

# Synthesis and Pharmacological Profile of Benzimidazoles

*Kantharaju Kamanna*

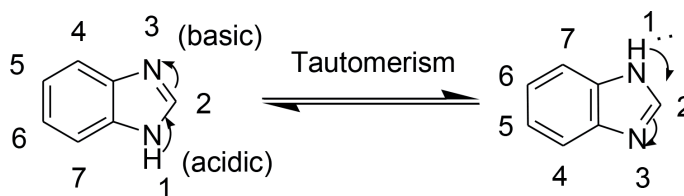
## Abstract

Benzimidazoles are a class of heterocyclic, aromatic compounds which share a fundamental structural characteristic of six-membered benzene fused to five-membered imidazole moiety. Molecules having benzimidazole motifs showed promising application in biological and clinical studies. Nowadays it is a moiety of choice which possesses many pharmacological properties extensively explored with a potent inhibitor of various enzymes involved in a wide range of therapeutic uses which are antidiabetic, anticancer, antimicrobial, antiparasitic, analgesics, antiviral, and antihistamine, as well as used in cardiovascular disease, neurology, endocrinology, ophthalmology, and more. The increased interest for benzimidazole compounds has been due to their excellent properties, like increased stability, bio-availability, and significant biological activity. This book chapter mainly discussed recent synthetic methods developed for the benzimidazole derivatives and their pharmacological properties exemplified on several derivatives.

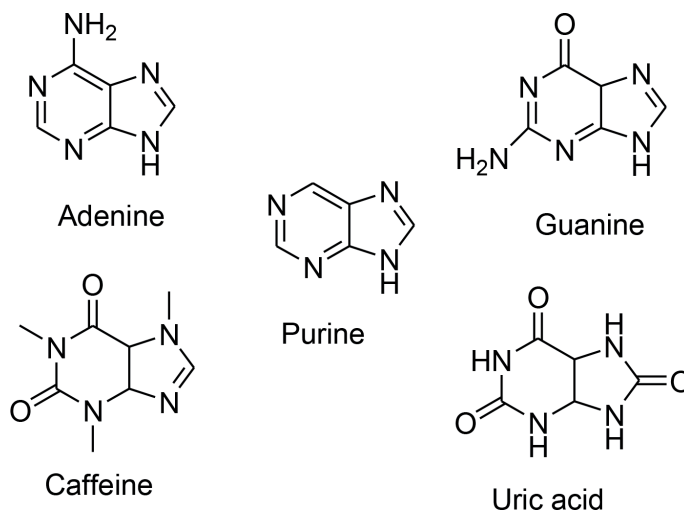
**Keywords:** benzimidazole, heterocycle, medicinal chemistry, structure activity relationship, biological activity

## 1. Introduction

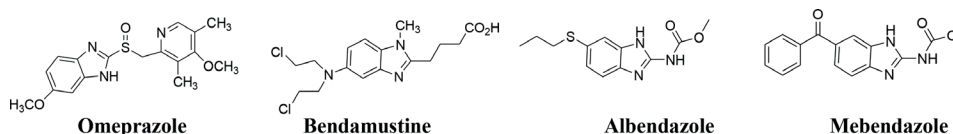
The biological application of benzimidazole nucleus is discovered way back 1944, when Woolley speculated that benzimidazoles resemble purine-like structure and elicit some biological application [1]. Hence benzimidazole structure found isosters of naturally occurring nucleotides, which allows them to contact easily with the biopolymers of the living system. Later, Brink discovered 5,6-dimethylbenzimidazole as a degradation product of vitamin B<sub>12</sub> and subsequently found some of its analogs having vitamin B<sub>12</sub>-like activity [2, 3]. These initial study reports emerged to explore various decorated benzimidazole motif discoveries by the medicinal chemist. Over the few decades of active research, benzimidazole has evolved as an important heterocyclic nucleus due to its wide range of pharmacological applications. Hence, it's worth to understand the basic chemistry and structure of such a wonderful molecule. Benzimidazole is formed by the fusion of benzene and imidazole moiety, and numbering system according to the IUPAC is depicted in **Figure 1**. Historically, the first benzimidazole was prepared in 1872 by Hoebrecker, who obtained 2,5 (or 2,6)-dimethylbenzimidazole by the reduction of 2-nitro-4-methylacetanilide [4]. Benzimidazoles which contain a hydrogen atom attached to nitrogen in the 1-position readily tautomerize, and this may be depicted in **Figure 1**. This basic "6 + 5" heterocyclic structure is shared by another class of chemical compounds existing in nature shown in **Figure 2**.



