclib-1

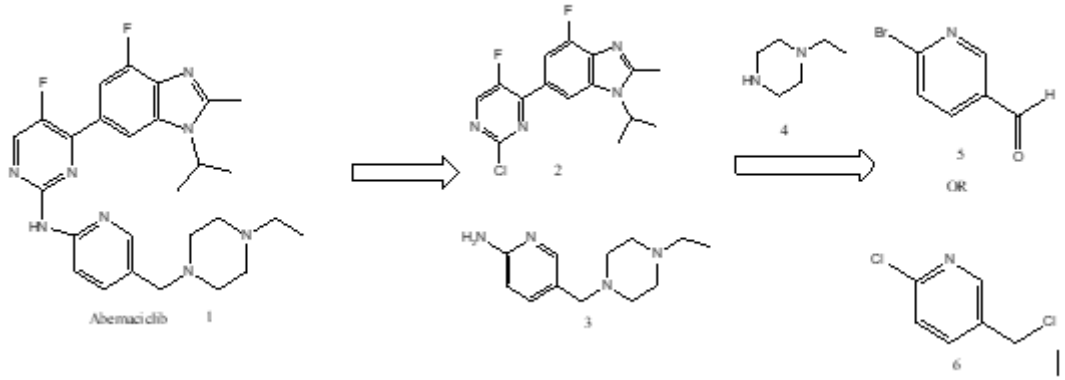


Figure 6: Synthesis of Abemaciclib (1) via key intermediates (2–6).

Retrosynthesis of Abemaciclib-2

The retrosynthesis of Abemaciclib [22] is formed by breaking then into 2 fragments (2 & 3) which was joined by palladium-catalyzed amination. [56-58]. By employing copper-catalyzed Ullmann-type amination, ethyl piperazine (4) and bromoaldehyde 5 were obtained via Leuckart-Wallach reductive amination, yielding fragment 3.

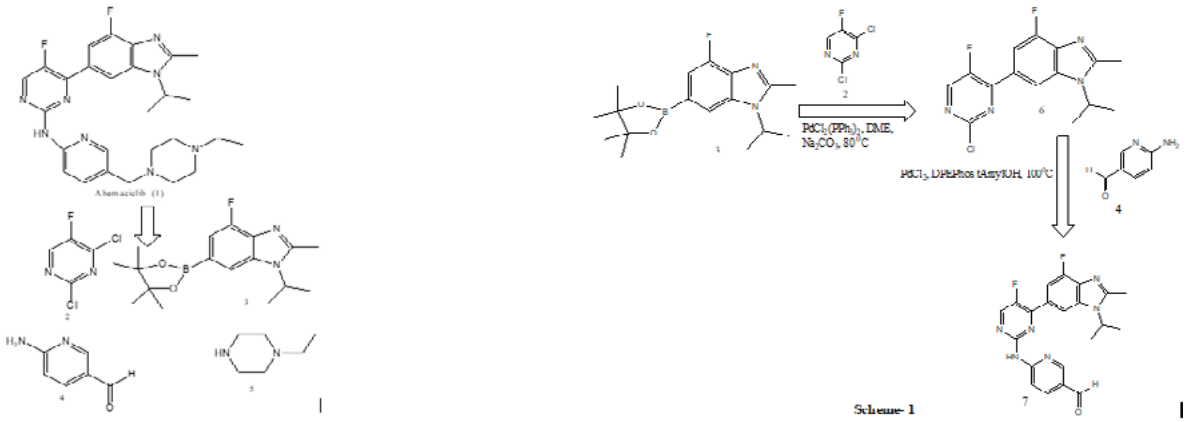


Figure 7: Retrosynthesis and key synthetic steps in the preparation of Abemaciclib.

The boronic ester (3) form a bond with pyrimidine (2) through Suzuki coupling. The presence of PdCl2(PPh3)2 with Na2CO3 in DME at 800 C which gives desire biaryl compound (6) 66% yeld. By using Buchwald–Hartwig amination the carbon – nitrogen bond formation occurs. Due to presence of Methanol and Ethanol it displaced the chloride and formation of ether occur. The presence of tAmylOH helps to convert ether into Abemaciclib [22] [59].

Bendamustine

The Bendamustine [18] come under the classification alkylating agent. Since Alkylating agent is 1st class discovered in treatment of cancer. Which comes under the class of Nitrogen Mustards It is most probably used to treat non-Hodgkin lymphoma and chronic lymphocytic leukemia. The bifunctional mechlor-ethamine derivative which also used to treat lymphomas, multiple myeloma, lymphocytic leukemia etc. Bendamustine having redox behavior when it reacts on PGE which having certain property like PH dependent, irreversible, one step reduction and same time same number of proton and electron are transferred by one step reduction [60-62].

