BENZIMIDAZOLE SCAFFOLD IN DRUG DISCOVERY: A CRITICAL ANALYSIS OF ITS DIVERSE PHARMACOLOGICAL ACTIVITIES AND FUTURE OPPORTUNITIES

Raghvendra Dubey[1] & Priyal Jain[1]*

1. Department of Pharmaceutical Chemistry, Institute of Pharmacy, SAGE University, Indore 452020, Madhya Pradesh, India.

*Corresponding author:
Department of Pharmaceutical Chemistry,
Institute of Pharmacy,
SAGE University, Indore 452020,
Madhya Pradesh, India.

ABSTRACT:

Benzimidazole derivatives have emerged as an important class of heterocyclic compounds with diverse pharmacological activities and therapeutic applications. This review provides a comprehensive overview of benzimidazole chemistry, including synthetic methodologies, structure-activity relationships, and biological properties. Various approaches for synthesizing benzimidazoles are discussed, highlighting both classical and modern synthetic strategies. The review explores benzimidazole derivatives' broad spectrum of pharmacological activities, including antimicrobial, antiparasitic, anticancer, antioxidant, anti-inflammatory, antihypertensive, anticonvulsant, and antiviral properties. Structure-activity relationship studies revealing key structural features influencing biological activity are examined. The clinical relevance of benzimidazole-based drugs currently in use or under development is also addressed. This review aims to provide researchers with insights into the therapeutic potential of benzimidazole derivatives and guide future drug discovery efforts targeting this versatile scaffold. The ongoing research in optimizing benzimidazole structures presents promising opportunities for developing novel therapeutic agents to address various diseases and medical conditions.

KEYWORDS: Benzimidazole, anticonvulsant, antitumor, analgesic, antiulcer, Fuzed Benzimidazoles, Natural Nucleotides.

INTRODUCTION

The discovery of the biological potential of benzimidazole compounds dates back to 1944 when Woolley hypothesized their structural similarity to purines, suggesting possible biological applications. This observation led to recognizing of benzimidazoles as isosteric analogs of naturally occurring nucleotides, enabling them to interact with biopolymers in living systems. A significant milestone was reached when Brink identified 5,6-dimethylbenzimidazole as a degradation product of vitamin B12 and subsequently discovered some of its analogs exhibiting vitamin B12-like activity, further highlighting the biological relevance of this scaffold. Over the few decades of active research, benzimidazole has evolved as an important heterocyclic nucleus due to its wide range of pharmacological applications.

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)-dimethyl benzimidazole by the reduction of 2-nitro-4-methylacetanilide. The benzimidazole scaffold shares structural resemblance with fundamental building blocks of biopolymers, such as the nucleic acid bases adenine and guanine, as well as naturally occurring molecules like uric acid and caffeine. Owing to this inherent structural similarity, it is unsurprising that the benzimidazole nucleus has emerged as a privileged pharmacophore in medicinal chemistry, exhibiting significant biological relevance and potential for drug development[1].

Benzimidazole, alternatively known as 1*H*-benzimidazole or 1,3-benzodiazole, is a bicyclic heterocyclic aromatic compound in which a benzene ring is fused to the 4 and 5 positions of an imidazole ring. The benzo derivative of imidazole is referred to as benzimidazole. Although benzimidazole is the commonest name of the parent compound of the series, other names such as benzimidazole and 1, 3-benzodiazole (1) are often used. Nitrogen atoms are at the 1 and 3 positions of the ring system[2].

Figure 1: Benzimidazole

Benzimidazole compounds are an important class of heterocyclic compounds that have gained significant attention due to their diverse pharmacological activities and potential therapeutic applications. These compounds have been extensively studied and explored for their biological properties, making them a valuable subject in medicinal chemistry research.

Among these currently marketed benzimidazole drugs to treat several diseases, we can mention bendamustine, selumetinib, galeterone, and pracinostat as antitumor agents; pantoprazole, lansoprazole, esomeprazole, and ilaprazole as

proton pump inhibitors; bezitramide as an analgesic; mebendazole, albendazole, thiabendazole, and flubendazole as antihelminthics; ridinilazole as antibacterial; astemizole and bilastine as antihistamines; enviradine, samatasvir, and maribavir as antivirals; and candesartan and mibefradil as antihypertensive[2]. All the structures of the drugs which are derivatives of benzimidazole are shown in figure 2.

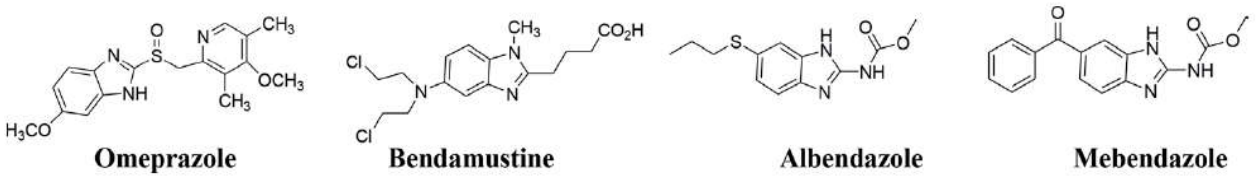


Figure 2: Derivatives of Benzimidazole

Overview of Benzimidazole Synthesis:

The commercial synthesis of benzimidazole involves the condensation of o-phenylenediamine with formic acid. Nature itself showcases the importance of this scaffold in the form of N-ribosyldimethylbenzimidazole, which serves as an axial ligand for cobalt in vitamin B12. Benzimidazole and its derivatives have demonstrated their therapeutic potential, finding applications as antiulcer and anthelmintic drugs. Additionally, an alternative synthetic route involves heating o-phenylenediamine with mono or dibasic acids, a method pioneered by Fischer in 1905[3]. This approach has proven useful in identifying fatty acids, as α-hydroxy acids, phenylacetic acid, and diphenylacetic acid can be converted into their corresponding benzimidazole counterparts when heated with o-phenylenediamine.

Phillips modification of the above procedure consists in refluxing with the o-phenylenediamine and mono basic acid in 4 N hydrochloric acid. The benzimidazole is then precipitated by neutralizing the solution with ammonium hydroxide. Benzoic acid gives only traces of 2-phenylbenzimidazole. Apparently this method is not applicable to the aromatic monobasic acid[4].

The synthesis of benzimidazoles, first reported by Hoebrecker in 1872, has undergone significant improvements and diversification over the past decades, driven by the scaffold's vast array of applications, which will be explored in the third part of this chapter. Advancements in classical synthetic methods have focused on optimizing reaction conditions, including the use of catalysts, solvents or solvent-free systems, alternative heating sources such as microwaves or ultrasound, and, importantly, the development of environmentally friendly or "green" protocols[5-7]. These efforts have aimed to enhance the efficiency and sustainability of benzimidazole synthesis, enabling broader accessibility and exploitation of this versatile heterocyclic scaffold.

Methods for synthesizing benzimidazole derivatives

Highlighting the diverse starting materials that can be employed for the synthesis of benzimidazoles: The vast majority of benzimidazole syntheses commence with benzene derivatives bearing nitrogen-containing functional groups in an ortho arrangement (Figure 3). In other words, the starting materials possess the structural motif represented by the given formula. Numerous synthetic methodologies have been reported for the construction of benzimidazoles, with most approaches relying on the condensation of ortho-phenylenediamine and its derivatives with carboxylic acids or aldehydes. This strategic choice of starting materials, featuring the requisite ortho-disposed nitrogen functions, sets the stage for the efficient assembly of the benzimidazole core through judicious selection and manipulation of the condensation partners[8].

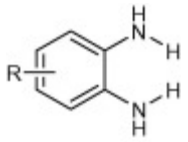


Figure 3: Benzene derivatives bearing nitrogen as functional groups

Benzimidazole compounds can be synthesized using various synthetic strategies, depending on the desired substituents and structural modifications. Some common methods for the synthesis of benzimidazole derivatives include:

1. Condensation Reactions: Benzimidazoles can be synthesized by the condensation of o-phenylenediamine with carboxylic acids, aldehydes, or their derivatives, such as nitriles, imidates, or orthoesters, under appropriate reaction conditions[9-10].

2. Phillips Reaction: The Phillips reaction involves the condensation of o-phenylenediamine with carboxylic acids or their derivatives in the presence of an acidic catalyst, such as polyphosphoric acid or conc. hydrochloric acid[11].

3. Oxidative Cyclization: Benzimidazoles can be obtained through the oxidative cyclization of o-phenylenediamines with suitable oxidizing agents, such as air, metal oxides, or hydrogen peroxide[12].

4. Transition Metal-Catalyzed Reactions: Various transition metal-catalyzed reactions, such as palladium-catalyzed cross-coupling reactions or copper-catalyzed amination reactions, have been employed for the synthesis of benzimidazole derivatives[13].

5. Microwave-Assisted Synthesis: Microwave irradiation has been utilized to accelerate the synthesis of benzimidazole compounds, often leading to improved yields and shorter reaction times compared to conventional heating methods.

6. Multicomponent Reactions: Benzimidazoles can be synthesized through multicomponent reactions, where three or more reactants are combined in a single step to form the desired product.

The synthetic strategies employed for the preparation of benzimidazole compounds often involve the optimization of reaction conditions, such as temperature, solvent, catalyst, and reaction time, to achieve efficient and selective synthesis.

Additionally, various protecting group strategies and functional group transformations may be employed to introduce desired substituents or modify the structure of the benzimidazole scaffold.

It is important to note that the specific synthetic route chosen for a particular benzimidazole derivative depends on factors such as the desired substituents, functional group compatibility, and the overall synthetic efficiency. Ongoing research in this field aims to develop more efficient, environmentally friendly, and cost-effective synthetic methodologies for the preparation of benzimidazole compounds with diverse biological activities and therapeutic applications.

The versatility of benzimidazole synthesis is exemplified by the wide range of starting materials that can be utilized, including:

1. O-Phenylenediamines, which serve as direct precursors through condensation reactions.
2. o-(N-acylamino and N-arylamino)arylamines and nitroarenes, providing access to substituted benzimidazoles.
3. o-Nitroarylamines and o-dinitroarenes, enabling the construction of the benzimidazole core through reduction and cyclization steps.
4. o-Substituted-N-benzylideneanilines, which undergo ring-closing reactions to form the desired heterocyclic scaffold.
5. Amidines, serving as valuable building blocks for benzimidazole synthesis through condensation pathways.
6. Other heterocyclic compounds, demonstrating the versatility of benzimidazole synthesis by exploiting the reactivity of diverse heterocyclic precursors.

This diversity in starting materials has facilitated the exploration and development of numerous synthetic strategies, expanding the accessibility and structural diversity of benzimidazole derivative[14].

1. **Synthesis of benzimidazoles by the reaction of substituted carboxylic acid with O-Phenylenediamines**

   Numerous catalyzed synthetic pathways have been explored for the preparation of benzimidazole derivatives. One such approach involves the condensation of o-phenylenediamine with ortho esters in the presence of Lewis acid catalysts, including ZrCl4, SnCl4, TiCl4, ZrOCl2·9H2O, and HFCl4. To provide a systematic overview, presenting the different synthetic methodologies for benzimidazoles according to the use of o-phenylenediamine as the starting material. This highlights the versatility of this precursor and the diverse strategies that have been developed to access the desired benzimidazole scaffolds from this common building block.

   Scheme-1: A comprehensive literature survey has demonstrated the facile reactivity of o-phenylenediamines with a wide range of carboxylic acids, enabling the synthesis of 2-substituted benzimidazoles in generally excellent yields. The condensation reaction is typically conducted by heating the reactants together under reflux

conditions, on a steam bath, or at elevated temperatures, including sealed-tube reactions. This straightforward and reliable approach, involving the direct coupling of o-phenylenediamines with carboxylic acid partners (figure 4), has emerged as a robust and widely employed strategy for accessing diverse 2-substituted benzimidazole derivatives, underscoring the synthetic utility of these readily available starting materials[15].

Figure 4: O-Phenylenediamine coupling with Carboxylic Acids

Scheme-2 : Among the various synthetic strategies, the Phillip's method[15] stands out as one of the most widely utilized approaches for the preparation of a diverse range of benzimidazoles. This method involves the condensation of o-diaminobenzenes with carboxylic acids or their derivatives, facilitated by heating the reactants in the presence of concentrated hydrochloric acid (figure 5). The robustness and generality of this acid-catalyzed condensation have rendered it a method of choice for accessing a broad spectrum of benzimidazole scaffolds. The prevalence of the Phillip's method can be attributed to its operational simplicity, mild reaction conditions, and the commercial availability of the requisite starting materials, making it a versatile and reliable synthetic tool in the benzimidazole chemistry repertoire.

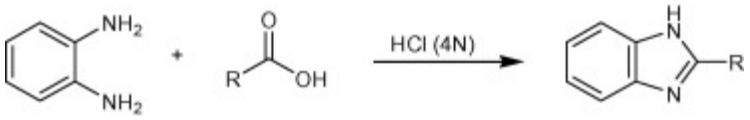


Figure 5: O-Phenylenediamine condensation with Carboxylic Acids in presence of HCl

Scheme-3 Hollan et al. who have reported the reaction of the appropriate imidate ester (trichloroacetimidate) with *o*-phenylenediamine or its salt gives the 2-trichloromethyl benzimidazole (figure 6) only at room temperature, and this is an important precursor for 2-carboxylic benzimidazoles[16].

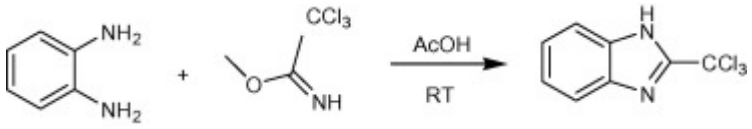


Figure 6: Synthesis of trichloromethyl benzimidazole

Scheme-4 Rithe et al. have reported various of 2-substituted benzimidazole derivatives in moderate to good yield have been prepared in one-spot reaction by condensation of *o*-phenylenediamine (0.01 mol) and different aromatic acid (0.01 mol) in the presence of ammonium chloride as catalyst at 80–90 °C (figure 7). The reaction is green and economically viable[17].

