

Applying Nanotechnology in the Synthesis of Benzimidazole Derivatives: A Pharmacological Approach

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Abstract: Benzimidazoles are classified as a category of heterocyclic compounds. They possess an essential structural feature of 6-membered benzene fused to 5-membered imidazole moiety. Molecules having benzimidazole motifs confirmed promising utility in organic and scientific studies. Various pharmacological residences were explored with a strong inhibitor of numerous enzymes. They are concerned with being efficient antidiabetic, anticancer, antimicrobial, antiparasitic, analgesics, antiviral and antihistaminic agents. Moreover, they can be utilized in cardiovascular disease, neurology, endocrinology, and ophthalmology. The multiple activities for benzimidazole compounds have emerged due to their stability, bioavailability, and good-sized organic activity. Modifications of some organic polymers were carried out by utilizing different azole moieties. This review is devoted to mention some of the various current techniques for the synthesis of benzimidazole derivatives and their pharmacological residences with representing numerous derivatives.

Keywords: benzimidazole; medicinal chemistry; nanocatalysis; nanoparticles; nanotechnology; polymer modification.

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1. Introduction

Benzimidazole or 1H-1,3-benzodiazole primarily based heterocycles are structurally much like evidently taking the place of nucleotides, i.e., adenine base of the DNA [1-3]. This is regarded in addition to a factor of vitamin B. This feature substantially has been utilized in drug synthesis and medicinal chemistry, showing a huge variety of organic and scientific applications. Benzimidazole is also named 3-azaindole, azindiole, benzimiinazole, benzoglyoxine. Benzimidazole is a vital modified structure that presents an extensive number of natural and pharmacologically active molecules. Magnetic nanoparticles (MNPs) have emerged as a new category of catalysts. This is referred to as ultrafine size and high surface area. They exhibit a better catalytic activity than a conventional heterogeneous catalyst. In general, there are artificial approaches for the synthesis of benzimidazole derivatives. The synthesized benzimidazole compounds have been organized from the condensation response between o-phenylenediamine and diverse carbonyl compounds. This process is carried out in the presence of ammonium chloride as a catalyst. Ammonium chloride is a commercial

catalyst. The yield of all benzimidazole derivatives turned to be 75-94% [4-7]. A condensation reaction takes place between *o*-phenylenediamine and aldehydes or alcohols. This occurs through a dehydrogenated coupling followed by an oxidative cyclodehydrogenation [8, 9]. Nevertheless, in some of those methods, a stoichiometric quantity of oxidizing markers is a prerequisite [10, 11]. Other strategies, along with thermal- or acid-promoted synthesis in addition to microwave, sonicator, or ultrasound strategies, are also known [8]. Interestingly, the direct regioselective C-2 arylation of imidazole with aryl halides generally calls for the usage of a Pd(II)/Cu(I)/Au/TiO₂ catalytic machine in a surplus of reagents beside the presence of additives, excessive temperature, or pressure [12, 13]. Benzimidazoles can easily interact with the biopolymers of the dwelling systems, which are chargeable for their several organic functions. In particular, benzimidazole derivatives showcase antimicrobial [14-16], antiviral [13, 17], anticancer [18-20], anti-inflammatory [21-23] and antioxidant [24] agents. Meanwhile, numerous derivatives were evolved as healing agents, inclusive of proton pump inhibitors [25], stage modulators [26], and antidiabetics [27, 28]. Recently, Benzimidazole derivatives were used in the modification of polymers such as nanostructured poly(benzimidazole) membranes [29], poly(imides), and poly(imides)/ionic liquid composites using a benzimidazole moiety [30]. The best advantage of magnetic nanoparticles is their easy separation from the reaction mixture using an external magnet.

In this article, we attempt to demonstrate the structures of some of the medicinally and biologically important benzimidazole and benzodiazepine derivatives accordingly. It is a study to cover conventional and new methods to synthesize certain pharmacologically active benzimidazole derivatives and different methods of building the benzimidazole nucleus.