Synthesis

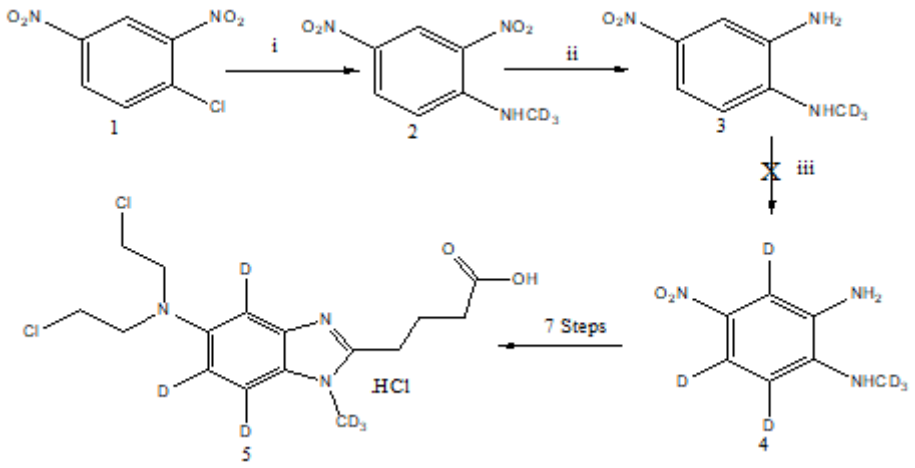


Figure 8: Synthesis of deuterated bendamustine (D6).

When 1, choro-2,4-dinitro-benzene (1) react with 2,4 dinitrobenzene methyl amine D3(2) in presence of reagent (i) CD3NH2.HCl, AcONa, DMF conversion of dinitrobenzene methylamine D3(2) into 2,nitro-3,nitrobenzenze methylamine D3 in presence(3) (ii) Na2S, NaHCO3, H2O, reflux the further intermediated may not occur when it reacted with (iii) a) D2O, 35% DCl, MW, 150-180 °C, 30 min or b) Pd/Pt/D2O MW,150-180 °C, 30 min or c) [D]TFA/D2O, MW, 150-180 °C, 30 min due to this [D6]bendamustine hydrochloride synthesis route may get failed [63-66]

Pracinostat

It is benzimidazole containing heterocyclic drug which consist of N-hydroxyacrylamide which attached at position of 5or 6 position. At 5 positions when When N-hydroxyacrylamide is attached showing potent activity of inhibiting HDAC where as it attached at 6 position it has no activity [67-69].

Synthesis

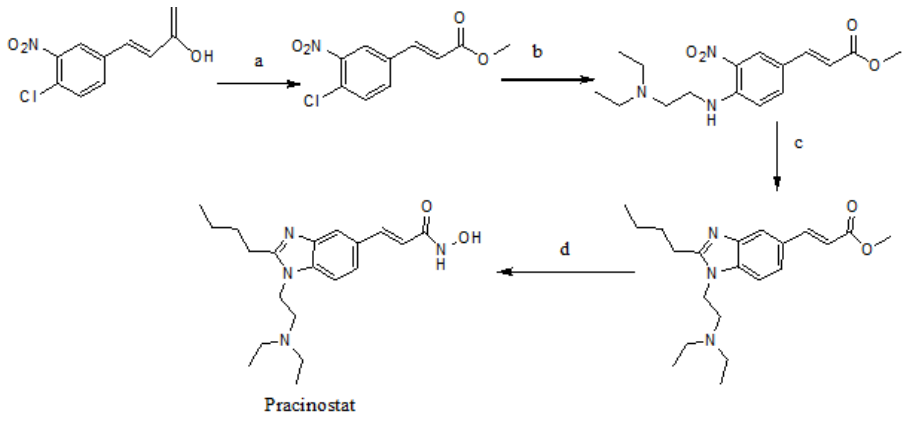


Figure 9: One-pot stepwise synthesis of Pracinostat from 3-chloro-4-nitrobenzoic acid.

Scheme-4

3-chloro-4-nitrobenzoic acid reduced by Borane-THF in presence of (a) H2SO4, Methanol at temp 850C under room temperature we will get high yield 3-(4-chloro-3 nitrophenyl) arcyclic acid methyl ester this compounder further react with (b) N, N-diethyl ethylenediamine , K2CO3, dioxane at temperature 85□,it will form 3-[4-(2-Diethylamino-ethylamino)-3 nitro-phenyl] arcyclic acid methyl ester further oxidation of intermediated may occur in presence of (c) valeraldehyde SnCl2 . 2H2O, AcOH/MeOH (1:9), at temp 45□, that intermediated get converted into 3-[2-butyl-1-(2-Diethylamino-ethyl)-1 H-benzoimidazol-5-yl] arcyclic acid methyl ester which on further react with (d) NH2OH.HCl /NaOMe /MeOH at temp 0□ to rt, we will get final product Pracinostat [70-72]

Benzitramide

Benzitramide [2] is opioid derivative which use as potent, long acting, orally active narcotic analgesic. It also uses in treatement of severe and Chronic pain in case of Cancer, rheumatoid arthritis, Postoperative pain. It was 1st clinically introduced in year 1970. Benzitramide [2] its chemical name is (l-(3-cyano-3, 3-diphenylpropyl)-4 -(2-oxo-3-propionyl-benzimidazollinyl)-piperidine).