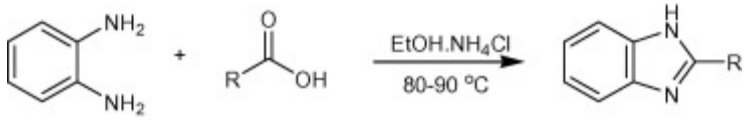


Figure 7: Synthesis of 2-substituted benzimidazole

2. Synthesis of benzimidazoles by the reaction of substituted aldehydes with O-Phenylenediamines (figure 8)

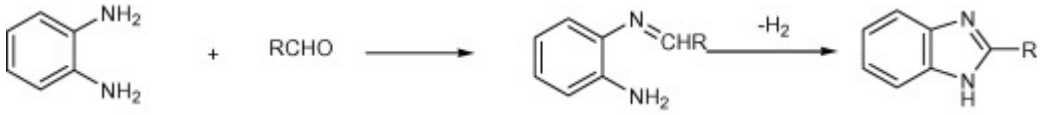


Figure 8: Synthesis of trichloromethyl benzimidazole

Scheme: 5 The condensation of phenylenediamines with aldehydes is achieved by various reported conditions. As shown in figure 9, this can be achieved in the presence of sodium metabisulphite[18].

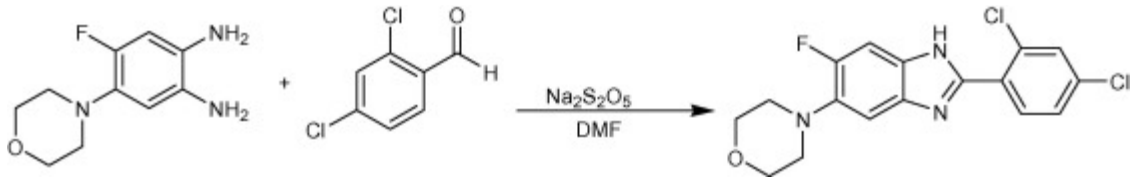


Figure 9: Synthesis of benzimidazoles catalyzed by sodium metabisulphite

Scheme: 6 Over heating in the presence of nitro benzene[19]. Mann et al. used a mixture of unsubstituted or substituted phenylenediamine and appropriate aldehyde in nitrobenzene heated at 140 °C., the mixture was cooled and filtered after adding water which gives benzamidazole (figure 10).

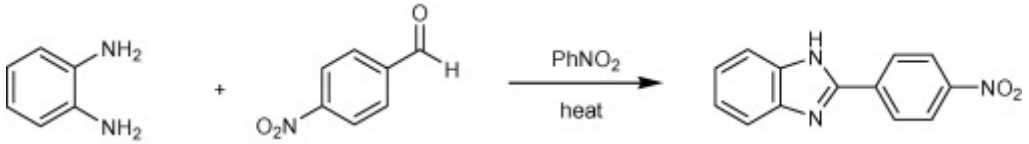


Figure 10: Synthesis of benzimidazoles using nitrobenzene as solvent

Scheme-7 Venkateswarlu et al. have reported the synthesis of benzimidazole derivatives, with the use of lanthanum chloride as an efficient catalyst One-pot synthesis of 2-substituted benzimidazole derivatives from *o*-phenylenediamine and a variety of aldehyde were carried out in the presence of lanthanum chloride (10 mol %) in acetonitrile at room temperature (figure 11)[20].

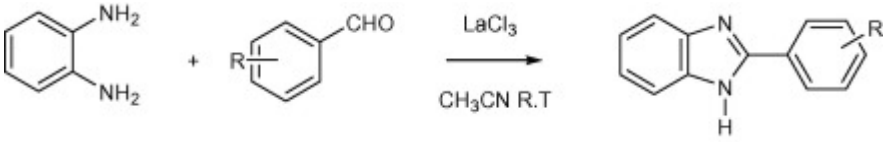


Figure 11: One-pot synthesis of 2-substituted benzimidazole derivatives

Scheme- 8 Rushi et al. have reported 2-substituted benzimidazoles have been synthesized in excellent yields in a single pot under solvent-free conditions from *o*-phenylenediamine and aldehydes in the presence of a catalytic amount of indium triflate [$In(OTf)_3$] (figure 12) at room temperature[21].

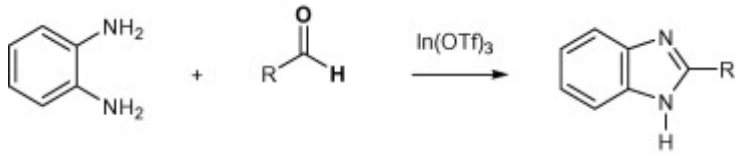


Figure 12: One-pot synthesis of 2-substituted benzimidazole derivatives

Scheme – 9 A series of benzimidazole derivatives were synthesized in good to high yields by reaction of *o*-phenylenediamine and different aromatic aldehydes in the presence of sodium hexafluroaluminate (figure 13), Na_3AlF_6, as an efficient catalyst at 50 °C [22].

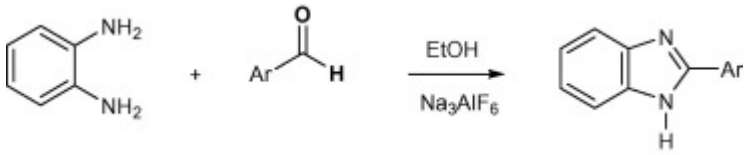


Figure 13: High yield synthesis of aromatic benzimidazole derivatives

Scheme- 10 Birajdar et al. have synthesized a mild and efficient approach for the synthesis of benzimidazole ring[23] through oxidative cyclization of *o*-phenylenediamine and different aldehydes using dioxane dibromide, as a user-friendly reagent (figure 14). This is a new, convenient and facile methodology for the synthesis of 2-substituted-1*H*-benzo[*d*]imidazoles.

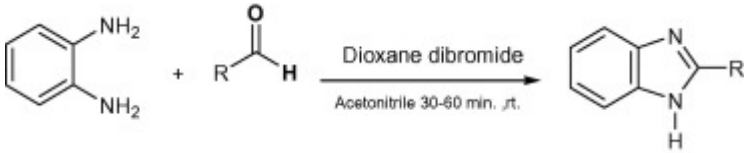


Figure 14: Efficient method of Synthesis of benzimidazole derivatives

Scheme – 11 Iodine catalyzed synthesis of 2-Aryl-1-arylmethyl-1*H*-benzimidazoles is demonstrated by Aniket et al. using phenylenediamine and aldehydes which are carried out at 80–90 °C (figure 15). New approach is promising and giving moderate yields with high purity and selectively single product in aqueous media[24].

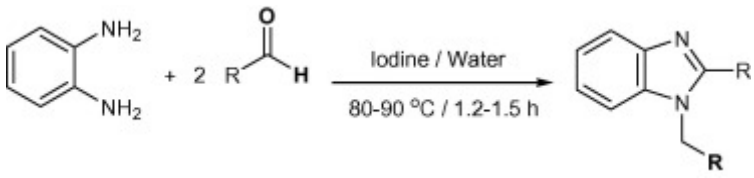


Figure 15: Iodine catalyzed synthesis of benzimidazole derivatives

3. Synthesis of benzimidazoles by the reaction of substituted acid anhydrides with O-Phenylenediamines

The reaction between acid anhydrides and o-phenylenediamines can produce two different types of products: benzimidazoles or N,N'-diacylphenylenediamines. Initially, it was believed that o-phenylenediamine reacts with acids to form benzimidazoles, while its reaction with acid anhydrides yields diacyl derivatives. However, this notion was later proven incorrect. The decisive factor influencing the product formation is the reaction time. If the reflux is prolonged for a sufficient duration, benzimidazoles can be obtained, often in good yields (figure 16). Specifically, when o-phenylenediamines are heated under reflux for several hours with acetic anhydride, they are completely converted to 2-methylbenzimidazole.

Figure 16: O-Phenylenediamines condensation with acid anhydrides

The reaction of *o*-phenylenediamines with acetic anhydride has been carried out with acetic anhydride alone or with acetic anhydride to which has been added sodium acetate, mineral acids, or acetic acid.

4. Synthesis of benzimidazoles by the reaction of esters with O-Phenylenediamines

Reaction of *o*-phenylenediamines with esters also yields benzimidazoles. Von Niementowski first investigated the reaction of esters and *o*-phenylenediamines to give benzimidazoles (figure 17). Equimolecular amounts of 3,4-diaminotoluene dihydrochloride and ethyl formate when heated in a sealed tube for 3 h at 225 °C give 84% of 5(or 6)-methylbenzimidazole hydrochloride[25].

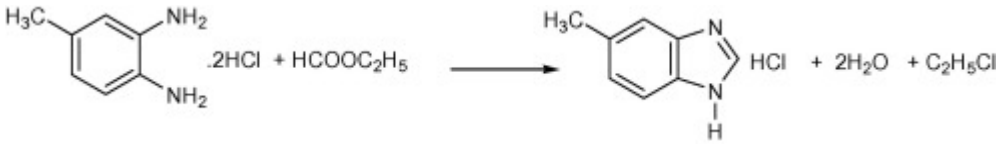
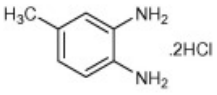
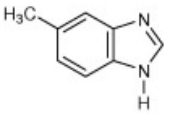
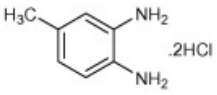
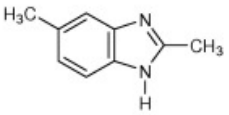
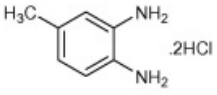
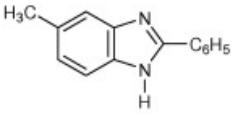


Figure 17: O-Phenylenediamines condensation with esters

5. Synthesis of benzimidazoles by the reaction of amides with O-Phenylenediamines

Relatively few amides have been used for the synthesis of benzimidazoles. However, good yields have been obtained in most cases. Equimolecular amounts of *o*-phenylenediamine dihydrochloride and benzamide when heated to 240–250 °C give an almost quantitative yield of 2-phenylbenzimidazole as shown in table 1.

Table 1: Synthesis of benzimidazole derivatives from amides

Diamine	Amide	Product
	$HCONH_2$	
	CH_3CONH_2	
	$C_6H_5CONH_2$	

6. Synthesis of benzimidazoles by the reaction of urea with O-Phenylenediamines

Rathod et al. have used *o*-phenylenediamine dihydrochloride and when it was heated with urea at 130 °C. gives 2(3H)-benzimidazolone[26]. By heating *o*-phenylenediamine and urea under reflux in amyl alcohol solution until the evolution of ammonia ceased (figure 18), Mistry and Guha have obtained a 95% yield of 2(3H)-benzimidazolone.

Figure 18: O-Phenylenediamines condensation with Urea

7. Synthesis of benzimidazoles by the reaction of acid chlorides with O-Phenylenediamines

The reaction between acid chlorides and o-phenylenediamines can lead to the formation of different products, depending on the experimental conditions employed. The products can be benzimidazoles, monoacylated o-phenylenediamines, or diacylated o-phenylenediamines. When acetyl chloride reacts with 3, 4-diaminotoluene in a benzene solution, the outcome varies based on the temperature of the reaction (figure 19). If the reaction is carried out without cooling, it yields 2, 5 (or 2, 6)-dimethylbenzimidazole. However, if the reaction is cooled, the product formed is diacetyl-o-phenylenediamine[27].

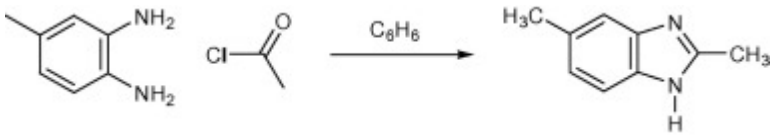


Figure 19: O-Phenylenediamines condensation with acid chlorides

8. Synthesis of benzimidazoles by the reaction of nitriles with O-Phenylenediamines

Cyanogen bromide will react with *o*-phenylenediamines to yield 2-aminobenzimidazoles in good yields; for example, 2-aminobenzimidazole (figure 20) may be prepared from cyanogen bromide and *o*-phenylenediamine[28].

Figure 20: O-Phenylenediamines condensation with nitriles

9. Synthesis of benzimidazoles by the reaction of ketones with O-Phenylenediamines

The reaction of *o*-phenylenediamines with a number of ketones has been investigated by Elderfield and Kreysa.

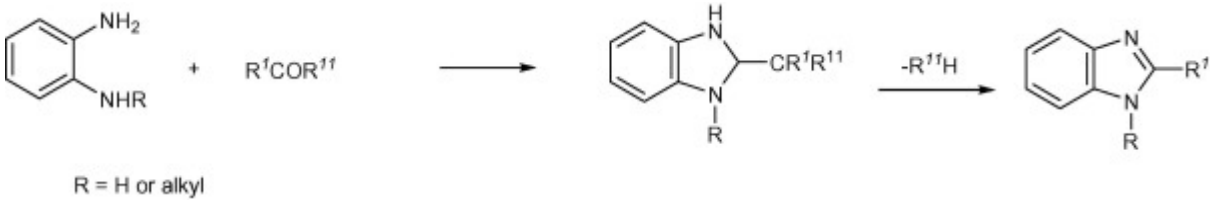


Figure 21: O-Phenylenediamines condensation with ketones

The reaction between o-phenylenediamine and ketones results in the formation of 2-disubstituted benzimidazolines. These benzimidazolines undergo decomposition upon heating, leading to the formation of a 2-substituted benzimidazole and a hydrocarbon (figure 21). In the case of unsymmetrically substituted benzimidazolines, the decomposition process can yield two different benzimidazoles, depending on whether the substituent R or the substituent R' is preferentially eliminated.

10. Synthesis of benzimidazoles by the reaction of potassium hydroxide and chloroform with O-Phenylenediamines

Grassi-Cristaldi and Lambarbi reported a convenient method for the synthesis of benzimidazole, which involves heating o-phenylenediamine with chloroform and potassium hydroxide dissolved in ethanol. This method is related to the approach involving the use of ethyl orthoformate (figure 22).