2. Application of Nanotechnology in the Syntheses of Benzimidazole Derivatives

Practically, all benzimidazoles synthesis methods start with benzene derivatives possessing nitrogen-containing functions *ortho* to each other [31, 32]. Among the various MNPs employed as the catalyst, Fe₃O₄-NPs are mentioned. It has been widely studied due to high surface area to bulk ratio, low toxicity, high activity, thermal stability, and surface modification capability with as easy dispersion [33-38]. A plausible mechanism for the model of benzimidazole synthesis is presented in Figure 1. Fe₃O₄-NPs as Lewis acid catalyst may invigorate the carbonyl group of aldehyde. Hence, this leads to an increase in the carbon atom's electrophilic character in the carbonyl group with lowering the transition state energy. It was followed by the attack of an amino group from *l*-phenylenediamine on the activated carbonyl group that resulted in an imine. The present NH₂ group in *o*-phenylenediamine is attacked by a carbon atom C=N group. This is followed by producing a proton that attracts the catalyst particles so that they can recover easily. The recovered Fe₃O₄-NPs were placed in ethanol and dried at 60 °C [39]. A green and efficient method for synthesizing Benzimidazole compounds was followed using Fe₃O₄-NPs with the continuous bubbling of air as the oxidant in PEG-400/H₂O aqueous solution at room temperature [40].

An effective and selective synthesis for 1, 2-disubstituted benzimidazole and 1, 5-benzodiazepine derivatives was performed using 1, 2-diamines and aldehydes or ketones. This process was carried out in the presence of catalytic and magnetically recoverable chitosan-supported iron oxide nanoparticles (Fe₃O₄/chitosan). This nanocomposite as a biodegradable one was immersed in ethanol at high ambient yields. The Fe₃O₄/chitosan nanocatalyst can be recovered easily and reused without any significant loss of the catalytic activity [41]. This

procedure takes place in the presence of mechano-chemically synthesized zinc oxide nanoparticles as a catalyst without solvent [42].