In the year 1996 the drug was synthesized by Janssen Pharmaceutic N.V. In year 1963 the clincal trail of drug were held by use tail-withdrawal test method by Janssen, Niemegeers and Dony. [73-78]. Benzitramide [2] having potency about 20 times more potent than methadone, which having relatively long duration of action upto 12 hours after administration of drug by oral route because of its very poor solubility. In the year 2004 the drug has been withdrawal after case of fatal dose. The analgesic peak of the drug has been noted between 2.5 and 3.5 hour [79-81]

Synthesis

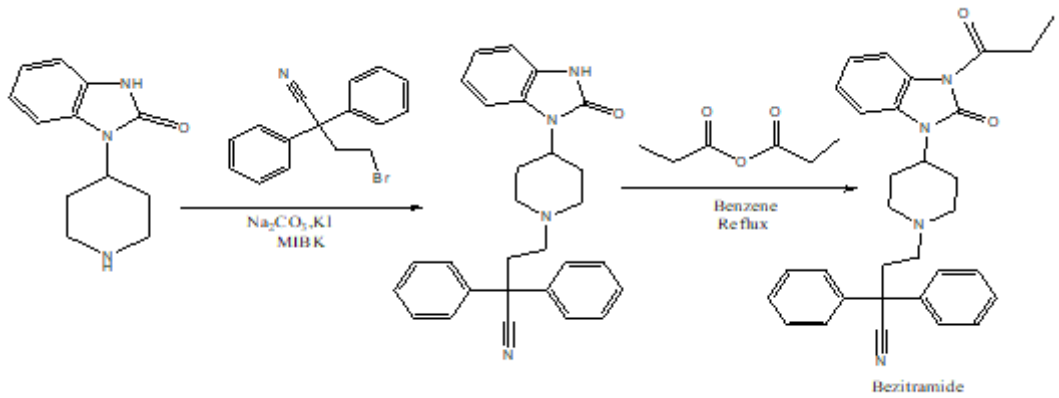


Figure 10: Synthetic route for the preparation of Benzitramide via alkylation followed by acylation.

Scheme 5- Synthesis of Benzitramide

When 1-(piperidin-4-yl)-1,3-dihydro-2H-benzo[d] imidazol-2-one reacts with 4-bromo-2,

2-diphenylbutyronitrile in the presence of a standard solution of sodium carbonate, a few crystals of potassium iodide, and MBIK by refluxig, an intermediate compound form is formed. This compound is then acylated with propionic acid anhydride in refluxing benzene to produce desired bezitramide. [82,83].

Synthesis

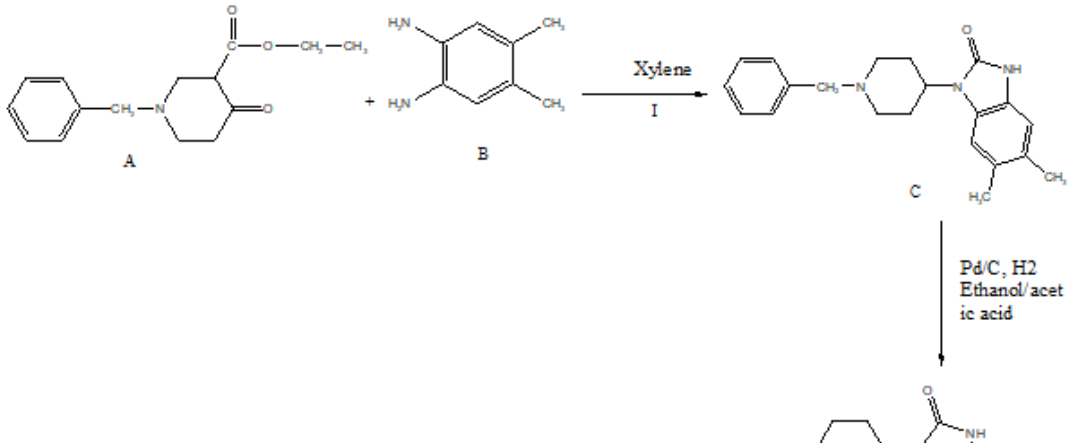


Figure 11: Synthesis of Benzitramide

When 1-Benzyl-4-oxo-piperidine-3-carboxylic acid ethyl ester (A)react with 4,5-Dimethyl-benzene-1,2-diamine (B) in presence Xylene it gives intermediate 1-(1-Benzyl-piperidin-4-yl)-5,6-dimethyl-1,3-dihydro-benzimidazol-2-one (C) when this intermediate reacts with Pd/C, H2 in presence of Ethanol or acetic acid it will give Benzitramide (D) [84-85].

Omeprazole

Omeprazole [9] having benzimidazole heterocyclic ring which inhibit the Protein Pump in case of acidity. Since they are number of drug that antibiotics, NSAIDs, or non-steroidal anti-inflammatory drugs, such Diclofenac and ibuprofen, aspirin etc produce adverse effect like ulceration, gastric bleeding and dyspepsia. It also having activity of Antioxidant etc. Because the pyridine ring is protonated in the stomach acid environment, these PPIs function as prodrugs. This leads to a chemical rearrangement that first creates sulfenic acid and subsequently sulphonamide by dehydration. [86-90]. Omeprazole [9] has emerged as the preferred medication for treating oesophageal reflux and

other gastrointestinal issues associated with acidity which was first introduced in the 1970s. Because omeprazole is a reversible "proton pump" inhibitor, its action is caused via a series of prototrophic mechanisms that reduce the protonic activity of parietal cells. To accurately analyse the drug's chemistry and pharmacology, it is necessary to understand omeprazole [9] phototropic behavior in the aqueous environment, as demonstrated by its pKa values. [91-93].