The use of ethyl orthoformate for the preparation of benzimidazoles was first introduced by von Walther and Kessler. They synthesized 1-phenyl-5-nitrobenzimidazole by reacting ethyl orthoformate with 4-nitro-2-aminodiphenylamine. This reaction demonstrated the utility of ethyl orthoformate in the synthesis of benzimidazole derivatives.

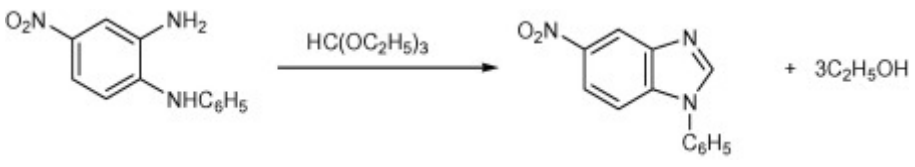


Figure 22: O-Phenylenediamines condensation with Chloroform

Diverse Pharmacological Activities of Benzimidazole derivatives

Through the course of many years of research, benzimidazole has emerged as an important heterocyclic system because of its existence in diverse biologically active compounds, such as antiparasitics, antimicrobials, antivirals, antifungals, anticonvulsants, antihypertensives, antihistaminics, analgesics, anti-inflammatory agents, anticancers, anticoagulants and proton pump inhibitors[29, 30].

The benzimidazole moiety gained prominence after its discovery as an integral part of the vitamin B12 structure in the 1950s. In the early 1960s, it was developed as plant fungicides and later as veterinary anthelmintics. Subsequently, various veterinary anthelmintics were developed and marketed, including parbendazole, fenbendazole, oxfendazole, and cambendazole. In 1962, thiabendazole became the first benzimidazole derivative approved for human use, followed by other clinically approved derivatives such as albendazole, mebendazole, and flubendazole as anthelmintics; omeprazole, lansoprazole, and pantoprazole as proton pump inhibitors; astemizole as an antihistamine; enviradine as an antiviral; and candesartan cilexetil and telmisartan as antihypertensives. Numerous substituted benzimidazole derivatives have demonstrated various therapeutic properties, including anticancer, antiproliferative, antimicrobial, antiviral, antiparasitic, anthelmintic, anticonvulsant, antioxidant, anti-inflammatory, antihypertensive, immunomodulatory, proton pump inhibitory, anticoagulant, hormone modulatory, and CNS stimulant, as well as antidepressant, antidiabetic, anti-HIV, lipid level modulatory activities, among others (figure 23). The benzimidazole scaffold has proven to be crucial for the development of new therapeutic agents[31, 32].

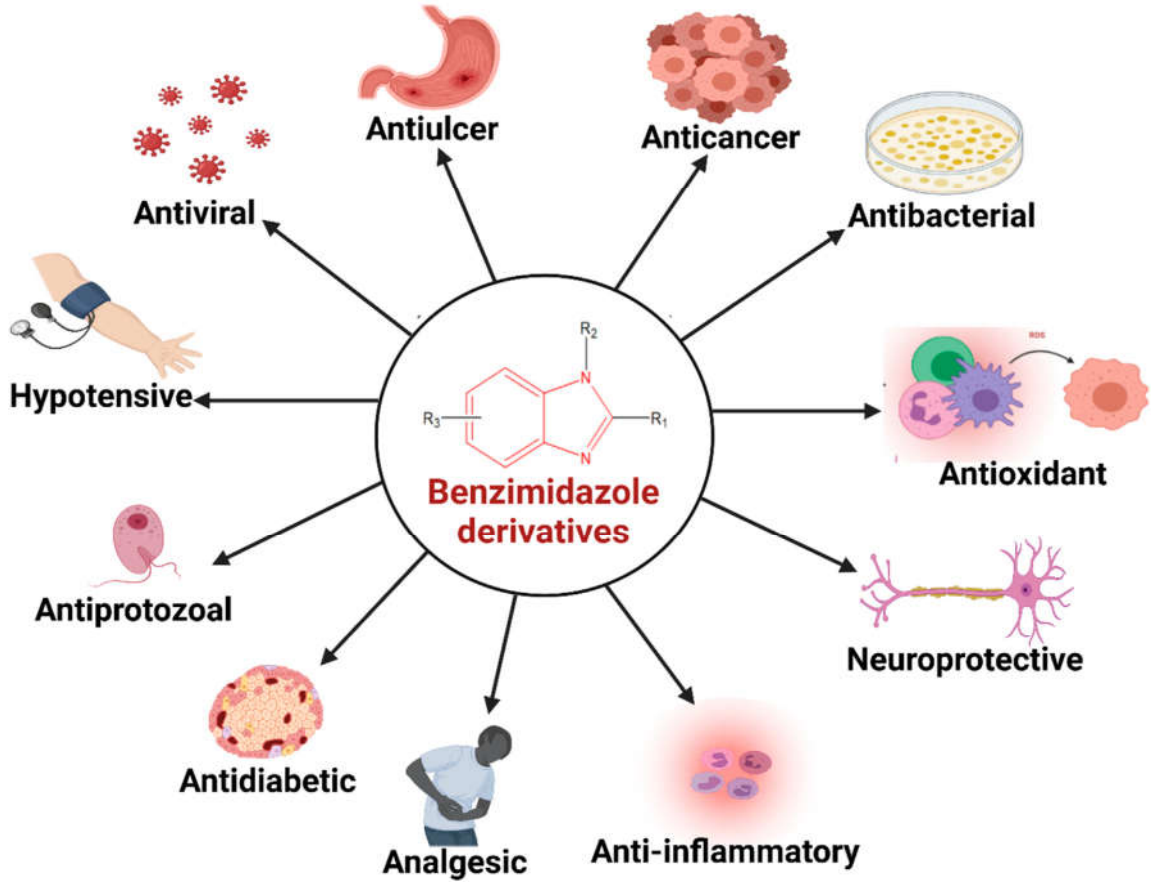


Figure 23: Various Pharmacological activities of Benzimidazole derivatives

Recent research recommends benzimidazole derivatives as potential EGFR and erbB2 inhibitors[33, 34], DNA/RNA binding ligands[35, 36], antitumor agents[37, 38], anti-Alzheimer agents[39], antidiabetic agents[40, 41], antiparasitic agents[42], antimicrobial agents[43, 44], antiquorum-sensing agents[45, 46], and antimalarial agents[47]. Intensive studies have demonstrated the use of the benzimidazole scaffold as key pharmacophore in clinically approved analgesic and anti-inflammatory agents[48]. Chiral benzimidazole derivatives were found to be NaV1.8 (voltage-gated sodium channels) blockers, which play a key role in the transmission of pain signals, with excellent preclinical in vitro ADME and safety profile[49]. Other benzimidazole derivatives have been shown to be anti- HIV-1 agents through the protection of APOBEC3G protein[50]. Benzimidazoles grafted with aromatic nuclei have been noted as antioxidant agents[51]. A correlation of the grafted organic functions on the benzimidazole scaffold has been found with their therapeutic potential[52]. Thus, carboxylic acids, carbamates, and amidines have been shown to be effective anticancer drugs[53], benzimidazole esters were reported as antifungal agents[54], and 2-aminobenzimidazole derivatives possesses very good antimicrobial activity[55].

Structure-activity relationship (SAR) studies have shown that 1,2,5,6-substituted benzimidazoles with various substituents are analgesic and anti-inflammatory agents[56]. Also, SAR studies were accomplished for antiviral, anticancer, antihelminthic, antimicrobial, antimycobacterial, antidiabetic, antiprotozoal, antipsychotic, antidepressant, and antioxidant benzimidazole derivatives[57-61].

1. Antimicrobial Activity: Many benzimidazole derivatives exhibit potent antimicrobial activity against a wide range of microorganisms, including bacteria, fungi, and viruses. They have been investigated for their potential use as antibacterial, antifungal, and antiviral agents.

The antimicrobial potential of benzimidazole moiety has been explored notably since late 1990s and early 2000s [62]. Considering the huge dimension of research conducted on antimicrobial property of benzimidazole derivatives after 2012, the following section focuses on the up-to-date information on antibacterial and antifungal activities, while antiviral, antiulcer, antiprotozoal and antitubercular properties are discussed in separate sections. Different benzimidazole based compounds with antibacterial and antifungal activities are shown in Figure 24[63].

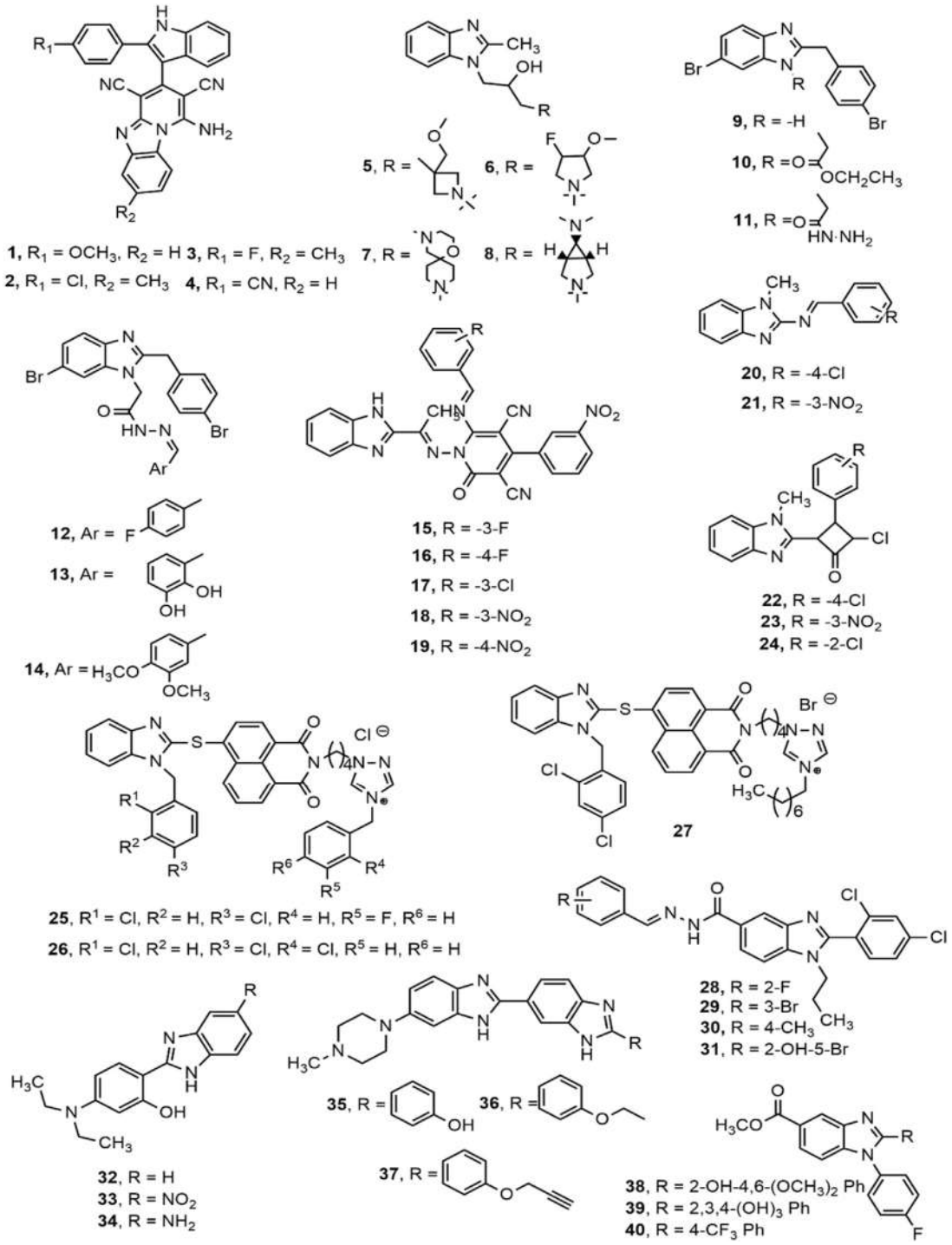


Figure 24: Benzimidazole based compounds with antibacterial and antifungal activities

2. Antiparasitic Activity: Benzimidazole compounds have shown promising activity against various parasites, such as helminths (worms) and protozoa. Some benzimidazole derivatives are used as anthelmintic drugs for the treatment of parasitic infections in humans and animals[64].

3. Anticancer Activity: Certain benzimidazole compounds have demonstrated anticancer properties by inhibiting the growth and proliferation of cancer cells. They have been studied for their potential use as anticancer agents, either alone or in combination with other chemotherapeutic drugs.

Among the anticancer drugs discovered in recent years, various benzimidazole derivatives have gained attention in anticancer agent development due to their diverse biological activities and clinical applications. The unique core structure of benzimidazole and its minimal toxicity property has made it an excellent scaffold in anticancer drug development[65]. Benzimidazole (also known as 1*H*-benzimidazole, 1,3-benzodiazole, benzoglyoxaline, iminazole, and imidazole) is an aromatic organic compound that contains a benzene ring fused to an imidazole ring at 4,5-position to form a bicyclic ring[66,67]. Historically, benzimidazole (*i.e*., 2,6-dimethylbenzimidazole) was first synthesized by Hoebrecker, followed by Ladenberg and Wundt in the 1870s[68]. Benzimidazole has a molecular weight of 118.14 g/mol and appears as white tabular crystals. Benzimidazole contains a hydrogen atom attached to nitrogen in the 1-position and can form a tautomer upon interaction with aprotic solvents, such as water or the existence of more than one benzimidazole molecule[69]. Nonetheless, substitution at position N will prohibit the tautomerism. Benzimidazole is a weak base with a p*K* value at 5.3 and 12.3 for pK_{a1} and pK_{a2}, respectively[70]. Therefore, the benzimidazole ring is highly stable and can withstand extreme conditions such as being heated under pressure up to 270 °C in a concentrated sulphuric acid solution or vigorous treatment with hot hydrochloric acid or with alkalis (figure 25)[71].