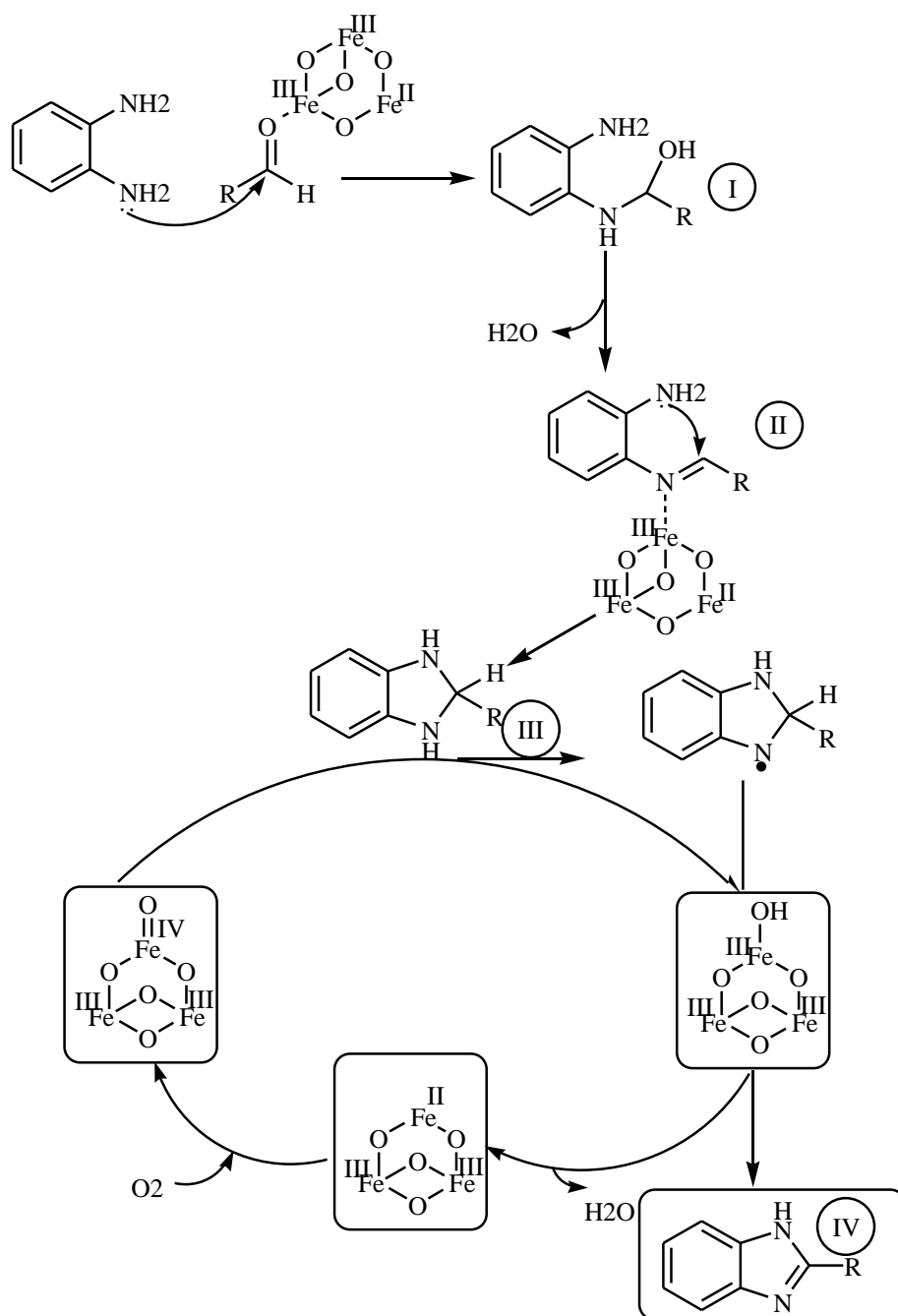


Figure 1. Mechanism of synthesizing benzimidazoles, catalyzed by Fe_3O_4 -NPs.

A series of 2,4,5-trisubstituted imidazoles and 1,2-disubstituted Benzimidazoles catalyst by ZrO_2 nanoparticles- supported β -cyclodextrin nanoparticles (ZrO_2 - β CD) was prepared by a simple one-pot co-precipitation method by using $\text{ZrO Cl}_2 \cdot 8\text{H}_2\text{O}$ and NH_4OH [43]. The high electrocatalytic activity of a composite, formed by supporting Ni_3N nanoparticles on benzimidazole covalent organic frame (COF) for oxygen evaluation reaction, was achieved [43]. The syntheses of COF and its nanocomposite were achieved via reacting 3,3'- diaminobenzidine and 1,3,5-triformyl phloroglucinol in a mixture of mesitylene and 1,4-dioxan. IISERP-COF3- Ni_3N was prepared by loading nickel nitride nanoparticles onto the COF *via* a solid-state synthesis, as displayed in Figure 2.