Synthesis

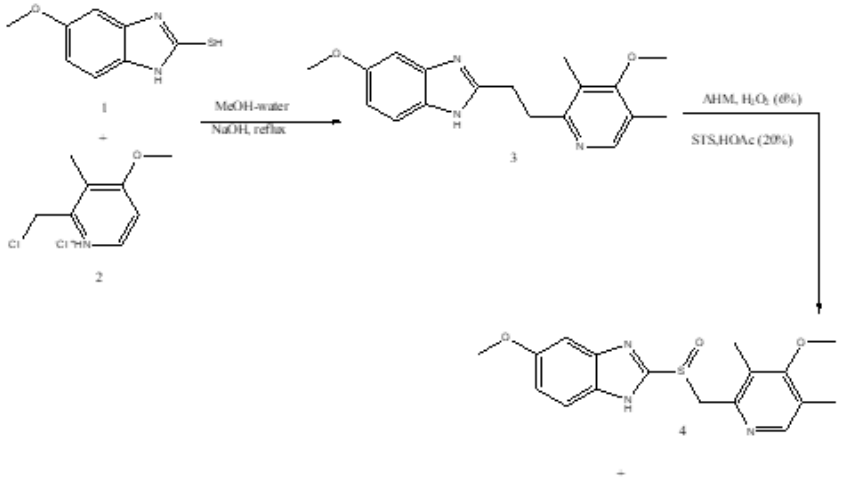


Figure 12: Key reaction conditions for the synthesis of omeprazole.

Scheme 7

When MTX 1 react with water and methanol in presence of NaOH, to increase solubility of MTX the, OMP-Cl2 is added. The mixture was stirred at refluxing at temperature for 60 min

The mixture was stirred at reflux temperature for 60 minutes before cooling to 20 degrees Celsius. The resultant suspension, sulfuric acid 3, was added with an AHM (1.78 g, 1.44 mmol) solution in water (40 mL). The agitation setting was 400 rpm. Using a dropping funnel, the mixture was progressively mixed with a 6% (w/w) aqueous H2O2 solution (172 mL, 303.44 mmol) over 90 minutes, keeping the temperature between 20 and 25°CTo keep the pH of the mixture at 9.3, a 40% (w/w) aqueous NaOH solution was added. STS (1.42 g, 5.72 mmol) was added to stop the reaction five minutes after the H2O2 was introduced. To crystallize the product, omeprazole 4, the pH was raised to 9.1 with a 20% aqueous HOAc solution. Throughout the next three hours, the mixture was agitated to maintain a pH of 9.1 and a temperature of 20-25°C. The suspension was then run through a Büchner funnel to filter. The product was washed twice with 100 mL of water and then dried in a vacuum tray dryer at 30°C until it reached a consistent mass. Produced 76.19 grams. [94,95]

Pantoprazole

Pantoprazole [10] is belonged to benzimidazole ring which having ability to inhibit Proton Pump Inhibitor such as gastric H+, K+ -ATPase inhibitors. It having therapeutic effect towards peptic ulcer and gastroesophageal reflux disease [96,97]. Pantoprazole [10] having chemical name 5-(difluoromethoxy)-2- [[(3,4- dimethoxy-2-pyridinyl) methyl] sulfinyl]-1H-benzimidazole [98-99]. The frog stomach was shown to have the enzyme hydrogen-potassium-adenosine triphosphatase (H'K'-ATPase), also known as a proton pump, in the early 1970s. The gastric parietal cell surfaces that line the secretory canaliculi were shown to be the site of this pump's activity. [100,102].

Synthesis

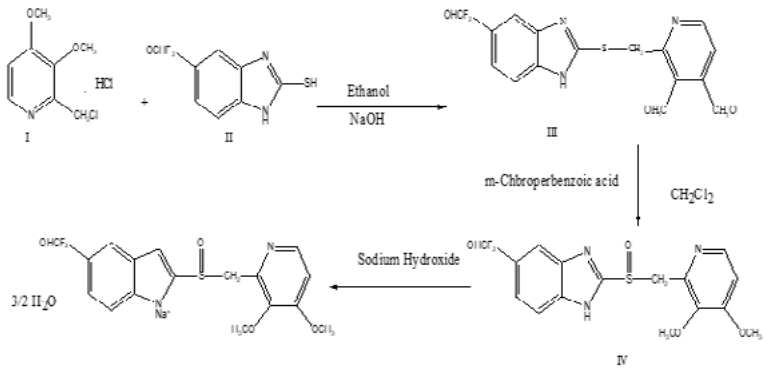


Figure 13: Preparation of pantoprazole sodium.

When 2-Chloromethyl-3,4-dimethoxy-pyridine (I) react with 5-Fluro-1H-benzoimidazole-2-thiol formyl fluoride (II) in presence of ethanol and sodium hydroxide it will form 2-(5-Fluro-1H-benzoimidazol-2-ylsulfanylmethyl)-pyridine-3,4-dicarbaldehyde (III) when this react with m-Chloro perbenzoic acid in presence of Dichloromethane it will of intermediate of 2-(3,4-Dimethoxy-pyridin-2-ylmethanesulfinyl)-5-methyl-1H-benzimidazole (IV) react with sodium hydroxide it will form Pantoprazole. [103,104].

Telmisartan

In 1998, telmisartan [6], a nonpeptide ACE II inhibitor that is highly selective and competitive, received approval for the treatment of hypertension. Over the last 20 years, chemists attempted to investigate telmisartan's sustainable green chemical method.