**Figure 1.**  
Tautomeric forms of benzimidazole.



**Figure 2.**  
Common biomolecules with a "6 + 5" heterocyclic structure.



**Figure 3.**  
Benzimidazole-based drugs.

Among the members of this group of molecules are well-known building blocks for biopolymers, such as adenine and guanine, two of the five nucleic acid bases, uric acid, and caffeine. From this basic structural similarity, it is not too surprising that benzimidazole nucleus has emerged biologically as an important pharmacophore with a privileged structure in medicinal chemistry. Nowadays it is a moiety of choice which possesses many pharmacological properties. The most prominent benzimidazole compound in nature is *N*-riboseyl-dimethylbenzimidazole, which serves as an axial ligand for cobalt in vitamin B<sub>12</sub>. The pharmacological application of benzimidazole analogs found potent inhibitors of various enzymes involved and therapeutic uses including as antidiabetic, anticancer, antimicrobial, antiparasitic, analgesics, antiviral, antihistamine, and also neurological, endocrinological, and ophthalmological drugs [5–13].

The use of benzimidazole started many years back in 1990 onward, a vast number of benzimidazole analogs synthesis were reported, which resulted in increased stability, bioavailability, and significant biological activity. Some of the well-known active drugs with benzimidazole ring are mentioned in **Figure 3**, omeprazole, bendamustine,

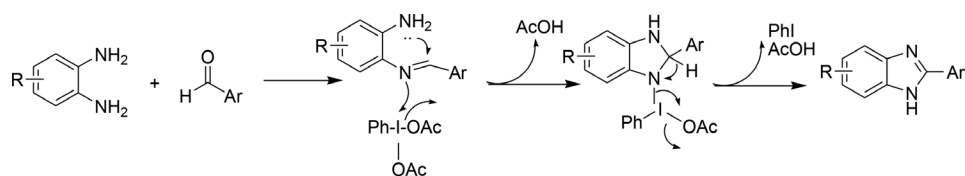
albendazole, and mebendazole. This chapter is mainly focused on the chemistry of the benzimidazoles and on the recently reported synthesis and mechanisms, structural aspects, and pharmacological applications with biological and clinical studies.

## 2. Overview of benzimidazole synthesis

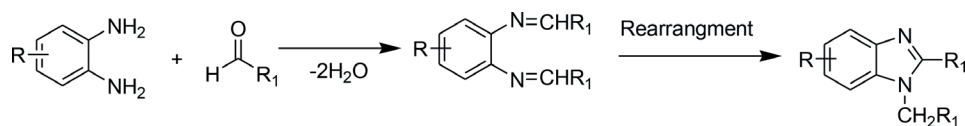
Experimentally the simple method for the synthesis of benzimidazole derivatives begin with benzene containing nitrogen functions at *ortho*-position to each other *o*-phenylenediamine (OPD) is well documented. In this section several synthetic methodologies are grouped according to the starting material which is used for the benzimidazole motif synthesis reviewed.

### 2.1 Synthesis of benzimidazoles by the reaction of substituted aldehyde with OPD

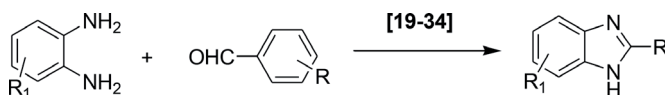
The reaction of OPD with aromatic/aliphatic aldehyde under suitable condition for the synthesis of 2-substituted benzimidazoles is well-known. Since the reaction involved oxidation, it required oxidative condition. The oxidation reaction may be carried out in the presence of air or more conveniently by oxidizing agent such as cupric acetate first introduced by Weidenhagen [14–16]. This method reported the reaction of OPD with aldehyde in the presence of water or alcoholic solution in the presence of cupric acetate. The formed cuprous salt of benzimidazole is decomposed with hydrogen sulfide which gave free benzimidazole after filtration. This method isolated excellent yields of 2-substituted benzimidazoles of alkyl, aryl, and heterocyclic substituted moiety. Further Wright's group reported the synthesis of *N*-alkylated benzimidazoles using *N*-alkylated-*o*-phenylenediamine with aldehydes gave good yields of 1-substituted benzimidazole. The mechanism found the initial formation of a Schiff intermediate by the reaction of aldehyde with one of the amines of OPD, followed by cyclization to form the product (Figure 4). The researcher observed that, the reaction between OPD and aldehyde in the absence of a specific oxidizing agent results to either 2-substituted benzimidazoles or aldimines (Figure 5) product formation in some cases aldimines major and some cases 2-substituted benzimidazoles are the major or both form exists in equal amounts. Rao and Smith et al. independently reviewed the reaction between OPD and Aldehydes (Figure 6) as a simple and efficient method to synthesize benzimidazoles [17, 18]. Numerous methods