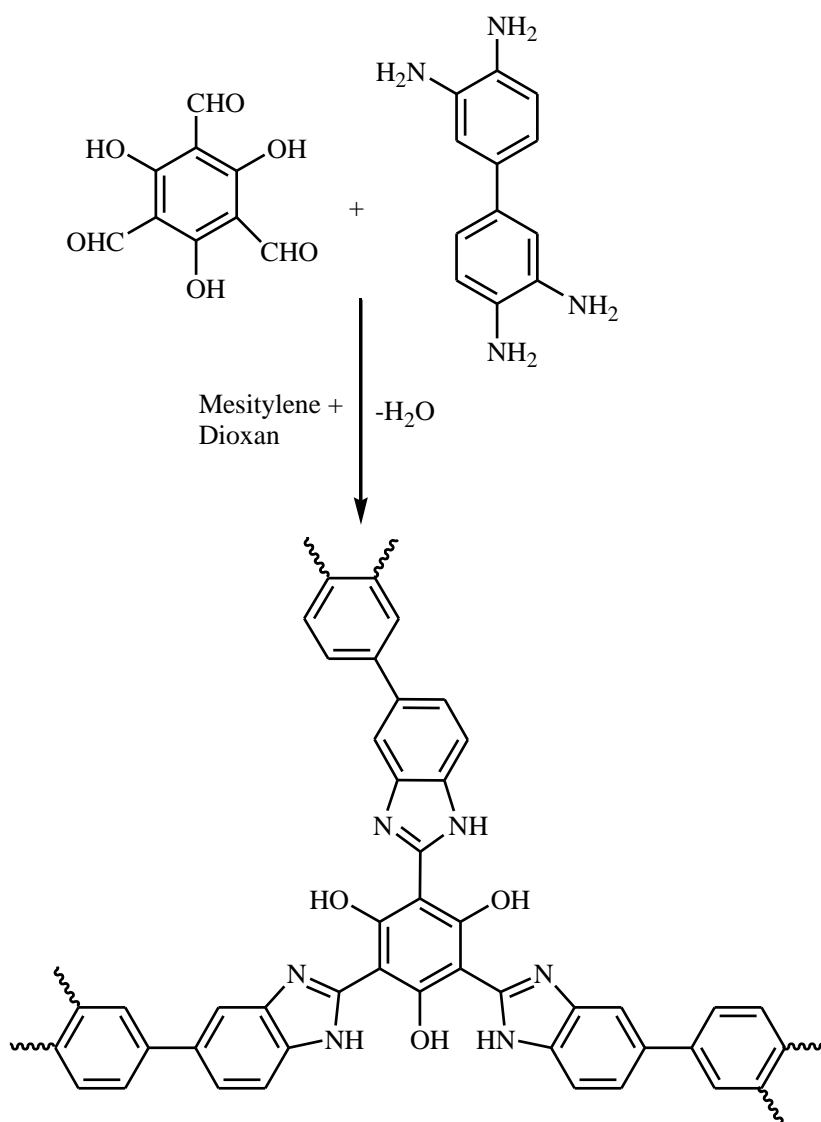


Figure 2. A co-precipitation method to prepare benzimidazoles by using $\text{ZrO Cl}_2 \cdot 8\text{H}_2\text{O}$ then by using nickel nitride nanoparticles, respectively.

Some azoles and azido derivatives [44-47] were loaded to organic polymers and metal nanoparticles [48, 49], showing antimicrobial activities. Besides, chitosan [50-53] is considered among the common polymers that can bear biomedical agents. Heterocyclic aromatic polymers are considered among the high-performance materials. They possess high chemical resistance, flame retardancy, radiation stability, and excellent mechanical strength over a broad temperature range [54]. The structure of poly-benzimidazole (PBI) nanofibers resembled that of a nonwoven fabric. These fibers were formed by the precipitation of oligoimidazoles and their subsequent polymerization with the developing crystal structure. The nanofibers exhibited excellent thermal stability. The monomer's form affected the reaction-induced phase separation participates in making variations in the morphology of the precipitates. The monomer structure is a vital factor that controls the morphology. Benimidazol-2-ylidenes with gold nanoparticles (AuNPs) were studied as reactive compounds. A collective experimental and computational approach was employed [55]. Grafting of benimidazol-2-ylidenes with benzyl groups on the nitrogen atom was depicted. This was followed by comparing structurally similar N-heterocyclic carbenes (NHCs) loaded with another N- group. A significant reactivity was noticed for all NHC. However, eroding AuNPs has occurred under the NHC effect with originated bis(NHC) gold complexes. DFT

calculations examined the modes of grafting of such ligands by defining the absorption energies.

Benzimidazole derivatives were synthesized by using Copper (II) oxide (CuO) nanoparticles. Copper (II) oxide (CuO) nanoparticles were prepared through a facile precipitation procedure to copper acetate. The produce nanoparticles asserted to act as an effective catalyst for C-N coupling reactions of benzimidazole with arylhalides [56]. The influence of the particle size on N-arylation of benzimidazole with 4-chlorobenzonitrile was investigated.