Essential hypertension is a major risk factor for cardiovascular disease, responsible for one-third of all deaths worldwide. The majority of antihypertensive medications target the renin angiotensin system (RAS), which regulates blood pressure and electrolyte /fluid balance. According to Rise, telmisartan was synthesized for the first time with an overall yield of 21%. Large-scale production has exacerbated a number of the route's disadvantages.

These include:

a) Excessive nitric acid and sulfuric acid in the nitration of three leads to environmental pollution problems

b) Purification of eight generated amount of waste liquid; and

c) The alkylation of eight generates regio isomer.

There have since been reports of additional synthetic pathways for telmisartan. A technique using Suzuki cross coupling with a palladium catalyst was reported by Alex. O-cresol was the starting material selected by Wang et al. to achieve a 19% overall yield of telmisartan.

The optimal procedures that are frequently employed in the manufacturing of telmisartan for commercial usage were disclosed by Shen et al. [105-114]

Synthesis

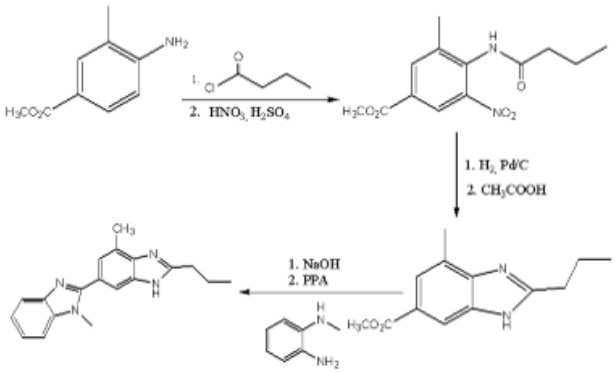


Figure 14: Synthesis of the benzimidazole intermediate (1) from 4-amino-3-methylbenzoic acid methyl ester via multi-step functional group transformations.

Scheme 9

It began with the raw material 4-amino-3-methylbenzoic acid methyl ester 2 and proceeded to generate the benzimidazole derivative 5 through amidation, mixed acid nitration, nitro group reduction, and amine cyclization. The target intermediate 1 was generated by saponifying 5 and condensing it with N-methyl-1,2-phenylenediamine 6 at 150 °C in the presence of polyphosphoric acid (PPA).

Unfortunately, the use of expensive raw materials and pricy or hazardous reagents, such as flammable palladium-carbon (Pd/C), excess PPA for cyclization as a dehydrating agent and solvent, and mixed acid for nitration, made this protocol complex to operate, increase the risk of safety hazards, result in high production costs, and seriously pollute the environment. [115-119]

Albendazole

Albendazole [ABZ, 14], also known as methyl-[(5-propylthio)-1H-benzimidazozol2-yl], is a popular broad-spectrum anthelmintic medication used in both veterinary and human medicine to prevent and cure infectious disorders caused or transmitted by parasites. Carbamate [120-124]. ABZ [14] has shown high efficacy in treating neurocysticercosis, the most common parasitic infection of the central nervous system caused by the larval form of Taenia solium and the main cause of acquired epilepsy, in the Andean region of South America, Brazil, Central America and Mexico, China, the Indian subcontinent and South-East Asia, and sub-Saharan Africa. [125-127]. The medicine is characterized as forming as colorless crystals with a melting temperature between 2080C and 2100C and being essentially insoluble in water. The compound was

patented in 19753. [128-130]. Even though ABZ [14] has been known for more than 35 years and is widely used in treatment [131]. Chiral chromatography is among the most effective of the many techniques available for large-scale enantiomeric separation. Preparative chromatography is a valuable choice for enantiomeric separation due to its robustness, speed, simplicity, and application, especially with the advancement of chiral stationary phases (CSPs) and chromatographic instruments. [132,133].

Synthesis

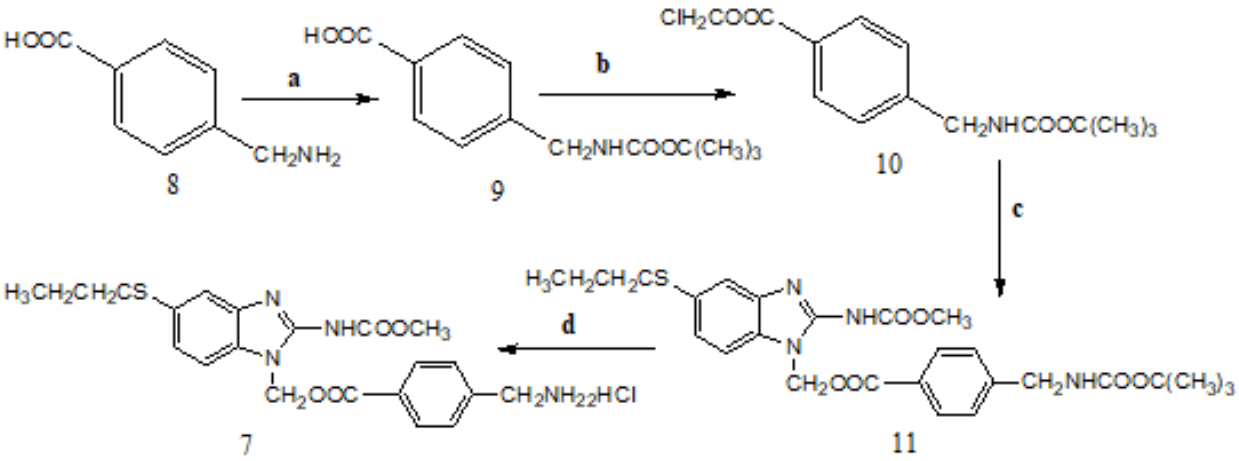


Figure 15: Synthesis of the albendazole derivative (7) through protection, coupling, and deprotection steps.