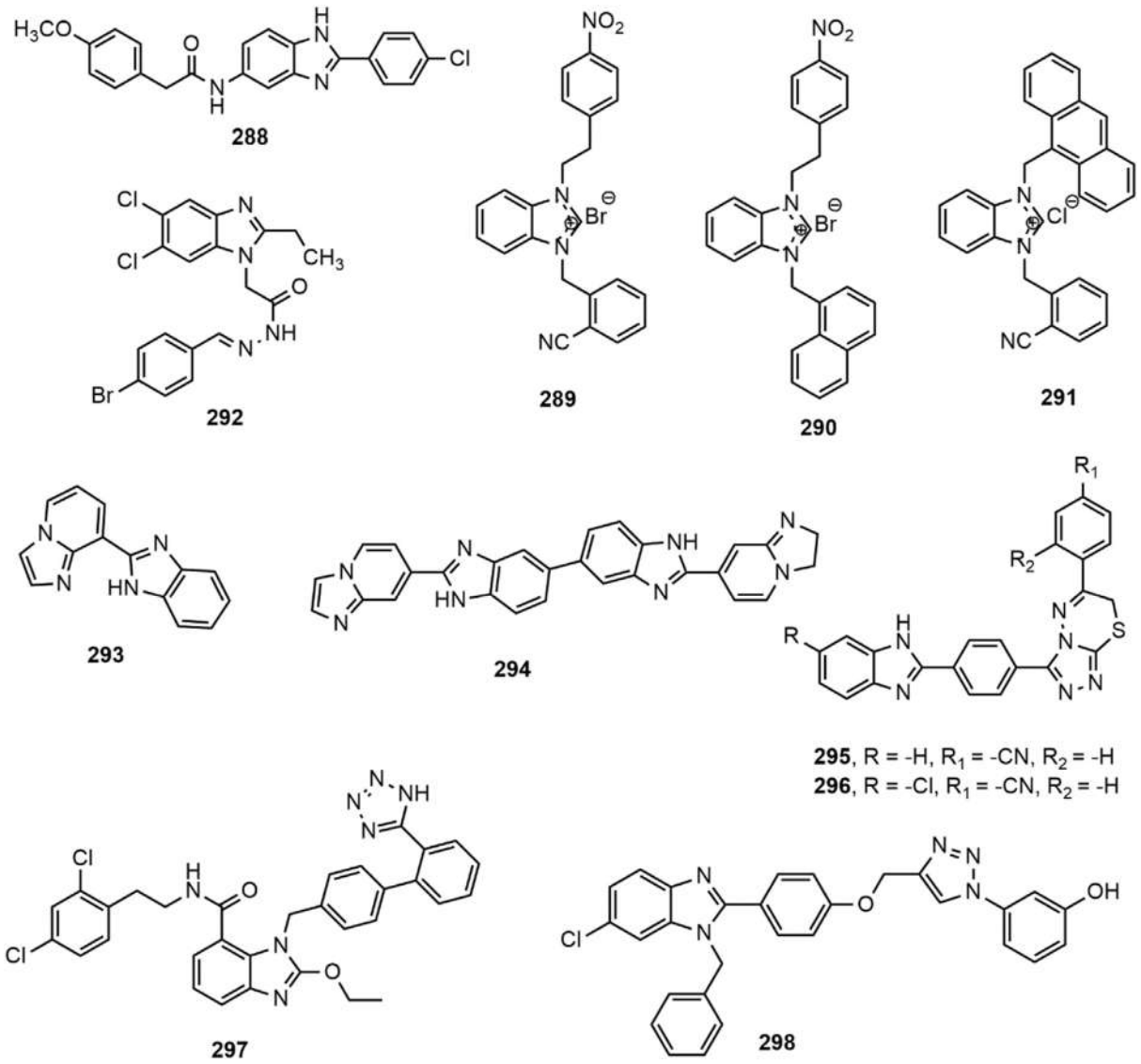


Figure 25: Anticancer benzimidazole derivatives

4. Antioxidant Activity: Some benzimidazole derivatives possess antioxidant properties, which make them potentially useful in the prevention and treatment of oxidative stress-related diseases, such as cardiovascular disorders, neurodegenerative diseases, and aging-related conditions[72].

Benzimidazoles (BMZs) are a family of anti-helminth drugs widely used in humans and livestock since 1960s to treat parasitic infections[73]. Many members of this family including albendazole (ABZ), fenbendazole (FBZ), mebendazole (MBZ) and thiabendazole (TBZ), are cost-effective FDA-approved drugs which are associated with very mild side effects (figure 26)[74]. In recent years, many studies have reported the anti-cancer effect of these drugs on a broad range of cancers[75-76]. The new findings have a great importance not only because of offering cancer chemotherapeutics with minimum side effects but also due to the considerable reduction of Research and Development (R & D) and commercializing costs compared to the costs of developing new anti-cancer agents, a substantial challenge of global pharmaceutical industry at the moment[77].

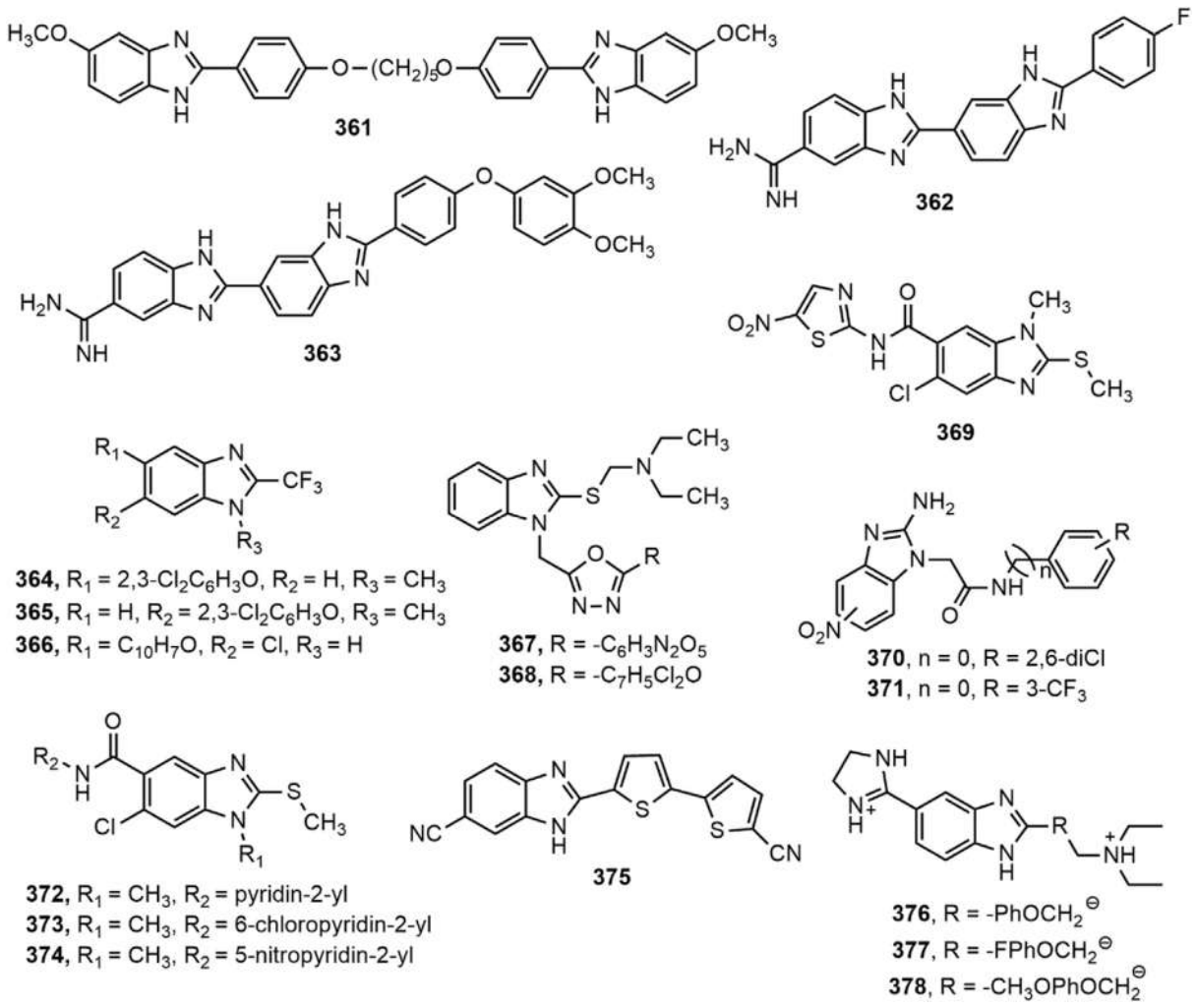


Figure 26: Antioxidant Benzimidazole derivatives

5. Anti-inflammatory & Analgesic Activity: Benzimidazole compounds have exhibited anti-inflammatory properties by modulating various inflammatory pathways and mediators[78]. They have been explored for their potential use in the treatment of inflammatory diseases, such as arthritis and autoimmune disorders.

Benzimidazole based compounds are of great importance as anti-inflammatory and analgesic agents because of their property to inhibit cyclooxygenases (COXs), enzymes involved in biosynthesis of important inflammatory mediators called prostaglandins[79]. Apart from the cyclooxygenases (COX), the benzimidazole derivatives interact with transient receptor potential vanilloid-1, cannabinoid receptors, bradykinin receptors, specific cytokines, and 5- lipoxygenase (5-LOX) activating protein. Thus, the compounds derived from benzimidazole moiety show the anti-inflammatory property[80]. Different benzimidazole derivatives with analgesic and anti-inflammatory properties are shown in Figure 26.

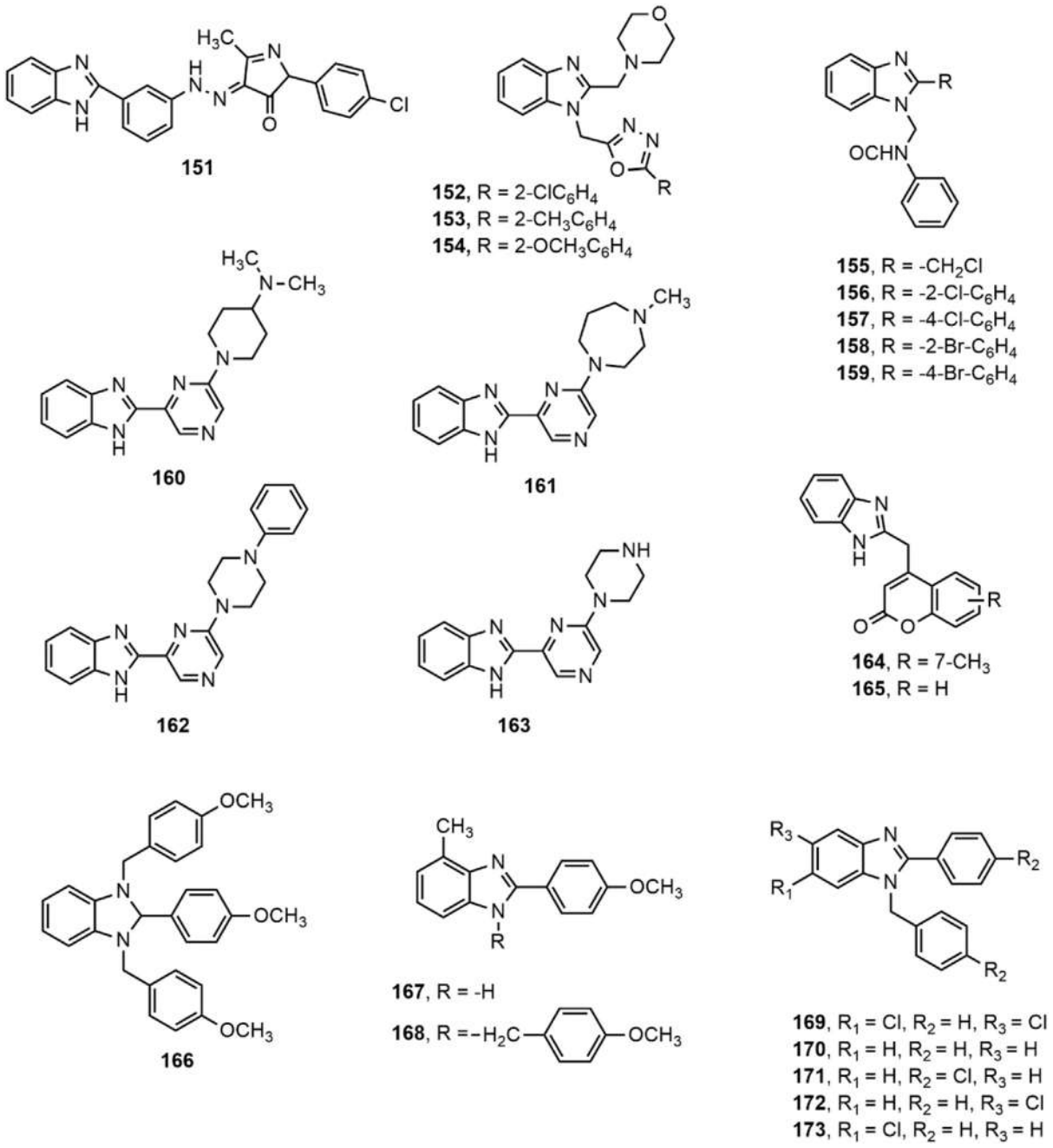


Figure 26: Analgesic & anti-inflammatory Benzimidazole Derivatives

6. Antihypertensive Activity: Certain benzimidazole derivatives have shown the ability to modulate blood pressure and have been studied for their potential use as antihypertensive agents.

A number of marketed antihypertensive drugs comprise benzimidazole moiety, Candesartan cilexetil and Telmisartan are two major examples. Categorically they are the antagonists of angiotensin II receptor playing important role in managing hypertension[81]. In recent years, a number of scientists have conducted research to prepare benzimidazole based novel antihypertensive agents which provided similar or even better efficacy than the conventional types of antihypertensive drugs. Different benzimidazole derivatives with antihypertensive activity are shown in Figure 27.