**Figure 4.**  
Mechanism of formation of benzimidazole catalyzed by oxidizing agent  $[PhI(OAc)_2]$ .



**Figure 5.**  
Synthesis of benzimidazoles via aldiminic intermediates in the absence of catalyst.



**Figure 6.**  
Synthesis of benzimidazole derivatives from OPD and aldehydes.

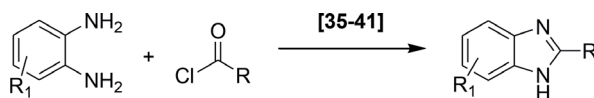
are reported for the condensation of substituted OPD with aryl/alkyl/heterocyclic aldehydes catalyzed by different oxidizing agents or metal triflate such as Sc (OTf)<sub>3</sub> or Yb (OTf)<sub>3</sub> [19], sulfamic acid [20], H<sub>2</sub>O<sub>2</sub>-HCl [21], FeBr<sub>3</sub> [22], PhI (OAc)<sub>2</sub> [23], LaCl<sub>3</sub> [24], H<sub>3</sub>IO<sub>6</sub>-SiO<sub>2</sub> [25], Ce (NO<sub>3</sub>)<sub>3</sub>.6H<sub>2</sub>O [26], NaHSO<sub>4</sub>-SiO<sub>2</sub> [27], mercuric oxide [28], chloranil [29], manganese dioxide [30], and I<sub>2</sub>/TBHP [31] and more methods [32–34]. This method isolated excellent yields of 2-substituted benzimidazoles with alkyl, aryl, and heterocyclic substituted moiety (**Figure 6**).

## 2.2 Synthesis of benzimidazoles by the reaction of aryl/alkyl/heterocyclic acid chloride with OPD

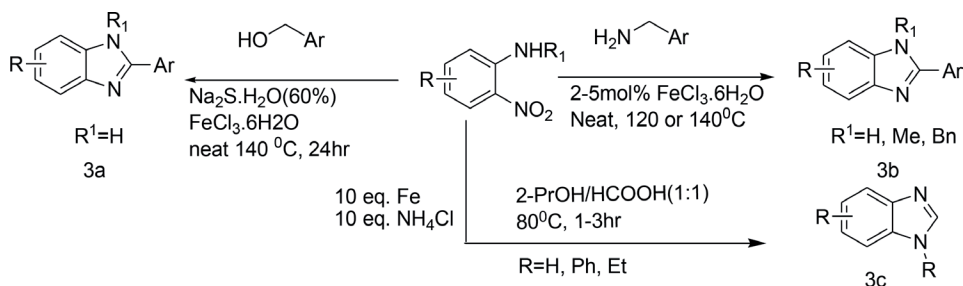
Other synthetic routes involved carboxylic acid with an OPD-required harsh condition in the presence of a strong acid at elevated temperatures with poor yield reported for the benzimidazole. Alternatively, a two-step synthesis is reported, wherein the OPD is treated with one equivalent of an acid chloride derivative and the resulting mono-acylated product is subjected to cyclodehydration under various conditions such as heating in aqueous acids/solvents or by greener methods such as glycerol [35], ionic liquid [Hbim] BF<sub>4</sub> [36], agro-waste extract WEPBA [37], heteropolyacid [38], BF<sub>3</sub>.Et<sub>2</sub>O [39], zeolite [40], KF-Al<sub>2</sub>O<sub>3</sub> [41], and more (**Figure 7**).