Scheme 10

(a) O[CO2C(CH3)3]2, tert-BuOH; (b) ClCH2OSO2Cl, CH2Cl2, H2O, [CH3(CH2)3]4N(HSO4), NaHCO3; (c) 1, DMF; (d) HCl/EtOH.

Using the method described by Binderup et al., commercial 8 was treated with ditert-butyldicarbonate to yield 9. This could then be converted to 10.6. Following a two-hour reaction mixture of one and NaH in DMF, a solution of ten in DMF was added. 1-[4-(tert-butoxy-carbonylaminomethyl) benzoyloxymethyl]-albendazole, as a combination of two isomers, was obtained by filtering the suspension after adding water after the reaction had been going on for 12 hours. A second part of compound 11 remained in the mother liquor together with the otherisomer, but their separation was unsuccessful. Compound 11 was produced by recrystallization of the residue from benzene. After compound 11 was dissolved in ethyl acetate, ethanol was added to a 3 N hydrochloric acid solution. To obtain the dihydrochloride of 7, the precipitate was recovered and recrystallized from methyl-ether (Scheme 1). IR, 1 H NMR, 13C NMR, and MS data were used to determine the structures [134-140].

Astemizole

The molecular structures of histamine and the traditional antihistamines are unrelated to those of astemizole [16]. There are also noticeable pharmacological variations. Right now, astemizole is the most effective and selective HI antagonist that is currently understood. It acts for an incredibly long time without having any central (sedative) effects. [141-142]. Janssen Pharmaceutica made the first identification of astemizole in 1977. It was first marketed under the trade name Hismanal after receiving approval from the US Food and Drug Administration in 1988. The product, known as “Astemizole Hismanal,” was initially offered for sale in North American markets by Janssen Pharmaceutica (now Johnson and Johnson) in the middle of the 1980s. In 1999, the business decided to remove it from international markets. When exposed to allergies and histamine, astemizole can prevent bronchial and nasal reactions. Astemizole [16] has been shown in multiple investigations to have antimalarial properties as well as selectivity for dopamine, muscarinic acetylcholine, and 5-HT receptors. [143-145]. The primary and potentially lethal toxicity associated with astemizole therapy is cardiotoxicity, often known as torsades de pointes arrhythmia. Although the exact mechanism of astemizole’s cardiotoxic effects is unknown, it is believed to follow a similar, if not the same, one as terfenidine. Astemizole and its principal desmethylastemizole metabolite seem to function similarly to terfenidine in inhibiting cardiac delayed potassium rectifier (Ik) channels. [146-148]

Synthesis

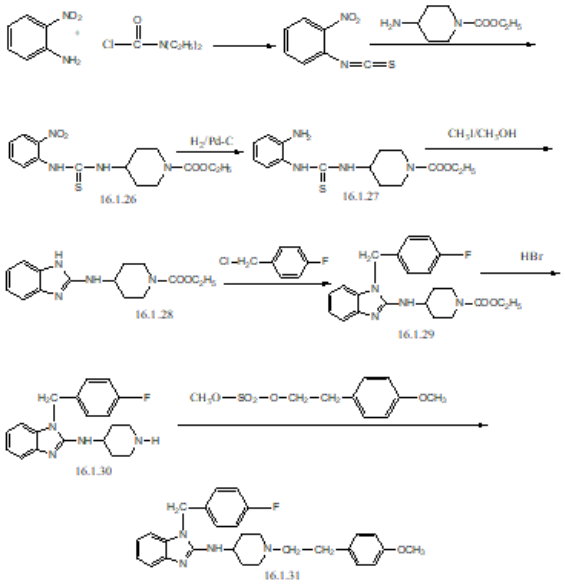


Figure 16: Synthesis of the albendazole derivative (7) through protection, coupling, and deprotection steps.

Scheme 11

Astemizole,1- [(4-fluorophenyl) methyl]-N-[1-[2-(4-methoxyphenyl) ethyl] [4-piperidinyl]-benzimidazol-2-amine (16.1.31) is produced by a multi-step synthesis of 2-nitroisothiocyanobenzol and 1-carbethoxy-4-aminopiperidine, which leads to the creation of a thiourea (16.1.26) derivative. The product's nitro group is reduced and further S-methoxidized. Intermolecular cyclization under reaction circumstances results in N-[1-[2-(4-carethoxy)]], a derivative of benimidazol. There is -4-piperidinyl]benzimidazol-2-amine (16.1.28). After being synthesized, the derivative of aminobenzimidazole is alkylated using 4-fluorobenzylchoride to form 1-[(flurophenyl)methyl]. - N-[1-[2-(4carethoxy)] Benzimidazol-2-amine [4-piperidinyl] (16.1.29). Hydrobromic acid hydrolyzes the carbethoxyl group of the resultant product (16.1.29) to generate a non-substituted derivative of piperidine (16.1.30), which is then alkylated with 2-(4-methoxyphenyl) ethylmetanesulfonate to form astemizole (16.1.31) [149-157].