3. Some Pharmacological Aspects of Benzimidazole and Substituted Benzimidazoles

Various chemical modifications were carried out so far around the benzimidazole backbone (core) to improve its various biological activities. Benzimidazoles have emerged as an important heterocyclic compound because of their broad spectrum of biological activities. In this review, anti-inflammatory, anthelmintic, anticancer, and antiviral activities of benzimidazole and its derivatives are determined.

3.1. Antiviral and antitumor activities

The antiviral properties of different benzimidazole derivatives have been reported in a variety of studies using different virus strains, such as human immunodeficiency virus (HIV) [57-61], hepatitis C virus (HCV) [62-69], human cytomegalovirus (HCMV) [70-74] and herpes simplex virus-1 (HSV-1) [75].

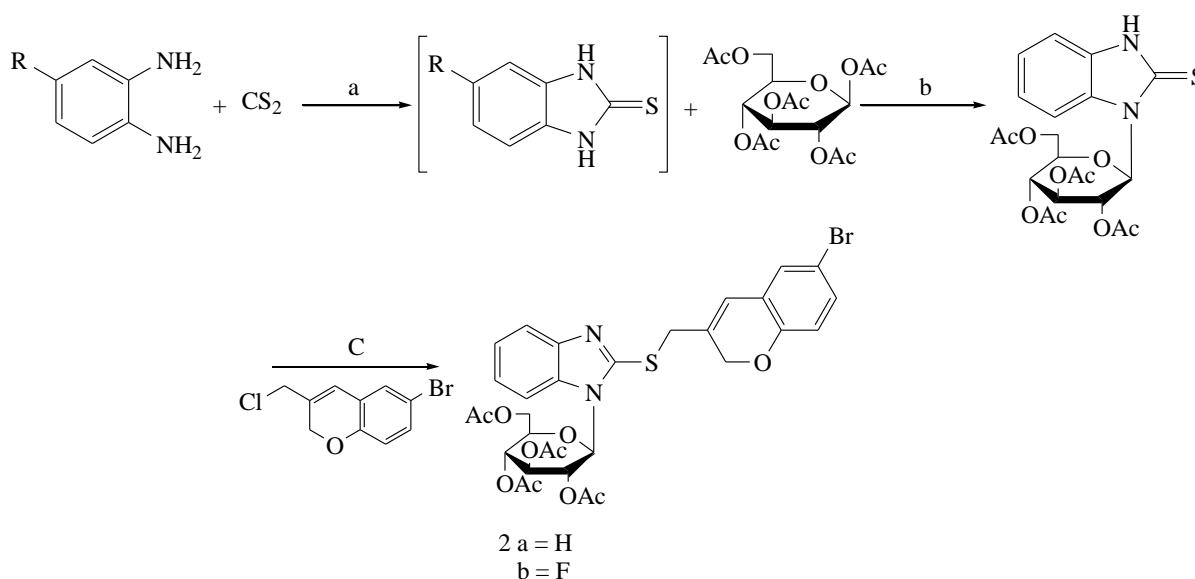


Figure 3. Synthesis of some benzimidazole derivatives with antiviral activities. Reagents and conditions: (a) KOH/EtOH/H₂O. (b) BSA/Me₃SiOTf/CH₃CN/80°C. (c) 35% NH₄OH/CH₃CN/ H₂O (at 25 °C).

A series of 1-aryl-1*H*,3*H*-thiazolo[3,4-*a*] benzimidazoles (TBZs) was found to be highly active as HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs) [57, 58]. 1-(2,6-difluorophenyl)-1*H*,3*H*-thiazolo [3,4-*a*] benzimidazole (TBZ, NSC 625487) manifested to be an efficient inhibitor for HIV-1 induced cytopathic effect [59-62]. Several new benzimidazole-coumarin conjugates showed an inhibitory effect on HCV replication; some compounds were synthesized according to Figure 3 and showed EC₅₀ values of 3.4 μM and 4.1 μM, respectively [62].