## 2.3 Synthesis of benzimidazoles by the reaction of substituted alcohol or amines with *o*-nitroarylamines

Researcher demonstrated alternative substrate *o*-nitroarylamine reaction with substituted alcohol or amines by using various reducing/redox agents (FeCl<sub>3</sub>) for the synthesis of benzimidazole in a single step. This procedure has got commercial importance due to reasonable yield isolation (**Figure 8**) [42–44].



**Figure 7.**  
Synthesis of benzimidazole starting OPD with acyl chloride derivatives.



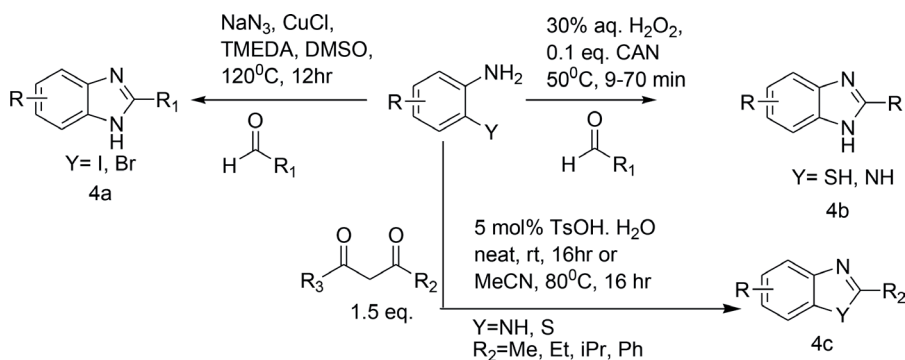
**Figure 8.**  
Synthesis of benzimidazoles starting *o*-nitroarylamines.

## 2.4 Synthesis of benzimidazoles by the reaction of aldehyde or EAA with *o*-substituted arylamines

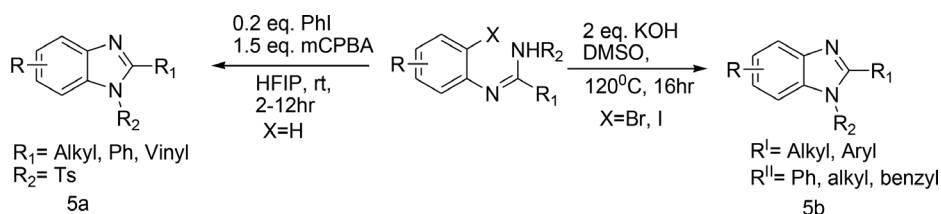
One-pot three-component reaction of 2-haloanilines, aldehydes, and  $\text{NaN}_3$  is also reported for the synthesis of benzimidazole [45]. The reaction catalyzed  $\text{CuCl}$  (5 mol%), and 5 mol% of TMEDA was reacted in DMSO at  $120^\circ\text{C}$  which gave the product good yields (**4a**). The reaction showed tolerance toward aliphatic, heterocyclic aldehydes, and functional groups such as ester, nitro, and chloro on aromatic afforded the desired products in moderate yields. Bahrami et al. reported useful synthetic methodology for the synthesis of benzimidazoles using catalytic redox cycling based on  $(\text{Ce(IV)}/\text{Ce(III)})/\text{H}_2\text{O}_2$  redox-mediated oxidation of the Schiff intermediate derived from differently substituted aromatic 1,2-phenyldiamines/2-thiol with a variety of aromatic aldehydes which resulted in isolation of the product in good yield (**4b**) [46]. Further, Bao et al. found Brønsted acid-catalyzed (TsOH) cyclization reactions of 2-amino anilines with ethylacetoacetate (EAA) under oxidant-, metal-, and radiation-free conditions (**4c**). In this method various 2-substituted benzimidazoles are obtained with different groups such as methyl, chloro, nitro, and methoxy linked on benzene rings which were tolerated (**Figure 9**) [47].

## 2.5 Synthesis of benzimidazoles by C-H amination of *N*-substituted amidines

Researcher demonstrated oxidative C-H amination of *N*'-aryl-*N*'-tosyl/*N*'-methylsulfonylamidines and *N,N'*-bis(aryl)amidines using iodobenzene as a catalyst to obtain 1,2-disubstituted benzimidazoles in the presence of *m*-CPBA which gave target product moderate to high yields (**5a**) [48]. Alternatively, other research group reported intramolecular *N*-arylations of amidines mediated by KOH in DMSO at  $120^\circ\text{C}$  (**5b**). The method allows diversely substituted products in moderate to very good yields (**Figure 10**) [49].