Therapeutic application of Benzimidazole

Antineoplastic

In 2017, the United States Food and Drug Administration (USFDA) approved abelacilib [ABM, 22] as antineoplastic medication for the treatment of human epidermal growth factor receptor 2 (HER2)-advanced or metastatic hormone receptor (HR)-positive or negative breast cancer. Cell cycle disruption is typically the first step toward the expansion of cancerous cells. A protein known as retinablastoma (Rb) suppresses cancer by limiting the cell cycle during the G1 to S phase transition. Cancer cells' hyperproliferation and disruption of the cell cycle are caused by the phosphorylation of this protein by cyclin-dependent kinases (CDK 4 & 6). By dual inhibiting the CDK 4 and 6 enzyme complex, ABM [22] indirectly limits the phosphorylation of the Rb proteins, which further causes cell cycle arrest in the G1 stage phase and restricts the proliferation of cancer cells. [158-162]. The orally bioavailable CDK4/6 inhibitor to be approved is abelacicol (Verzenio, LY2835219). Abemaciclib [22] inhibits Rb phosphorylation, which results in G1 arrest, as predicted by its capacity to inhibit CDKs. Abemaciclib [22] showed exceptional efficacy against several tumor types in xenograft tumors, including lung, colorectal, MCL, Glioblastoma and AML [163-165]. It also used in treatement of Prostate cancer. Since they are two type of prostate cancer [166-169]. In 2018 by the European Medicines Agency (EMA) was approve to treat postmenopausal women with metastatic breast cancer that is hormone receptor positive (HR+) and human epidermal growth factor receptor 2 negative (HER2). [170-173].

When the bendamustine [18] redox behavior was studied at PGE, it was shown to exhibit a one-step reduction and an irreversible, pH-dependent oxidation that happens when the equal amount of protons and electrons are transferred. An alkylating derivative is bendamustine [18]. [174-175]. Bendamustine [18], initially created by Ozegowski and Krebs, is a highly promising medication that can be used to treat a variety of tumor illnesses, including multiple myeloma and non-Hodgkin's lymphoma. [176-184]. A strong pan-HDAC inhibitor with advantageous pharmacokinetic characteristics is pracinostat. HDACs have become common and useful therapeutic targets for anticancer drugs. Five HDAC inhibitors have been licensed thus far for use in cancer treatment, and numerous others are undergoing various stages of clinical studies for

a variety of purposes. [185-190]. The US Food and Drug Administration (US FDA) has approved four HDACis for the treatment of multiple myeloma, colorectal cancer (CRC), skin/peripheral T-cell lymphoma, and belinostat. These are vorinostat, romidepsin, panobinostat, and belinostat. In addition to having strong anticancer action, Pracinostat [20] is an oral active pan-HDACi with good absorption, distribution, metabolism, excretion, high bioavailability, and safety. Pracinostat [20] inhibits the interleukin 6/signal transducer and activator of transcription 3 (STAT3) signaling pathway, hence suppressing the spread and proliferation of breast cancer. [191-196]. A novel hydroxamic acid HDACI that is active on the oral route, pracinostat [20] (SB939), selectively inhibits class I, II, and IV histone deacetylases in vitro and exhibits strong antiproliferative action against a broad range of tumor cell lines. It is effective in preclinical models of AML, especially those with FLT3-ITD or JAK2 or JAK2 inhibitors. It works both by itself and in conjunction with pacritinib alterations involving internal tandem duplication [197-200].

Analgesic

Benzitramide [18] (Anquil) and droperidol are structurally similar; the only difference is that the piperidine ring's 4,5 position does not have a double bond. It is categorized as an antipsychotic drug and also falls within the pharmacological group of D2 antagonists. Benperidol, which treats schizophrenia and regulates deviant, antisocial sexual behavior, has sedative, serotonin-, N-cholinoblocking, and somewhat M-cholinomimetic properties. [201-204]

Antiparasitic

In poor nations, parasitic diseases continue to be a serious health concern, primarily affecting the younger population. According to reports, benzimidazole 2-carbamates (BZC), which are primarily employed as anthelmintic drugs, such as mebendazole (Mbz) and albendazole (Abz), prevent protozoa from growing in vitro. Trichomonas vaginalis with Giardia lamblia

Albendaazole [14] interacts with Giardia cytoskeleton tubulin as part of its anti-Giardia lamblia attack. [205-209]. In underdeveloped countries with low resources for maternal health, it is crucial to properly record the health advantages of anthelmintic treatment during pregnancy. A study was conducted in western Sierra Leone to assess the effectiveness of albendazole and iron-folate supplements in managing maternal iron deficiency and anemia. The goal was to prioritize interventions. [210-213]. The anthelmintic drug albendazole [14] is used to treat many parasitic worm species in both humans and animals. It is a member of the benzimidazole methylcarbamates class of compounds. As ivermectin, praziquantel, and ABZ are three of the most significant anthelmintic medications. [214-216]. A parasite infection spread by food that damages muscles is called trichinellosis. where it was treated with albendazole [14,217-218]. Benzoldehyde's therapeutic effect in angiostrongyliasis. The central nervous system's various alterations were examined in a BALB/c mouse model, and the preventive benefits of benzaldehyde plus albendazole were examined [219-221].