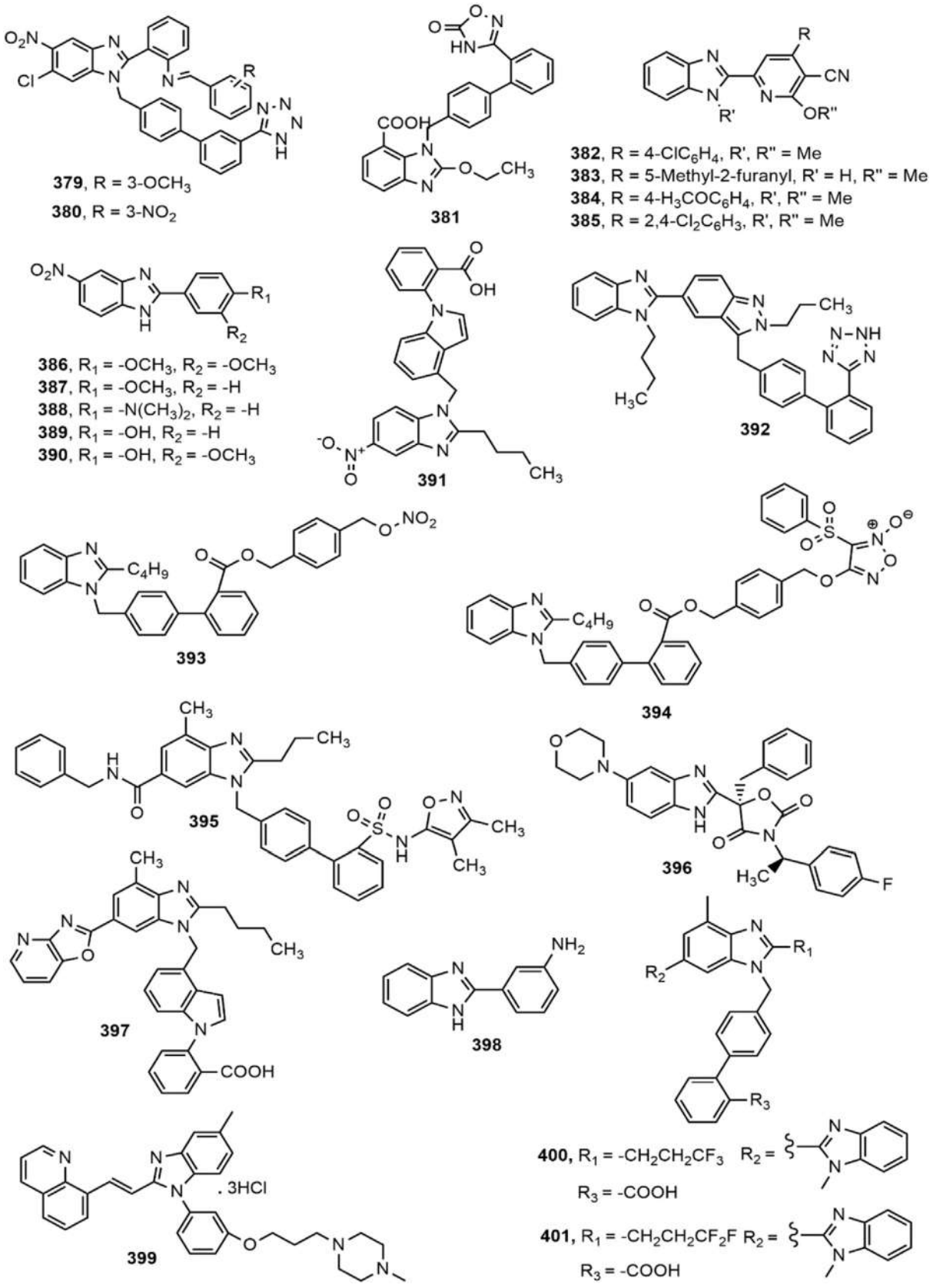


Figure 27: Benzimidazole derivatives with antihypertensive activity

7. Anticonvulsant Activity: Some benzimidazole compounds have demonstrated anticonvulsant properties, making them potential candidates for the treatment of epilepsy and other seizure disorders.

Epilepsy is one of the most prevalent and serious neurological disorders, and recurrent seizures or convulsions are its characteristic syndrome. Around one-third of patients in the world show poor response to currently available antiepileptic drugs[82]. In search of novel clinically effective anticonvulsant medications, benzimidazole nucleus has recently been explored by scientists with promising results. The benzimidazole derivatives with anticonvulsant property are shown in Figure 28.

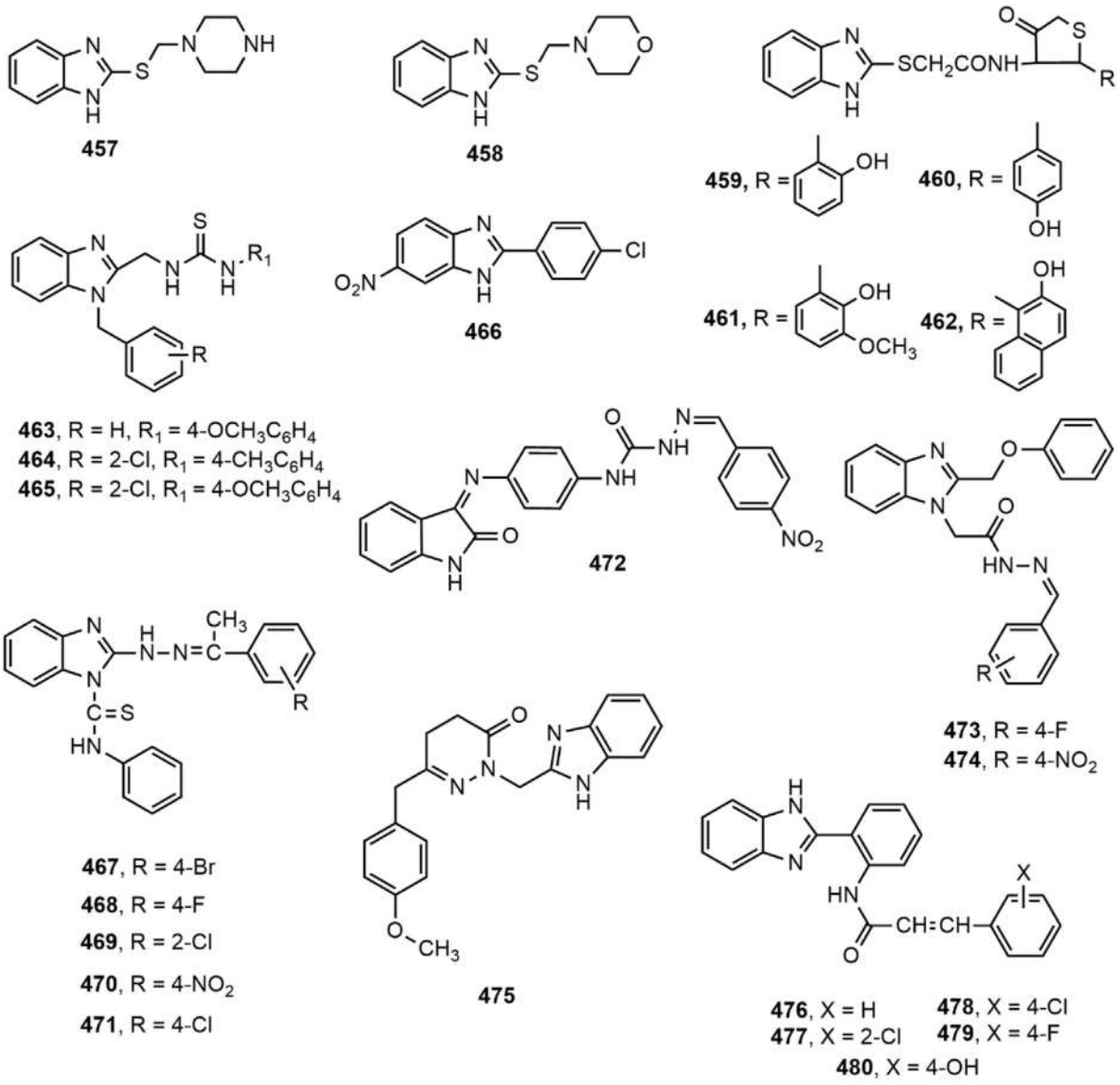


Figure 28: Benzimidazole derivatives with anticonvulsant activity

8. Antiviral Activity: The antiviral properties of benzimidazole derivatives have been tested against different viral strains; human immunodeficiency virus (HIV), hepatitis B and C virus (HBV and HCV), enteroviruses, respiratory syncytial virus (RSV), human cytomegalovirus (HCMV), bovine viral diarrhea virus (BVDV) and herpes simplex virus-1 (HSV-1) are some to mention[83]. This section focuses on the recent studies involving varied antiviral properties of different benzimidazole derivatives, and their structures are shown in Figure 29.

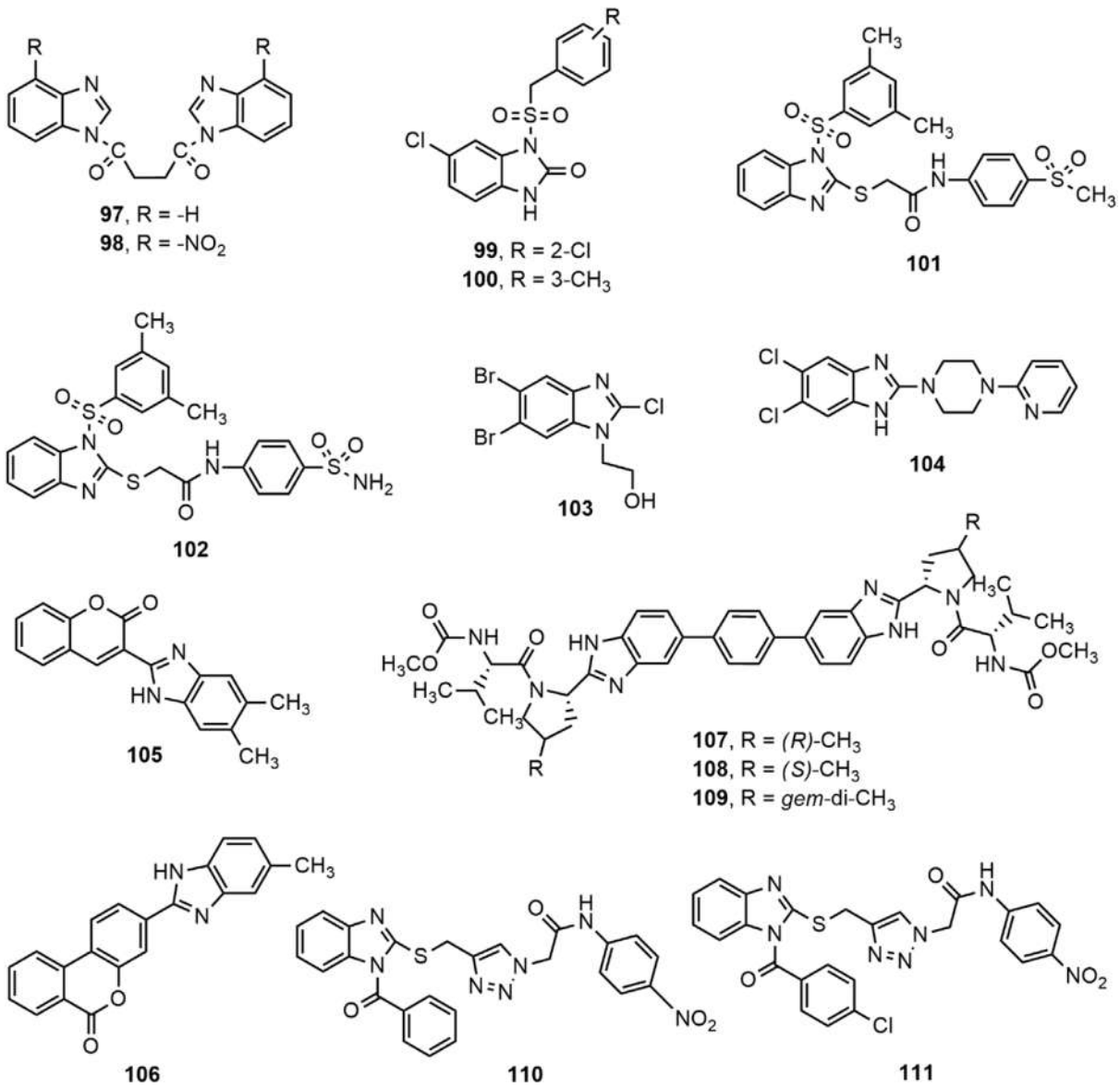


Figure 28: Benzimidazole derivatives with antiviral activity

9. Antiulcer Activity: Many benzimidazole derivatives are known to possess potent antiulcer activity and H+/K+-ATPase inhibitory properties[84]. During recent times, several new synthetic benzimidazole based compounds were developed which exhibited similar or better antiulcerogenic potentials compared to the established market preparations. The benzimidazole derivatives with antiulcer activity are shown in Figure 29.