**Figure 9.**  
 One-pot three-component reaction for the synthesis of benzimidazole.



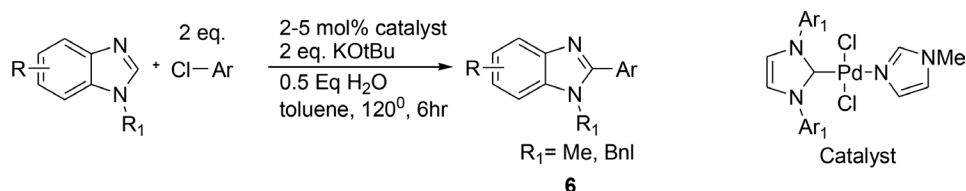
**Figure 10.**  
 Synthesis of benzimidazoles using *N*-substituted amidines.

## 2.6 Functionalization of benzimidazole to 2-substituted (hetero)aryl benzimidazole

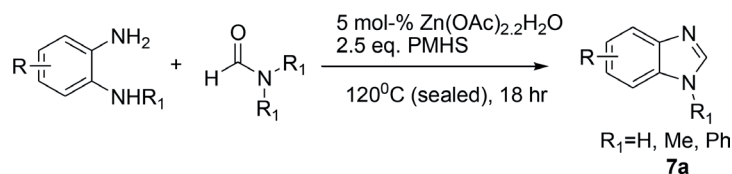
Shao et al. recently reported the synthesis of benzimidazoles via direct C–H bond arylation in the presence of a NHC–Pd(II)-Im complex. The method is tolerable to various activated and deactivated (hetero)aryl chlorides to get 2-(hetero)aryl benzimidazoles in high yields. It is a facile and an alternative methodology for the direct C–H bond arylation of (*benz*)imidazoles (**Figure 11**) [50].

## 2.7 Synthesis by the reaction of *N*-substituted formamides with OPD derivatives

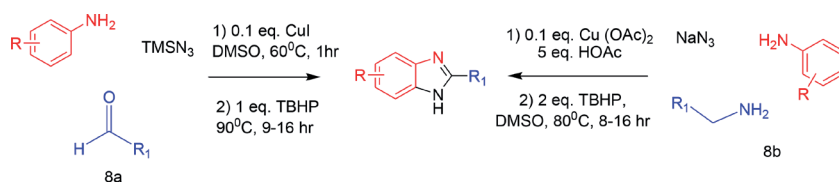
Bhanage et al. demonstrated efficient and convenient one-pot protocol synthesis of a benzimidazole derivative using various OPD derivatives and *N*-substituted formamides (C1 sources) in a zinc acetate-catalyzed cyclization in the presence of poly(methylhydrosiloxane) to afford corresponding products in good yields (**Figure 12**) [51].



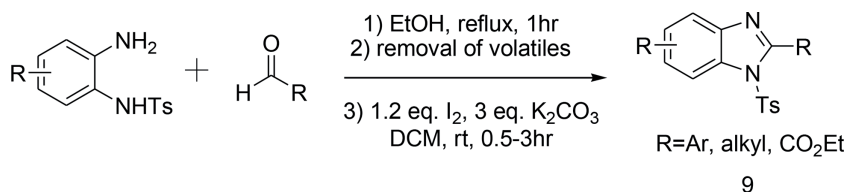
**Figure 11.**  
Synthesis of 2-substituted (hetero)aryl benzimidazoles.



**Figure 12.**  
*N*-Substituted formamides as C1 sources for the synthesis of benzimidazole.



**Figure 13.**  
One-pot three-component reaction.



**Figure 14.**  
Synthesis of 1,2-disubstituted benzimidazole.

## 2.8 Synthesis by one-pot three-component reaction

Punniyamurthy's group reported copper-catalyzed one-pot, three-component reaction of *N*-aryl imines, in which imine acts as a directing group by chelating to the metal center, which affords a potential route for the transformation of the commercial aryl amines, aldehydes, and azides into valuable benzimidazole with vast substrate scope and diversity (**8a**). Further, the same group is reported in copper(II)-catalyzed oxidative cross-coupling of anilines, primary alkyl amines, and sodium azide in the presence of TBHP at moderate temperature (**8b**). This one-pot protocol involves a domino C-H functionalization, transamination, *ortho*-selective amination, and cyclization sequence. The method is found tolerable to broad functional group and can be extended to the coupling of benzyl alcohols (**Figure 13**) [52, 53].