Antacid

A new series of benzimidazole derivatives with modified pyrid-2-yl moiety and polyhydroxy sugar attached to the N-benzimidazole moiety have been produced and assessed as orally bio-available anti-inflammatory and anti-ulcerogenic medicines. These substances' anti-inflammatory and anti-ulcerogenic properties were compared to diclofenac and omeprazole. The medications include omeprazole [9], lansoprazole, pantoprazole [10], rabeprazole, and esomeprazole. PPIs are commonly used to treat acid reflux and other gastrointestinal issues. [222-227]. To treat gastric acid hypersecretion disorders, UniDesign redesigns CYP102A1 for stereoselective metabolism of omeprazole (OMP) [9], a proton pump inhibitor, starting from an active but nonstereoselective triple mutant. [228-229]. Helicobacter pylori (H. pylori) is a pathogenic bacterium that affects the stomach. Omeprazole is used to treat Helicobacter pylori [228-233]. Omeprazole [9] is a powerful anti-acid medication. Its absorption and mechanism of action are intimately tied to its prototropic behaviour. [234].

Electrochemical impedance spectroscopy and electrochemical polarization curves were used to analyze Omeprazole (OMP)'s corrosion inhibition performance on X60 steel in 0.5M H2SO4.Omeprazole can oxidize and decrease in a variety of supportive electrolytes. Both processes rely heavily on the pH of the fluid. Omeprazole [9] showed distinct oxidation and reduction signals at both high and low pH levels in the supporting electrolyte. [235-237]. The DOTA connection was strategically placed in the pantoprazole [10] molecule to reduce any potential detrimental effects of the structural change. This chemical is expected to improve functional MRI of the human GI system by delineating the stomach and colon walls [238-240]. Pantoprazole [10], a novel proton pump inhibitor (PPI) licensed in the US, is used to treat erosive esophagitis associated with GERD [241-244].

Anti-Histamine

Astemizole [16] can be a histamine. I antagonist has minimal blood-brain barrier penetration. It preferentially binds to lung histamine receptors over cerebellar histamine. The reduced incidence of central nervous system (eNS) effects in humans could be attributed to the presence of vreceptors. It has little affinity for acetylcholine receptors and lacks beta-adrenergic action. High dosages show signs of serotonin antagonism and affinity for alpha-adrenergic receptors. [245-250]. Astemizole [16] is a

long-acting H1-histamine receptor antagonist that has no molecular similarities to recognized medicines. When administered in low doses to guinea pigs, astemizole binds less to cerebellum H1-histamine receptors than to lung H1-histamine receptors. This may explain why human volunteers did not experience sedation or decreased psychomotor performance. [251-254]. Clinical studies in humans have demonstrated Astemizole's [16] great efficacy and long-lasting activity against histamine and allergens in the skin, nose, and bronchi. Astemizole [16] inhibited wheal and flare responses to intradermal histamine in a dose-dependent and long-lasting manner. [255-259]. Astemizole [16], unlike first-generation antihistamines like diphenhydramine and hydroxyzine, is termed 'nonsedating' and lacks the anticholinergic effects of first-generation H-1 antagonists. Patients presenting with astemizole overdose are typically awake or mildly drugged [260-262].

Cardiovascular

Essential hypertension is a major risk factor for cardiovascular disease, accounting for one-third of global fatalities. Antihypertensive medications primarily target the renin angiotensin system (RAS), which regulates blood pressure and electrolyte/fluid balance [263-264].

Telmisartan, marketed as MICARDIS, is a top-selling antihypertensive medication known for its great binding affinity to the AT1 receptor, good absorption, and once-daily dose. (265-266

The FDA approved telmisartan, a highly selective angiotensin II receptor antagonist, as an effective antihypertensive medication [269]. Telmisartan's [6] ability to cross the blood-brain barrier and sluggish clearance from the brain leads to prolonged activity in the brain. It also has an impact on the phenotype of reactive astrocytes under neuroinflammatory situations. [270-272] Additionally, the Telmisartan [6] is thought to prevent Alphavirus-induced encephalitis [273-274]. Telmisartan [6] has been shown to prevent ischemia/reperfusion injury in a mouse model by blocking AT1R. It also provides brain protection, including anti-apoptosis, anti-inflammatory, and anti-oxidant advantages in intracerebral haemorrhage rats [275-277].

Summary and Discussion

Benzimidazole (Abemaciclib, Bendamustin, and Pracinostate) is being explored for the treatment of malignancies such as breast, ovarian, cervical, lung, liver, colorectal, prostate, and pancreatic. Analgesic (Benzitramide), acidic (Omeprazole, Pantaprazole), cardiovascular (Telmisartan), parasitic (Albendazole), histaminic or allergic (Astemizole). Telmisartan has both cardiovascular and anti-diabetic activity and will also inhibit CHIKV. Benzimidazole has been used to create a variety of medications and compounds with a wide range of actions. Molecular docking and other software applications have been used to determine distinct protein bindings with different benzimidazole derivatives.

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Citation: Manoj Ramesh Kumbhare, Pravin R. Dighe, Siddhi M. Chandak, Darshana Santosh Varma, Harsha I. Narkhede and Ajaykumar R. Surana. "A Comprehensive insight into Synthesis and Applications of Benzimidazole Derivatives." J Chem Analyt Biochem (2025):106. DOI: 10.59462/JCAB.2.1.106