A series of 1-cycloalkyl-2-[(4-diarylmethoxy)phenyl]-benzimidazole-5-carboxylic acid derivatives were reported to have inhibitory activity against hepatitis C virus NS5B RNA-dependent RNA polymerase (HCV NS5B RdRp). The synthesized compounds were found to have, in addition to their RNA polymerase inhibitory activity, selective activity against DNA polymerases with low cytotoxicity was also observed [63]. A new investigated series of benzimidazole derivatives bearing a diarylmethylene group was tested for its inhibitory activity against HCV NS5B RdRp. These compounds exhibited favorable pharmacokinetic profiles, high selectivity for NS5B polymerase, and good safety profiles, suggesting the potential for a clinical candidate to treat hepatitis C [64, 65]. Some benzimidazole-5-carboxylic acid derivatives were detected to specifically inhibit HCV NS5B RdRp and regarded as potent compounds [66] for such purpose. Optimizing the previously discovered series of substituted-5-carboxybenzimidazole by replacing the ionizable carboxylic acid with neutral substituents modified their physicochemical properties and increased their cellular permeability. Modification to one of these compounds improved cell culture activity and was not cytotoxic to the host cells [67-59]. 2-Bromo-5,6-dichloro-1-(β -D-ribofuranosyl)benzimidazole (BDCRB) and its 2-chloro analog (TCRB) were determined as efficient and selective inhibitors of HCMV replication. However, these compounds were found to have low *in vivo* activity due to rapid metabolic cleavage of the glycosidic linkage at the 1-position [70]. Efforts were exerted to overcome the limitation above. It led to the discovery of Maribavir, (GW1263W94). This compound was one of the most promising anti-HCMV drugs in clinical development. It showed advantages over other existing anti-HCMV drugs in their *in vitro* potency, bioavailability, the safety profile in acute, chronic, and genetic toxicology testing. Meanwhile, the lack of cross-resistance is inherent in its novel mechanism of action, which involves inhibiting viral DNA synthesis [70, 72].

Several benzimidazole nucleosides and acyclonucleosides have been studied for their antiviral activity against HCMV and HSV-1. Only the 2-thiobenzyl analogs showed high activity, confirming the favorable influence of the thioether linkage at the 2-position on the antiviral activity [36, 37]. Some *N*-benzene-sulphonyl-benzimidazoles were reported to have good antiviral activity against HCMV and HSV-1 at micromolar concentrations [75-78]. A series of 2-pyridyl-1*H*-benzimidazole-4-(*N*-substituted-carboxamide) derivatives was found to have excellent inhibitory activity against Cocksackie virus B3. They were synthesized and explored to be far more active than ribavirin [78]. Studying the 2-substituted-5-amidino-benzimidazoles antiviral activity revealed that compounds having a pyridine moiety at C-2 showed the most distinct and selective activity against coxsackieviruses and echoviruses [77]. Enviroxime compounds exhibited potent broad-spectrum anti-rhinovirus and anti-enterovirus activity. Preliminary studies indicated that their action mechanism involves inhibition of viral RNA synthesis [77-80]. 1-Cyclopropyl-1,3-dihydro-3-[[1-(4-hydroxybutyl)-1*H*-benzimidazol-2-yl)methyl]-2*H*-imidazo[4,5-*c*]pyridin-2-one, (BMS-433771) is determined as an efficient respiratory syncytial virus (RSV) inhibitor showing acceptable oral bioavailability [81-85]. The benzimidazole derivative (JNJ 2408068) or known as (R170591), was discovered to have inhibitory activity against RSV at nanomolar concentration, which was about 100,000 times better than that of ribavirin [86]. Recently, 2,6-dihalophenyl-substituted-1*H*,3*H*-thiazolo[3,4-*a*]benzimidazoles (TBZs) were tested against enteroviruses. The structure-activity analysis detected that the substituents at position 6 of the tricyclic system positively affect antiviral activity. Hence, any substitution at position 7 was not recommended. Meanwhile, it was not cytotoxic at high concentrations [87]. Several promising antitumor active agents were found to

contain the benzimidazole ring system. They were explored to exert their antitumor activity by acting mainly as topoisomerase inhibitors [88-92], alkylating agents [17, 93-96], antiangiogenic agents [97-101], and protein kinase inhibitors [102-107]. A series of benimidazol-furanhybrids was designed and synthesized through synthetic facial pathways and evaluated in vitro cytotoxic activity against breast (MCF-7) and hepatocellular (HepG2) carcinoma cell lines [108].