## 2.9 Synthesis of 1,2-disubstituted benzimidazole

Chang et al. demonstrated intramolecular C–H amidation using molecular iodine under basic conditions. The imine substrates required were readily prepared by condensation of aldehydes with OPD derivatives. The reaction is carried out in the absence of metal-free cyclization, works well with crude imines, and allows synthesis of series of *N*-substituted benzimidazoles. This method is tolerable to a variety of aromatic, aliphatic, and cinnamic aldehydes to produce diverse 1,2-disubstituted benzimidazoles (**Figure 14**) [54].

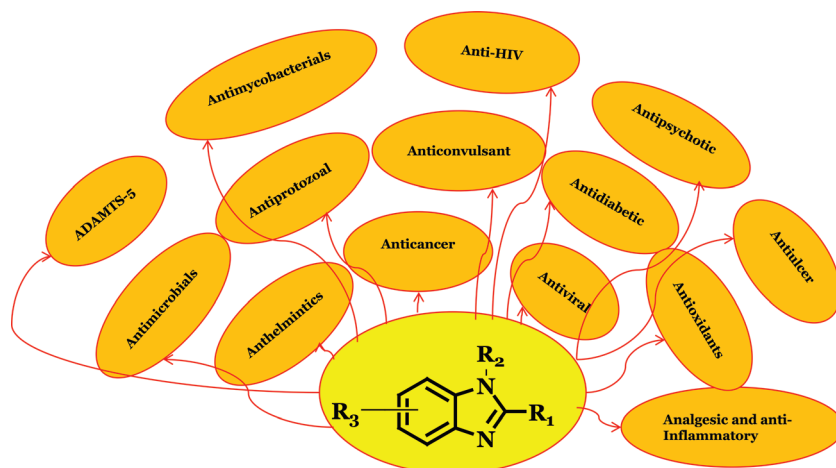
## 3. Pharmacological profile of benzimidazole derivatives

Benzimidazole moiety came in scenic after discovery of it as an integral part of the structure of the vitamin B<sub>12</sub> in the 1950s. In the early 1960s, it was developed as plant fungicides and later as veterinary anthelmintic. Further, a variety of veterinary anthelmintics were developed and marketed, including parabendazole, fenbendazole, oxfendazole, and cambendazole. In 1962 the first benzimidazole developed and licensed for human use was thiabendazole, and present more derivatives of benzimidazole that have been clinically approved are albendazole, mebendazole, and flubendazole as anthelmintic; omeprazole, lansoprazole, and pantoprazole as proton pump inhibitors; astemizole as antihistaminic; envirodine as antiviral; and candesartan cilexetil and telmisartan as antihypertensives. In literature various substituted derivatives of benzimidazole demonstrated various therapeutic agents such as anticancer, antiproliferative, antimicrobials, antivirals, antiparasites, anthelmintic activity, anticonvulsant, antioxidants, anti-inflammatory, antihypertensive, immunomodulators, proton pump inhibitors, anticoagulants, hormone modulators, and CNS stimulants as well as antidepressants, antidiabetics, anti-HIV, lipid level modulators, etc. and have made an important scaffold for the development of new therapeutic agents (**Figure 15**) [10, 12, 13, 55–79].