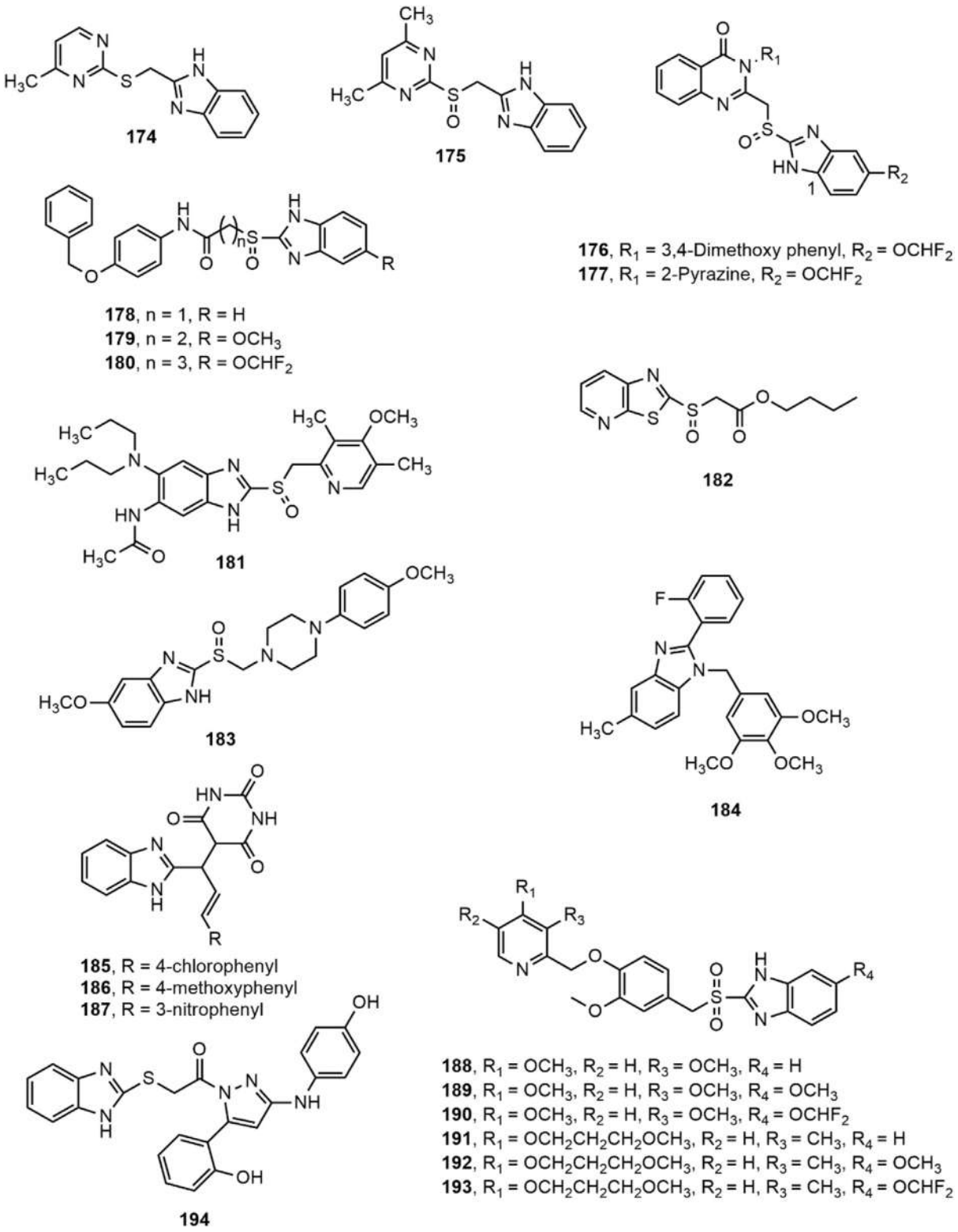


Figure 29: Benzimidazole derivatives with antiulcer activity

Conclusion:

Benzimidazole derivatives constitute a versatile class of compounds that have attracted significant attention in medicinal chemistry due to their diverse pharmacological activities. These heterocyclic compounds have been extensively explored and modified through various structural alterations, leading to the development of potential therapeutic agents with a wide range of biological activities.

The diverse pharmacological activities of benzimidazole derivatives have been extensively explored through various structural alterations. These modifications have involved the introduction of different substituents, the incorporation of heterocyclic rings, or the addition of aryl or heteroaryl groups, among others. These structural changes have led to the development of benzimidazole derivatives with enhanced biological activities, improved selectivity, and optimized pharmacokinetic properties.

The structural diversity of benzimidazole derivatives has opened up numerous opportunities for the development of potential therapeutic agents targeting a wide range of diseases and conditions. However, further research is needed to fully understand the structure-activity relationships, optimize the pharmacokinetic and toxicological profiles, and explore the potential clinical applications of these promising compounds.

CONFLICT OF INTEREST:

The authors have no conflicts of interest regarding this investigation**.**

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REFERENCES:

1. Woolley DW. Some biological effects produced by benzimidazole and their reversal by purines. The Journal of Biological Chemistry. 1944;**152**:225-232
2. Brink NG, Flokers K. Vitamin-B12. Vi. 5,6-Dimethylbenzimidazole, a degradation product of vitamin-B12. Journal of the American Chemical Society. 1949;**71**:2951.
3. Epstein SS. Effect of some benzimidazoles on a vitamin B12- requiring alga. Nature. 1960;**188**: 143-144.
4. Wright JB. Chemistry of benzimidazoles. Chemical Reviews. 1951;**48**:397-541.

5. McKellar QA, Scott EW. The benzimidazole anthelmintic agents—A review. Journal of Veterinary Pharmacology and Therapeutics. 1990;**13**:223-247.
6. Spasov AA, Yozhitsa IN, Bugaeva LI, Anisimova VA. Benzimidazole derivatives: Spectrum of pharmacological activity and toxicological properties (a review). Pharmaceutical Chemistry Journal. 1999;**33**:232-243.
7. Rossignol JF, Maisonneuve H. Benzimidazoles in the treatment of trichuriasis: A review. Annals of Tropical Medicine and Parasitology. 1984;**78**:135-144.
8. Patil A, Ganguly S, Surana S. A systematic review of benzimidazole derivatives as an antiulcer agent. Rasayan Journal of Chemistry. 2008;**1**:447-460
9. Boiani M, Gonzalez M. Imidazole and benzimidazole derivatives as chemotherapeutic agents. Mini Reviews in Medicinal Chemistry. 2005;**5**:409-424.
10. Narasimhan B, Sharma D, Kumar P. Benzimidazole: A medicinally important heterocyclic moiety. Medicinal
11. Chemistry Research. 2012;**21**:269-283.
12. Sivakumar R, Pradeepchandran R, Jayaveera KN, Kumarnallasivan P, Vijaianand PR, Venkatnarayanan R. Benzimidazole: An attractive pharmacophore in medicinal chemistry. International Journal of Pharmaceutical Research. 2011;**3**:19-31
13. Geeta Y, Swastika G. Structure activity relationship (SAR) study of benzimidazole scaffold for different biological activities: A mini-review. European Journal of Medicinal Chemistry. 2015;**97**:419-443.
14. Yogita B, Om S. The therapeutic journey of benzimidazoles: A review. Bioorganic & Medicinal Chemistry. 2012;**20**:6208-6236.
15. Hofmann K. Imidazole and its Derivatives Part-1. New York: Wiley Interscience; 1953 [15] Preston PN. Synthesis, reactions, and spectroscopic properties of benzimidazoles. Chemical Reviews. 1974;**74**(3):279-314.

16. John BW. The chemistry of the benzimidazoles. Chemical Reviews. 1951;**48**:398-541.
17. James GS, Isaac H. Organic redox reactions during the interaction of o-phenylenediamine with benzaldehyde. Tetrahedron Letters. 1971;**38**:351-3544
18. Veeranagaiah V, Rao NVS, Ratnam CV. Studies in the formation of heterocyclic rings containing nitrogen. Proceedings of the Indian Academy of Science, Section A. 1974;**79**:230-235.
19. Liyan F, Wen C, Lulu K. Highly chemoselective synthesis of benzimidazoles in Sc(OTf)3-catalyzed system. Heterocycles. 2015;**91**:2306.
20. Heravi MM, Derikvand F, Ranjbar L. Sulfamic acid-catalyzed, three-component, one-pot synthesis of [1,2,4]triazolo/benzimidazolo quinazolinone derivatives. Synthetic Communications. 2010;**40**:677-685.
21. Bahrami K, Khodaei MM, Kavianinia I. H2O2/HCl as a new and efficient system for synthesis of 2-substituted benzimidazoles. Journal of Chemical Research. 2006;**12**:783-784.
22. Ma H, Han X, Wang Y, Wang J. A simple and efficient method for synthesis of benzimidazoles using FeBr3 or Fe(NO3)3·9H2O as catalyst. ChemInform. 2007;**38**:49.
23. Du L-H, Wang Y-G. A rapid and efficient synthesis of benzimidazoles using hypervalent iodine as oxidant. Synthesis. 2007;**5**:675-678.
24. Venkateswarlu Y, Kumar SR, Leelavathi P. Facile and efficient onepot synthesis of benzimidazoles using lanthanum chloride. Organic and Medicinal Chemistry Letters. 2013;**3**:7.
25. Sontakke VA, Ghosh S, Lawande PP, Chopade BA, Shinde VS. A simple, efficient synthesis of 2-aryl benzimidazoles using silica supported periodic acid catalyst and evaluation of anticancer activity. ISRN Organic Chemistry. 2013:1-7.

26. Martins GM, Puccinelli T, Gariani RA, Xavier FR, Silveira CC, Mendes SR. Facile and efficient aerobic one-pot synthesis of benzimidazoles using Ce(NO3)3·6H2O as promoter. Tetrahedron Letters. 2017;**58**:1969-1972.

27. Kumar KR, Satyanarayana PVV, Reddy BS. NaHSO4-SiO2 promoted synthesis of benzimidazole derivatives. Archives of Applied Science Research. 2012;**4**:1517-1521

28. Bhatnagar KS, George MV. Oxidation with metal oxides-II: Oxidation of chalcone phenylhydrazones, pyrazolines, o-aminobenzylidine anils and o-hydroxy benzylidine with MnO2. Tetrahedron. 1968; **24:1293**-1298

29. K. Anand, S. Wakode, Development of drugs based on Benzimidazole Heterocycle: recent advancement and insights, IJCS 5 (2) (2017) 350–362.

30. D. Singh Negi, G. Kumar, M. Singh, N. Singh, Antibacterial activity of benzimidazole derivatives: a mini review, Res. Rev.: J. Chem. 6 (3) (2017) 18–28.

31. Z. Wang, X. Deng, S. Xiong, R. Xiong, J. Liu, L. Zou, X. Lei, X. Cao, Z. Xie, Y. Chen, Y. Liu, X. Zheng, G. Tang, Design, synthesis and biological evaluation of chrysin benzimidazole derivatives as potential anticancer agents, Nat. Prod. Res. 32 (24) (2018) 2900–2909.

32. G.R. Morais, E. Palma, F. Marques, L. Gano, M.C. Oliveira, A. Abrunhosa, H. V. Miranda, T.F. Outeiro, I. Santos, A. Paulo, Synthesis and biological evaluation of novel 2-aryl benzimidazoles as chemotherapeutic agents, J. Heterocyclic Chem. 54 (1) (2017) 255–267.

33. Y.M. Shaker, M.A. Omar, K. Mahmoud, S.M. Elhallouty, W.M. El-Senousy, M. M. Ali, A.E. Mahmoud, A.H. Abdel-Halim, S.M. Soliman, H.I. El Diwani, Synthesis, in vitro and in vivo antitumor and antiviral activity of novel 1-substituted benzimidazole derivatives, J. Enzyme Inhib. Med. Chem. 30 (5) (2015) 826–845.

34. V. Onnis, M. Demurtas, A. Deplano, G. Balboni, A. Baldisserotto, S. Manfredini, S. Pacifico, S. Liekens, J. Balzarini, Design, synthesis and evaluation of antiproliferative activity of new benzimidazolehydrazones, J. Balzarin Mol. 21 (5) (2016) 579–588.

35. U. Acar Çevik, B.N. Sa˘glık, B. Korkut, Y. ¨Ozkay, S. Ilgın, Antiproliferative cytotoxic, and apoptotic effects of new benzimidazole derivatives bearing hydrazone moiety, J. Heterocyclic Chem. 55 (1) (2018) 138–148.

36. A.H. Alanazi, Md.T. Alam, M. Imran, Design, molecular docking studies, in silico drug likeliness prediction and synthesis of some benzimidazole derivatives as antihypertensive agents, Md. Imranl. Indo American J. of Pharmaceutical Sci. 4 (04) (2017) 926–936.

37. R. Kankate, A. Pangare, R. Kakad, P. Gide, V. Nathe, Synthesis and biological evaluation of benzimidazolyl biphenyl derivatives as antihypertensive agents, Int. J. Chem. Concepts 2 (2) (2016) 111–119.

38. R. Sharma, A. Bali, B. Chandhari, Synthesis of methanesulphonamido-benzimidazole derivatives as gastro-sparing antiinflammatory agents with antioxidant effect, Bioorg. Med. Chem. Lett. 27 (2017) 3007–3013.

39. P. Sethi, Y. Bansal, G. Bansal, Synthesis and PASS-assisted evaluation of coumarin–benzimidazole derivatives as potential anti-inflammatory and anthelmintic agents, Med. Chem. Res. 27 (1) (2017) 61–72.

40. M. Gaba, C. Mohan, Design, synthesis and biological evaluation of novel 1, 2, 5- substituted benzimidazole derivatives as gastroprotective anti-inflammatory and analgesic agents, Med. Chem. 5 (2) (2015) 58–63.

41. N. Gohary, M. Shaaban, Synthesis and biological evaluation of a new series of benzimidazole derivatives as antimicrobial, antiquorum-sensing and antitumor agents, Eur. J. Med. Chem. 131 (2017) 255–262.

42. L.R. Singh, S.R. Avula, S. Raj, A. Srivastava, G.R. Palnati, C.K.M. Tripathi, M. Pasupuleti, K.V. Sashidhara, Coumarin–benzimidazole hybrids as a potent antimicrobial agent: synthesis and biological elevation, J. Antibiotics 70 (9) (2017) 954–961.

43. O. Ajani, D. Aderohunmu, S. Olorunshola, C. Ikpo, I. Olanrewaju, Facile synthesis, characterization and antimicrobial activity of 2-alkanamino benzimidazole derivatives, Oriental J. Chem. 32 (1) (2016) 109–120.

A. Kapoor, N. Dhiman, Synthesis and evaluation of 2-aryl substituted benzimidazole derivatives bearing 1,3,4-oxadiazole nucleus for antimicrobial activity, Der. Pharmacia Lett. 8 (12) (2016) 97–104.

44. S. Shinde, R. Tale, A. Rodg, A. Raote, K. Patil, R. Pawar, Design, synthesis and biological evaluation of novel ureidobezimadazole hybrid as potent TNF-α and IL-6 inhibitor, and antimicrobial agents, J. Chem. Pharm. Res. 8 (4) (2016) 395–401.

45. S. Garrepalli, S. Tatipamula, A. Gade, K. Yadeli, R. Guggila, Synthesis, characterization and evaluation of new benzimidazole derivatives, World J. Pharm. Sci. 4910 (2016) 39–42.