3.2. Alkylating and antiangiogenic agents.

Pyrrolo[1,2-*a*]benzimidazoles-4,7-dione (PBIs) derivatives represented a different class of antitumor agents exhibiting cytotoxic activity against various cancer cell lines. Their mechanism of cytotoxicity involves N (7) purine alkylation followed by depurination and backbone cleavage at the guanine and adenine bases. It was determined that the presence of an ester group at the 3-position was required for optimal cytotoxicity because it provides lipophilicity [17, 91-95]. A series of 2-substituted benzimidazole-4,7-dione was synthesized and evaluated for its cytotoxic activity. They succeeded in showing excellent cytotoxic activity comparable to that of mitomycin C [96]. Angiogenesis expressing the formation of new blood vessels from existing vasculature was considered a critical event for the growth and metastasis of solid tumors. Growth factors, including vascular endothelial growth factor, fibroblast growth factor, and platelet-derived growth factor, are considered the most important positive regulators of angiogenesis. So, any inhibitor showing these growth factors and their tyrosine kinase receptors drew the attention of potent anticancer drugs [109]. These receptors comprise platelet-derived growth factor receptor (PDGFR) and insulin-like growth factor receptor-1 (IGF-1R). A class of 1-phenylbenzimidazoles was reported as a selective inhibitor of PDGFR. The structure-activity relationship revealed that only substituents in the 5-and 6-positions enhance the activity. 5-OMe derivative was found to be the most potent and the most PDGFR selective. In addition, analogs bearing cationic solubilizing groups at this position showed 3-fold increased potency with retaining good selectivity [97-98]. A series of 3-(1*H*-benzo[*d*]imidazol-2-yl)pyridin-2(1*H*)-one was synthesized and tested for its inhibitory activity against IGF-1R. Although some compounds were found to have high inhibitory activity, potent cytochrome P450 (CYP) inhibition profiles were also observed. Results described have demonstrated that the pendant imidazole was primarily responsible for potent (CYP) inhibition. By replacing this moiety with other groups such as imidazoline, greater separation of IGF-1R activity versus (CYP) inhibition was observed [99]. Benzimidazole derivatives containing styryl sulfone moiety at the 2-position were tested for their antiproliferative activity. Some of the synthesized compounds showed efficacy against HT-29 human carcinoma inhibiting 51% of the tumor growth at low micromolar concentration [110]. A series of 2-methyl-5(6)-nitro-1*H*-benzimidazole derivatives was synthesized and evaluated for their cytotoxic activity against breast cancer (MCF7). Among this series, two compounds were found to have high cytotoxic activity [111]. A series of 2-(1-benzyl-2-methyl-1*H*-benzimidazol-5-ylimino)-3-(substituted)-thiazolidin-4-ones was synthesized and evaluated for its inhibitory activity against Burkitt's lymphoma promotion to show significant inhibitory activity [112].

4. Conclusions

Benzimidazole derivatives are among the most important heterocyclic compounds. This may be because they are much like evidently taking place nucleotides. This review highlights

the importance of using nanotechnology to synthesize benzimidazoles as anticancer agents with their diverse biological profiles. Being commercially derived in very sort of therapeutic agents, this review can facilitate chemists designing novel compounds. This approach is comprised in the frame of synthesizing highly active biological compounds against cancer cells alongside being antifungal and bacterial agents. Moreover, this review refers to polymer modification by using azole compounds. We aimed to point out some contemporary applied techniques to synthesize the benzimidazole derivatives. Moreover, their pharmacological potencies with representing numerous derivatives are monitored.

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Conflicts of Interest

The authors declare no conflict of interest.

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