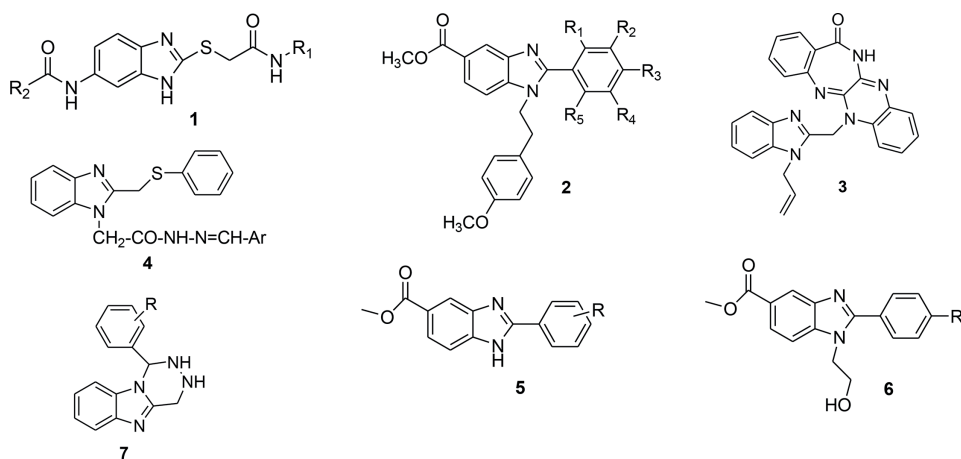
### 3.1 Anticancer activity

Yang et al. optimized the solubility problem of lead benzimidazole (**1**) through introducing *N*-methylpiperazine groups at the 2-position showing preliminary in vitro anticancer activities [80]. Raghavan et al. demonstrated synthesis and evaluation of 1-(4-methoxyphenethyl)-1H-benzimidazole-5-carboxylic acid derivatives (**2**). Caused maximum cell death in leukemic cells with a micromolar concentration [81]. Omar et al. demonstrated synthesis and docking studies of new series benzimidazole-pyrrole and tetracycline conjugates (**3**) tested against lung cancer cell line A549 and breast cancer cell line MCF-7 and found these molecules exhibited





**Figure 15.**  
Pharmacological profile of benzimidazole nucleus.



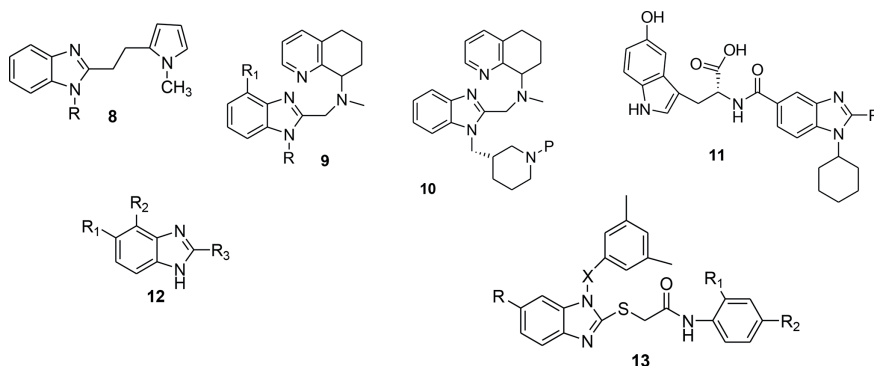
**Figure 16.**  
Benzimidazole derivatives with anticancer effect.

remarkable higher activity than standard [82]. Karthikeyan et al. discovered derivatives of benzimidazoles 2-(phenyl)-3*H*-benzo[*d*]imidazole-5-carboxylic acids (4) and its methyl esters for anti-breast cancer agents [83]. Yoon et al. demonstrated novel benzimidazole derivatives (5) in sirtuin inhibitors (SIRT1 and SIRT2) with antitumor activities [84]. El-Nassan's group showed novel 1,2,3,4-tetrahydro[1,2,4] triazino[4,5-*a*]benzimidazole (6) analogs of aryl and heteroaryl groups showing antitumor activity in human breast adenocarcinoma cell line (MCF-7) [85]. Singh and Tandon demonstrated 2-aryl-substituted 2-*bis*-1*H*-benzimidazoles (7) evaluated as a topoisomerase-I inhibitor, and more benzimidazole derivatives are in line for the development of drug candidates (Figure 16) [86, 87].