46. R.H. Turkey, A.A.R.M. Kubba, Synthesis, characterization and antibacterial activity of new 5-ethoxy-2-mercaptobenzimidazole derivatives, J. Pharm. Res. 10 (12) (2016) 814–824.

47. S.R. Archie, B. Das, M.S. Hossain, U. Kumar, A.S.S. Rauf, Synthesis and antioxidant activity of 2-substituted-5-nitro benzimidazole derivatives, Int. J. Pharm. Pharm. Sci. 9 (1) (2017) 308–310.

48. S.N. Abd, F.M.A. Soliman, Synthesis, some reactions, cytotoxic evaluation and antioxidant study of novel benzimidazole derivatives, Der Pharma Chemica 7 (4) (2015) 71–84.

49. M. Bellam, M. Gundluru, S. Sarva, S. Chadive, V.R. Netala, V. Tartte, S.R. Cirandur, Synthesis and antioxidant activity of some new N-alkylated pyrazole-containing benzimidazoles, Chem. Heterocycl. Compd. 53 (2) (2017) 173–178.

50. H. Yang, Y. Ren, X. Gao, Y. Gao, Synthesis and anticoagulant bioactivity evaluation of 1,2,5-trisubstituted benzimidazole fluorinated derivatives, Chem. Res. Chin. Univ. 32 (6) (2016) 973–978.

51. F. Wang, Y.-J. Ren, Design, synthesis, biological evaluation and molecular docking of novel substituted 1-ethyl-1H-benzimidazole fluorinated derivatives as thrombin inhibitors, J. Iran. Chem. Soc. 13 (2016) 1155–1166.

52. S. Nair, J. Beevi, N. Merlin, B. Emmanuel, S. Dharan, C. Remya, Insilico design, synthesis and in vitro antidiabetic and anti-inflammatory activities of 1,3,4-thiadiazole substituted 2-methylbenzimidazole derivatives, J. Pharm. Res. Clin. Pract. 6 (1) (2016) 27–36.

53. R. Singalapur, K. Hosamani, R. Keri, M. Hugar, Derivatives of benzimidazole pharmacophore: synthesis, anticonvulsant, antidiabetic and DNA cleavage studies, Eur. J. Med. Chem. 45 (2010) 1753–1759.

54. R. Kenchappa, D. Yadav, Bodke, S. Telkar, M. Sindhe, Antifungal and anthelmintic activity of novel benzofuran derivatives containing thiazolo benzimidazole nucleus: of novel substituted 1-ethyl-1H-benzimidazole fluorinated derivatives as thrombin inhibitors, J. Iran. Chem. Soc. 13 (2016) 1155–1166.

A. Faruk, B. Dey, K. Sharma, A. Chakraborty, K. Pallab, Synthesis, antimicrobial and anthelmintic activity of some novel benzimidazole derivatives, Int. J. Drug Res. Tech. 4 (3) (2014) 31–38.

55. S. Lingala, R. Nerella, S. Rao, Synthesis, antimicrobial and anthelmintic activity of some novel benzimidazole derivatives, Der Pharma Chemica 3 (4) (2011) 344–352.

56. M.M. Vandeputte, K. Van Uytfanghe, N.K. Layle, D.M. St. Germaine, D.M. Iula, C. P. Stove, Synthesis, chemical characterization, and μ-opioid receptor activity assessment of the emerging group of “Nitazene” 2-benzylbenzimidazole synthetic opioids, ACS Chem. Neurosci. 12 (7) (2021) 1241–1251.

57. Bansal Y, Silakari O. The therapeutic journey of benzimidazoles: A review. European Journal of Medicinal Chemistry. 2012;**20**(21):6208-6236.

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

59. Rajesakhar S, Maiti B, Balamurali MM, Chanda K. Synthesis and medicinal applications of benzimidazoles: An overview. Current Organic Synthesis. 2017;**14**(1):40-60.

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

61. Moniruzzaman RS, Mahmud T. Quantum chemical and pharmacokinetic studies of some proton pump inhibitor drugs. American Journal of Biomedical Sciences & Research. 2019;**2**(1):3-8.

62. Scholten WK, Christensen AE, Olesen AE, Drewes AM. Quantifying the adequacy of opioid analgesic consumption globally: An updated method and early findings. American Journal of Public Health (AJPH). 2019;**109**(1):52-57.

63. Tahlan S, Kumar S, Ramasamy K, Lim SM, Shah SAA, Mani V, et al. Design, synthesis and biological profile of heterocyclic benzimidazole analogues as prospective antimicrobial and antiproliferative agents. BMC Chemistry. 2019;**13**(50):1-15.

64. Celik I, Ayhan-Kilcigil G, Guven B, Kara Z, Gurkan AAS, Karayel A, et al. Design, synthesis and docking studies of benzimidazole derivatives as potential EGFR inhibitors. European Journal of Medicinal Chemistry. 2019;**173**:240-249.

65. Akhtar MJ, Siddiqui AA, Khan AA, Ali Z, Dewangan RP, Pasha S, et al. Design, synthesis, docking and QSAR study of substituted benzimidazole linked oxadiazole as cytotoxic

agents, EGFR and erbB2 receptor inhibitors. European Journal of Medicinal Chemistry. 2017;**126**:853-869.

66. Popov AB, Stolic I, Krstulovic L, Taylor MC, Kelly JM, Tomic S, et al. Novel symmetric bis-benzimidazoles: Synthesis, DNA/RNA binding and antitrypanosomal activity. European Journal of Medicinal Chemistry. 2019;**173**:63-75.
67. Afaf, H.E., Fahmy, H.H., Abdelwal, S.H., 2000. Molecules 5, 1429. Amari, M., Fodili, M., Nedjar-kolli, B., 2002. Reactivity studies on 4- aminopyrones: Access to benzimidazole and benzimidazolone derivatives. J. Heterocycl. Chem. 39, 811.
68. Ansari, K.F., Lal, C., 2009a. Synthesis and evaluation of some new benzimidazole derivatives as potential antimicrobial agents. Eur. J. Med. Chem. 44, 2294.
69. Ansari, K.F., Lal, C., 2009b. Synthesis, physicochemical properties and antimicrobial activity of some new benzimidazole derivatives. Eur. J. Med. Chem. 44, 4028.
70. Bansal, R.K., 2002. Herocyclic Chemistry, third ed. Publisher, New Delhi, New Age International, 401 pp.
71. Bishnoi, A., Pandey, V.K., Saxena, R., 1978. Synthesis and characterization of benzimidazolylphenothiazine derivatives and a study of their antiviral and antifungal activities. Ind. J. Chem. 41B, 1978.
72. Bistrzycki, Ulffers, 1980. Ueber Diacyl-o-Diamine. Ber. 23, 1876.
73. Campbell, W.C., Denham, D.A., 1983. Chemotherapy. In: Campbell, W.C. (Ed.), Trichinilla and Trichinosis. Plenum Press, USA and London, UK, 340 pp.
74. emirayak, S., Mohsen, U.A., Karaburun, A.C., 2002. Synthesis and anticancer and anti-HIV testing of some pyrazino[1,2-a]benzimidazole derivatives. Eur. J. Med. Chem. 37, 255.
75. Evans, D., Hicks, T.A., Williamson, W.R.N., Meacock, S.C.R., Kitchen, E.A., 1996. Synthesis of a group of 1H–benzimidazoles and their screening for antiinflammatory activity. Eur. J. Med. Chem. 31, 635.

76. Fischer, Veiel., 1905. The chemistry of benzimidazoles. Ber. 38, 320.

77. Gaba, M., Sing, D., Singh, S., Sharma, V., Gaba, P., 2010. Synthesis and pharmacological evaluation of novel 5-substituted-1-(phenylsulfonyl)- 2-methylbenzimidazole derivatives as anti-inflammatory and analgesic agents. Eur. J. Med. Chem. 45, 2245.

78. Gellis, A., Kovacic, H., Boufatah, N., Vanelle, P., 2008. Synthesis and cytotoxicity evaluation of some benzimidazole-4,7-diones as bioreductive anticancer agents. Eur. J. Med. Chem. 43, 1858.

79. Ghoneim, K.M., Essawi, M.Y.H., Mohamed, M.S., Kamal, A.M., 1998. Synthesis of 2-[(4-amino or 2,4-diaminophenyl)sulfonyl] derivatives of benzimidazole, benzothiazole and 6-methyluracil as potential antimicrobial agents. Ind. J. Chem. 37B, 904.

80. Gomez, H.T., Nunez, E.H., Rivera, I.L., Alvarez, J.G., Rivera, R.C., Puc, R.M., Ramos, R.A., Guttirez, M.C.R., Bacab, M.J.C., Vazquez, G.N., 2008. Design, synthesis and in vitro antiprotozoal activity of benzimidazole-pentamidine hybrids. Bioorg. Med. Chem. Lett. 18, 3147.

81. Gowda, J., Khadar, A.M.A., Kalluraya, B., Kumari, N.S., 2010. Microwave assisted synthesis of 1,3,4-oxadiazoles carrying benzimidazole moiety and their antimicrobial properties. Ind. J. Chem. 49B, 1130.

82. Gupta, S.P., Rani, S., 1997. Synthesis and fungitoxicity of some 5- substituted- 3-polynitrophenyl rhodanines. J. Ind. Chem. Soc., LIV, 478.

83. Hranjec, M., Starcevic, K., Pavelic, S.K., Lucin, P., Pavelic, K., Zamola, G.K., 2011. Synthesis, spectroscopic characterization and antiproliferative evaluation in vitro of novel Schiff bases related to benzimidazoles. Eur. J. Med. Chem. 46, 2274.

84. Ismail, M.A., Brun, R., Wenzler, T., Tanious, F.A., Wilson, W.D., Boykin, D.W., 2004. Dicationic biphenyl benzimidazole derivatives as antiprotozoal agents. Bioorg. Med. Chem. 12, 5405.

85. Kaghtara, P.R., Shah, N.S., Doshi, R.K., Parekh, H.H., 1999. Synthesis of 2,5-disubdtituted 1,3,4-oxadiazoles as biologically active heterocycles. Ind. J. Chem. 38B, 572.

86. Kazimierczuk, Z., Upcroft, J.A., Upcroft, P., Gorska, A., Starosciak, B., Laudy, A., 2002. Synthesis, antiprotozoal and antibacterial activity of nitro- and halogeno-substituted benzimidazole derivatives. Acta Biochim. Pol. 49, 185.

87. Abbhi, V., Saini, L., Mishra, S., Sethi, G., Kumar, A. P., and Piplani, P. (2017).

88. Design and Synthesis of Benzimidazole-Based Rho Kinase Inhibitors for the Treatment of Glaucoma. Bioorg. Med. Chem. 25, 6071–6085.

89. Abd El-All, A. S., Magd-El-Din, A. A., Ragab, F. A., ElHefnawi, M., Abdalla, M. M., Galal, S. A., et al. (2015). New Benzimidazoles and Their Antitumor Effects with Aurora A Kinase and KSP Inhibitory Activities. Arch. Pharm. (Weinheim) 348, 475–486.

90. Abdel-Motaal, M., Almohawes, K., and Tantawy, M. A. (2020). Antimicrobial Evaluation and Docking Study of Some New Substituted Benzimidazole-2yl Derivatives. Bioorg. Chem. 101, 103972.

91. Abdelgawad, M. A., Bakr, R. B., Ahmad, W., Al-Sanea, M. M., and Elshemy, H. A. H. (2019). New Pyrimidine-Benzoxazole/benzimidazole Hybrids: Synthesis, Antioxidant, Cytotoxic Activity, In Vitro Cyclooxygenase and Phospholipase A2-V Inhibition. Bioorg. Chem. 92, 103218.

92. Abou-Seri, S. M., Abouzid, K., and Abou El Ella, D. A. (2011). Molecular Modeling Study and Synthesis of Quinazolinone-Arylpiperazine Derivatives as α1- adrenoreceptor Antagonists. Eur. J. Med. Chem. 46, 647–658.

93. Abu-Bakr S. M. Bassyouni F. A. and Rehim M. A. Pharmacological Evaluation of Benzimidazole Derivatives with Potential Antiviral and Antitumor Activity. Res. Chem. Intermed. 2012; 38: 2523–2545.

94. Acar Çevik U. Kaya Çavuşoğlu B. Sağlık B. N. Osmaniye D. Levent S. Ilgın S. et al. Synthesis, Docking Studies and Biological Activity of New Benzimidazole-Triazolothiadiazine Derivatives as Aromatase Inhibitor. Molecules. 2020; 25: 1642.

95. Acar Çevik U. Sağlık B. N. Korkut B. Özkay Y. and Ilgın S. Antiproliferative, Cytotoxic, and Apoptotic Effects of New Benzimidazole Derivatives Bearing Hydrazone Moiety. J. Heterocyclic Chem. 2018; 55: 138–148.

96. Actor P. Anderson E. Dicuollo C. Ferlauto R. Hoover J. Pagano J. Ravin L. Scheidy S. Stedman R. Theodorides V. New broad spectrum anthelmintic, methyl 5 (6)-butyl-2-benzimidazolecarbamate. Nature. 1967; 215: 321-326.

97. Alagoz M.A. Ozdemir Z. Zenni Y.N. Yilmaz T. Onkol T. QSAR and pharmacophore analysis on pyridazinone derivatives as acetylcholinesterase. Inhibitors. Ann. Med. Res. 2020; 27: 266–270.

98. Arora R.K. Kaur N. Bansal Y. Bansal G. Novel coumarin–benzimidazole derivatives as antioxidants and safer anti-inflammatory agents. Acta Pharm. Sin. B. 2014; 4: 368–375.

99. Aslam S. Zaib S. Ahmad M. Gardiner J.M. Ahmad A. Hameed A. Furtmann N. Gütschow M. Bajorath J. Iqbal J. Novel structural hybrids of pyrazolobenzothiazines with benzimidazoles as cholinesterase inhibitors. Eur. J. Med. Chem. 2014; 78: 106–117.

100. Bandyopadhyay U. Das D. Banerjee R.K. Reactive oxygen species: oxidative damage and pathogenesis. Curr. Sci. 1999; 77: 658–666.

101. Bansal Y. Silakari O. The therapeutic journey of benzimidazoles: a review. Bioorg. Med. Chem. 2012; 20: 6208–6236.

102. Bansal Y. Silakari O. Synthesis and pharmacological evaluation of polyfunctional benzimidazole-NSAID chimeric molecules combining anti-inflammatory, immunomodulatory and antioxidant activities. Arch Pharm. Res. (Seoul). 2014; 37: 1426–1436.

103. Barbato L. Monge A. Stocchi F. Nordera G. Melperone in the treatment of iatrogenic psychosis in Parkinson's disease. Funct. Neurol. 1996; 11: 201–207.

104. Beil W. Staar U. Sewing K.F. Pantoprazole: a novel H+/K+ -ATPase inhibitor with an improved pH stability. Eur. J. Pharmacol. 1992; 218: 265–271.

105. Betancourt A. Lyon E. Horohov D. Characterisation of the inflammatory cytokine response to anthelmintic treatment in ponies. Equine Vet. J. 2015; 47: 240–244.

106. Bharadwaj S.S. Poojary B. Nandish S.K.M. Kengaiah J. Kirana M.P. Shankar M.K. Das A.J. Kulal A. Sannaningaiah D. Efficient synthesis and in silico studies of the benzimidazole hybrid scaffold with the quinolinyloxadiazole skeleton with potential α-glucosidase inhibitory, anticoagulant, and antiplatelet activities for type- II diabetes mellitus management and treating thrombotic disorders. ACS Omega. 2018; 3: 12562–12574.

107. Bielory L. Lien K.W. Bigelsen S. Efficacy and tolerability of newer antihistamines in the treatment of allergic conjunctivitis. Drugs. 2005; 65: 215–228.

108. Bosquesi P.L. Melo T.R.F. Vizioli E.O. Santos J.L.d. Chung M.C. Anti-inflammatory drug design using a molecular hybridization approach. Pharmaceuticals. 2011; 4: 1450–1474.

109. Brink N.G. Folkers K. Vitamin B12. VI. 5, 6-Dimethylbenzimidazole, a degradation product of vitamin B12. J. Am. Chem. Soc. 1949; 71: 271-275

110. Chavarría A.P. Swartzwelder J.C. Villarejos V.M. Zeledon R.O. Mebendazole, an effective broad spectrum anthelmintic. Am. J. Trop. Med. Hyg. 1973; 22: 592–595.

111. Chen C.Z. Kulakova L. Southall N. Marugan J.J. Galkin A. Austin C.P. Zheng W. High-throughput Giardia lamblia viability assay using bioluminescent ATP content measurements. Antimicrob. Agents Chemother. 2011; 55: 667–675. https://doi. org/10.1128/AAC.00618-10.

112. Choudhary S. Singh P.K. Verma H. Singh H. Silakari O. Success stories of natural product-based hybrid molecules for multi-factorial diseases. Eur. J. Med. Chem. 2018; 151: 62–97.

113. Corc´ostegui R. Labeaga L. Inner´arity A. Berisa A. Orjale A. Preclinical pharmacology of bilastine, a new selective histamine H 1 receptor antagonist. Drugs R. 2005; 6: 371–384.

114. Cummings J.L. Vinters H.V. Cole G.M. Khachaturia Z.S. Alzheimer's disease: etiologies, pathophysiology, cognitive reserve, and treatment opportunities. Neurology. 1998; 51: S2–S17.

115. Desai N. Pandya D. Joshi V. Rajpara K. Vaghani H. Satodiya H. Synthesis, characterization and antimicrobial screening of hybrid molecules containing benzimidazole-pyrazole and pyridine nucleus. Med. Chem. Res. 2012; 21: 4463–4472.

116. Dropulic L.K. Cohen J.I. Update on new antivirals under development for the treatment of double-stranded DNA virus infections. Clin. Pharmacol. Ther. 2010; 88: 610–619.

117. El-Gohary N. Shaaban M. Synthesis, antimicrobial, antiquorum-sensing and antitumor activities of new benzimidazole analogs. Eur. J. Med. Chem. 2017; 137: 439–449.

118. Emerson C.R. Marzella N. Dexlansoprazole: a proton pump inhibitor with a dual delayed-release system. Clin. Therapeut. 2010; 32: 1578–1596.

119. Fadeyi O.O. Adamson S.T. Myles E.L. Okoro C.O. Novel fluorinated acridone derivatives. Part 1: synthesis and evaluation as potential anticancer agents. Bioorg. Med. Chem. Letters. 2008: 18: 4172–4176.

120. Fang X.J. Jeyakkumar P. Avula. S.R. Zhou Q. Zhou C.H. Design, synthesis and biological evaluation of 5-fluorouracil-derived benzimidazoles as novel type of potential antimicrobial agents. Bioorg. Med. Chem. Letter. 2016; 26: 2584–2588.

121. Fatahala SS. Khedr MA. Mohamed MS. Synthesis and structure activity relationship of some indole derivatives as potential anti-inflammatory agents. Acta Chim. Slov. 2017; 64: 865–876.

Content (Times New Roman front 8)

1. Patil JS. Sarasija S. Pulmonary drug delivery strategies: A concise, systematic review. Lung India: Official Organ of Indian Chest Society. 2012; 29 (1):44.doi.org/10.4103/0970-2113.92361
2. Shaji J. Shaikh M. Current development in the evaluation methods of pulmonary drug delivery system. Indian Journal of Pharmaceutical Sciences. 2016; 78(3):294-306. doi.org/10.4172/pharmaceutical-sciences.1000118
3. Frijlink HW. De Boer AH. Dry powder inhalers for pulmonary drug delivery. Expert opinion on drug delivery. 2004; 1(1):67-86.doi.org/10.1517/17425247.1.1.67.
4. Islam N. Gladki E. Dry powder inhalers (DPIs)—a review of device reliability and innovation. International journal of pharmaceutics. 2008; 360(1-2):1-1. Doi.org/ 10.1016/j.ijpharm.2008.04.044.
5. Ballesteros B. Tobias G. Shao L. Pellicer E. Nogués J. Mendoza E. Green ML et al Steam Purification for the Removal of Graphitic Shells Coating Catalytic Particles and the Shortening of Single-Walled Carbon Nanotubes. Small. 2008; 4(9):1501-6.doi.org/10.1021/ja061680u (Model Journal reference)
6. Singh B. Lohan S. Sandhu PS. Jain A. Mehta SK. Functionalized carbon nanotubes and their promising applications in therapeutics and diagnostics. In Nanobiomaterials in Medical Imaging 2016; 455-478, William Andrew Publishing. https://doi.org/10.1021/nn700040t
7. Mehra NK. Jain K and Jain NK. Pharmaceutical and biomedical applications of surface engineered carbon nanotubes. Drug Discovery Today. 2015; 20(6):750-9. doi.org/10.1016/j.drudis.2015.01.006
8. Klinger-Strobel M. Lautenschläger C. Fischer D. Mainz JG. Bruns T. Tuchscherr L. Pletz MW. Makarewicz O. Aspects of pulmonary drug delivery strategies for infections in cystic fibrosis–where do we stand?. Expert Opinion on Drug Delivery. 2015; 12(8): 1351-74. Doi.org/ 10.1517/17425247.2015.1007949.
9. Strausbaugh SD. Davis PB. Cystic Fibrosis: A Review of Epidemiology and Pathology. Clinics in Chest Medicine.2007; 28(2): 279-88. doi.org/ 10.1016/j.ccm.2007.02.011.
10. Palmer GC. Whiteley M. Metabolism and pathogenicity of Pseudomonas aeruginosa infections in the lungs of individuals with cystic fibrosis. Metabolism and Bacterial Pathogenesis. 2015;185-213.https://doi.org/10.3389/fmicb.2015.00321
11. MizgerdJP. Lung infection—a public health priority. PLoS Med. 2006; 3(2):e76. https://doi.org/10.1371/journal.pmed.0030076
12. Oliver A. Cantón R. Campo P. Baquero F. Blázquez J. High frequency of hypermutable Pseudomonas aeruginosa in cystic fibrosis lung infection. Science. 2000; 288(5469): 1251–1253. doi.org/10.1126/science.288.5469.1251.
13. Guay DR. Cefdinir: an advanced-generation, broad-spectrum oral cephalosporin. Clinical therapeutics 2002; 24(4):473–489. doi.org/10.1016/s0149-2918(02)85125-6
14. Sader HS. Jones RN. Cefdinir: an oral cephalosporin for the treatment of respiratory tract infections and skin and skin structure infections. Expert review of anti-infective therapy 2007; 5(1):29–43. Doi.org/ 10.1586/14787210.5.1.29.
15. Perry CM. Scott LJ. Cefdinir. Drugs 2004; 64(13): 1433–1464. doi.org/10.2165/00003495-200464130-00004
16. Ghoshal S. Kushwaha SKS. Srivastava M. Tiwari P. Drug loading and release from functionalized multiwalled carbon nanotubes loaded with 6-mercaptopurine using incipient wetness impregnation method. Am J Adv Drug Del. 2014; 2(2):213–223.

17. Misra A. Tyagi PK. Rai P. Misra DS. FTIR Spectroscopy of multiwalled carbon nanotubes: a Simple approach to study the nitrogen doping. Journal of nanoscience and nanotechnology 2007; 7(6):1820–1823.
18. Li Y. Wang T. Wang J. Jiang T. Cheng G. Wang S. Functional and unmodified MWNTs for delivery of the water-insoluble drug Carvedilol–A drug-loading mechanism. Applied Surface Science 2011; 257(13): 5663–5670. https://doi.org/10.1021/ar020259h
19. Tang L. Zhang H. Han J. Wu X. Zhang Z. Fracture mechanisms of epoxy filled with ozone functionalized multi-wall carbon nanotubes. Composites science and technology 2011; 72(1):7–13. https://doi.org/10.1016/j.compositesa.2014.04.023
20. Mali AJ. Pawar AP. Bothiraja C. Improved lung delivery of budesonide from biopolymer based dry powder inhaler through natural inhalation of rat. Materials Technology2014; 29(6): 350–357. https://doi.org/10.1179/1753555714Y.0000000163
21. Bansal S. Aggarwal G. Chandel P. Harikumar SL. Design and development of cefdinirniosomes for oral delivery. J Pharm Bioallied Sci. 2013; 5(4): 318–25.doi.org/ 10.4103/0975-7406.120080
22. Abdullah EC. Geldart D. The use of bulk density measurements as flowability indicators. Powder technology 1999; 102(2):151–165. doi.org/ 10.1208/s12249-013-9994-5
23. Honmane S. Hajare A. More H. Osmani RAM. Salunkhe S. Lung delivery of nanoliposomal salbutamol sulfate dry powder inhalation for facilitated asthma therapy. Journal of liposome research 2019; 29(4):332–342. doi.org/10.1080/08982104.2018.1531022
24. Blott SJ. Croft DJ. Pye K. Saye SE. Wilson HE. Particle size analysis by laser diffraction. Geological Society, London, Special Publication. 2004; 232(1):63-73. doi.org/10.1144/GSL.SP.2004.232.01.08
25. Shazly G. Nawroth T. Langguth P. Comparison of dialysis and dispersion methods for in vitro release determination of drugs from multilamellar liposomes. Dissolution technologies 2008; 15(2):7. doi.org/10.14227/DT150208P7
26. Dhumal RS. Biradar SV. Paradkar AR. York P. Particle engineering using sonocrystallization: salbutamol sulphate for pulmonary delivery. International journal of pharmaceutics. 2009; 368(1–2):129–137. doi.org/: 10.1016/j.ijpharm.2008.10.006
27. Hassan MS. Lau RWM. Effect of particle shape on dry particle inhalation: study of flowability, aerosolization, and deposition properties. Aaps Pharmscitech. 2009; 10(4): 1252. doi.org/10.1208/s12249-009-9313-3
28. Ma-Hock L. Strauss V. Treumann S. Küttler K. Wohlleben W. Hofmann T. Comparative inhalation toxicity of multi-wall carbon nanotubes, graphene, graphite nanoplatelets and low surface carbon black. Particle and fibre toxicology. 2013; 10(1): 23. doi.org/ 10.1186/1743-8977-10-23
29. Ji JH. Jung JH. Kim SS. Yoon JU. Park JD. Choi BS. Twenty-eight-day inhalation toxicity study of silver nanoparticles in Sprague-Dawley rats. Inhalation toxicity.2007; 19(10):857-87. doi.org/10.1080/08958370701432108.
30. Jafarinejad S. Gilani K. Moazeni E. Ghazi Khansari M. Najafabadi AR. Mohajel N. Development of chitosan-based nanoparticles for pulmonary delivery of itraconazole as dry powder formulation. Powder technology.2012; 222:65–70. doi.org/10.4103/0250-474X.110584
31. Osswald S. Havel M. Gogotsi Y. Monitoring oxidation of multiwalled carbon nanotubes by Raman spectroscopy. Journal of Raman Spectroscopy An International Journal for Original Work in all Aspects of Raman Spectroscopy, Including Higher Order Processes, and also Brillouin and Rayleigh Scattering. 2007; 38(6):728–736. doi.org/10.1002/jrs.1686
32. Auriemma A.S. Dry powder inhalers of gentamicin and leucine: formulation parameters, aerosol performance and in vitro toxicity onCuFi1 cells. Int J Pharm.2012; 426 (1-2): 100-107. doi.org/10.1016/j.ijpharm.2012.01.026
33. Dolatabadi JEN. Hamishehkar H. Valizadeh H. Development of dry powder inhaler formulation loaded with alendronate solid lipid nanoparticles: solid-state characterization and aerosol dispersion performance. Drug Development and Industrial Pharmacy. 2015; 41(9):1431–7. doi.org/ 10.3109/03639045.2014.956111.

34. Siepmann J. Faisant N. Akiki J. Richard J. Benoit JP. Effect of the size of biodegradable microparticles on drug release: experiment and theory. Journal of Controlled Release.2004; 96(1):123–134. doi: 10.1016/j.jconrel.2004.01.011.