### 3.2 Antiviral activity

Benzimidazole and its derivatives showed antiviral activity via contact with different virus particles such as human cytomegalovirus (HCMV), human herpes simplex virus (HSV-1), human immunodeficiency virus (HIV), and hepatitis-B and hepatitis-C virus (HBV and HCV). Luo et al. demonstrated the hepatitis-B virus inhibition by





**Figure 17.**  
*Benzimidazole derivatives with antiviral activity.*

novel benzimidazole derivatives (**8**) in HepG2.2.15 cell line [88]. Gudmundsson et al. discovered alkyl and cyclic alkyl amine substituted *N*-(1*H*-benzimidazol-2-ylmethyl)-5,6,7,8-tetrahydro-8-quinolinamines (**9**) and screened them for anti-HIV-1 activity as CXCR4 antagonists [89]. Miller et al. demonstrated stereochemically defined *N*-substituted benzimidazoles containing cyclic alkyl amine side chains (**10**), and its SAR analogs showed CXCR<sub>4</sub> antagonist activity as anti-HIV agents [90]. Beaulieu et al. demonstrated few benzimidazole-based allosteric inhibitors (**11**) that bind to thumb pocket I of the HCV NS5B polymerase inhibition to HCV NS5B [91]. In another work, Wubulikasimu et al. evaluated a series of benzimidazoles bearing a heterocyclic ring as oxadiazole, thiadiazole, and triazole (**12**) for their inhibition against *Coxsackieviruses* B<sub>3</sub> and B<sub>6</sub> in Vero cells [92]. Monforte et al. reported *N*-1-aryl-benzimidazole 2-substituted analogs (**13**) inhibit HIV-1 nonnucleoside reverse transcriptase inhibitors (NNRTIs) [93]. Some of these analogs inhibited the replication of HIV at nanomolar concentration with low cytotoxicity (**Figure 17**) [94].

## 4. Conclusions

The modern drug discovery more emphasizes on benzimidazole nucleus containing pharmacophore extensively applied in the biological and clinical studies. In this book chapter reviewed, recent optimized synthetic methods reported by various research groups for the synthesis of benzimidazole derivatives are exemplified. Further, the therapeutic use of benzimidazole in important areas such as antidiabetic, anticancer, antimicrobial, antiparasitic, analgesics, antiviral, antihistamine, and more is discussed. In spite of the active, exhaustive, and target-based research on the development of many drug-like molecule development, the number of molecules that made its way to the market and clinic is not measurable. It can be probably due to lack of a comprehensive compilation of various research reports in each activity capable of giving an insight into the SAR of the compounds. The biological profiles of these new generations of benzimidazole would represent a fruitful matrix for further development of better medicinal agents.

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## Conflict of interest

The authors confirm that this book chapter content has no conflicts of interest.

## Abbreviations

2-PrOH	2-propanol
AcOH	acetic acid
ABTS	2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)
CAN	ceric ammonium nitrate
CH <sub>3</sub> CN	acetonitrile
Cu(OAc) <sub>2</sub>	cupric acetate
CuCl	copper chloride
CuI	copper iodide
DCM	dichloromethane
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
DPPH	2,2-diphenyl-1-picrylhydrazyl
EtOH	ethanol
EAA	ethyl acetoacetate
H <sub>2</sub> O <sub>2</sub>	hydrogen peroxide
H <sub>3</sub> IO <sub>6</sub> -SiO <sub>2</sub>	silica-supported periodic acid
HCl	hydrochloric acid
HCOOH	formic acid
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
I <sub>2</sub>	iodine
KOH	potassium hydroxide
KOtBu	potassium tertiary butoxide
<i>m</i> -CPBA	<i>m</i> -chloroperoxybenzoic acid
NaN <sub>3</sub>	sodium azide
NH <sub>4</sub> Cl	ammonium chloride
OPD	<i>o</i> -phenylenediamine
PhI(OAc) <sub>2</sub>	benzene (diacetoxyiodo)
PhI	iodobenzene
PMHS	poly(methylhydrosiloxane)
rt	room temperature
SAR	structure activity relationship
TBHP	<i>tert</i> -butyl hydroperoxide
TMEDA	<i>N,N,N',N'</i> -tetramethylethylenediamine
TMSN <sub>3</sub>	trimethylsilyl azide
TsOH	<i>p</i> -toluene sulfonic acid
WEPBA	water extract of papaya bark ash
Zn(OAc) <sub>2</sub>	zinc acetate

## **Author details**

Kantharaju Kamanna

Department of Chemistry, Peptide and Medicinal Chemistry Research Laboratory,  
Rani Channamma University, Belagavi, Karnataka, India

\*Address all correspondence to: [kk@rcub.ac.in](mailto:kk@rcub.ac.in)

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