Chapter

Introductory Chapter: Short Insight in Synthesis and Applications of Benzimidazole and Its Derivatives

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1. Introduction

Benzimidazole is well known as an important pharmacophore among heterocyclic compounds due to the remarkable medicinal and pharmacological properties of its derivatives [1–3]. 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 [1, 4–7]. Recent research recommends benzimidazole derivatives as potential EGFR and erbB2 inhibitors [8, 9], DNA/RNA binding ligands [10, 11], antitumor agents [12–14], anti-Alzheimer agents [15, 16], antidiabetic agents [17, 18], antiparasitic agents [10, 19], antimicrobial agents [20, 21], antiquorum-sensing agents [12], and antimalarial agents [19]. Intensive studies have demonstrated the use of the benzimidazole scaffold as key pharmacophore in clinically approved analgesic and anti-inflammatory agents [22]. Chiral benzimidazole derivatives were found to be $Na_V1.8$ (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 [23]. Other benzimidazole derivatives have been shown to be anti-HIV-1 agents through the protection of APOBEC3G protein [24]. Benzimidazoles grafted with aromatic nuclei have been noted as antioxidant agents [25]. A correlation of the grafted organic functions on the benzimidazole scaffold has been found with their therapeutic potential [26]. Thus, carboxylic acids, carbamates, and amidines have been shown to be effective anticancer drugs [26–28], benzimidazole esters were reported as antifungal agents [29], and 2-aminobenzimidazole derivatives possesses very good antimicrobial activity [30].

Structure-activity relationship (SAR) studies have shown that 1,2,5,6-substituted benzimidazoles with various substituents are analgesic and anti-inflammatory agents [22]. Also, SAR studies were accomplished for antiviral, anticancer, antihelminthic, antimicrobial, antimycobacterial, antidiabetic, antiprotozoal, antipsychotic, antidepressant, and antioxidant benzimidazole derivatives [1, 31–33].

2. Synthesis of the benzimidazole derivatives

Benzimidazole synthesis reported by Hoebrecker in 1872 has greatly improved and diversified over last decades precisely because of its very diverse applications which will be discussed in the third part of this chapter. Classical synthesis was improved in terms of reaction conditions: catalysts, solvents or solvent-free, heating source, microwaves or ultrasound, and of course, nonpollutant or 'green' conditions. In the following, we will make (1) a very short presentation of classical syntheses and (2) an introduction to benzimidazole syntheses by rearrangement reactions.

2.1 Classical syntheses of benzimidazoles

Synthesis methods of the benzimidazoles have been extensively summarized in previous studies, published by Wright [34] and Preston [35]. Actually, all classical syntheses of benzimidazoles represent modifications to two of the classic reactions [26]: (i) the Phillips-Ladenburg reaction, coupling 1,2-diaminobenzenes with carboxylic acids (see **Figure 1**) and (ii) Weitenhagen reaction, coupling of 1,2-diaminobenzenes with aldehydes and ketones (pathway 3) *via* benzimidazoline **3**. In the case of the Phillips-Ladenburg reaction, esters, acid anhydrides, acid chlorides, and lactones (pathway 1) can be used instead of the acids, and benzimidazoles were generated *via* amide **1** cyclization or amides, nitriles, amidines, guanidines and benzimidazoles were resulted *via* cyclization of amidine **2** (pathway 2). The Phillips synthesis of benzimidazoles uses 4 N hydrochloric acid or glacial acetic acid, but various methods applied today use sulfuric acid or polyphosphoric acid. Reaction temperatures are high, reaching 250–300°C.

2.2 Synthesis of benzimidazoles *via* rearrangement of quinoxalinones

The limitations of classical synthesis, especially with respect to the synthesis of heterocyclic substituted benzimidazoles, have led to other methods [36].

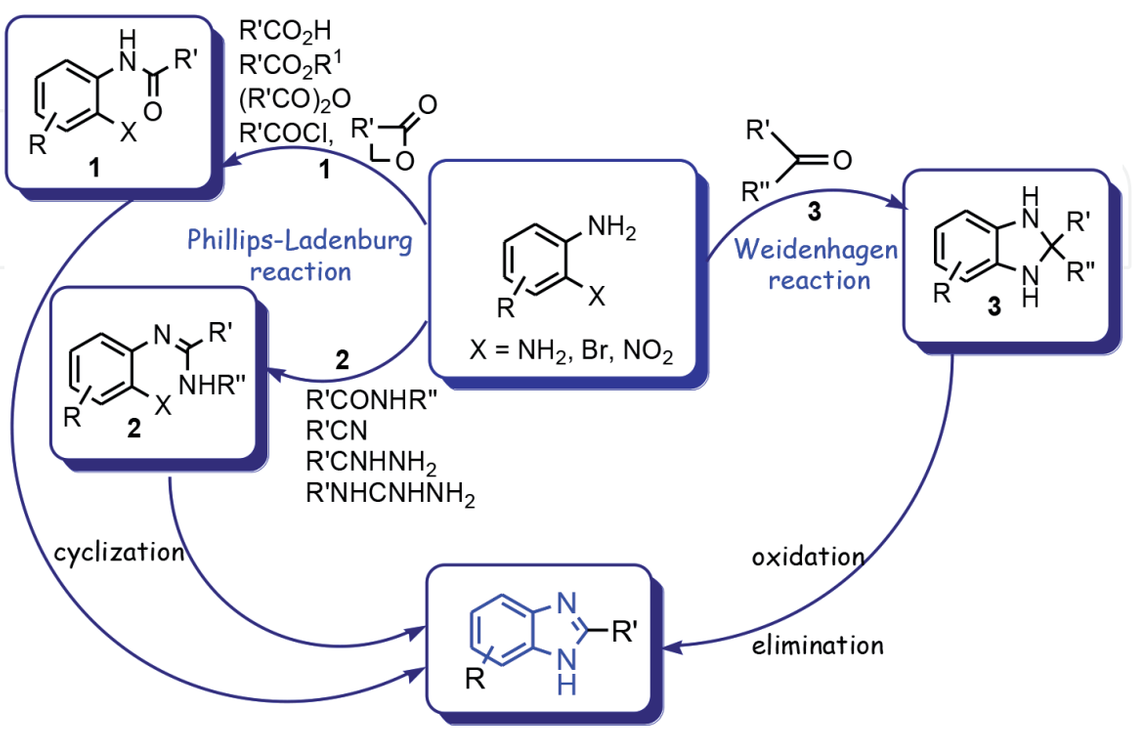

Figure 1.
Classical methods for synthesis of benzimidazoles.

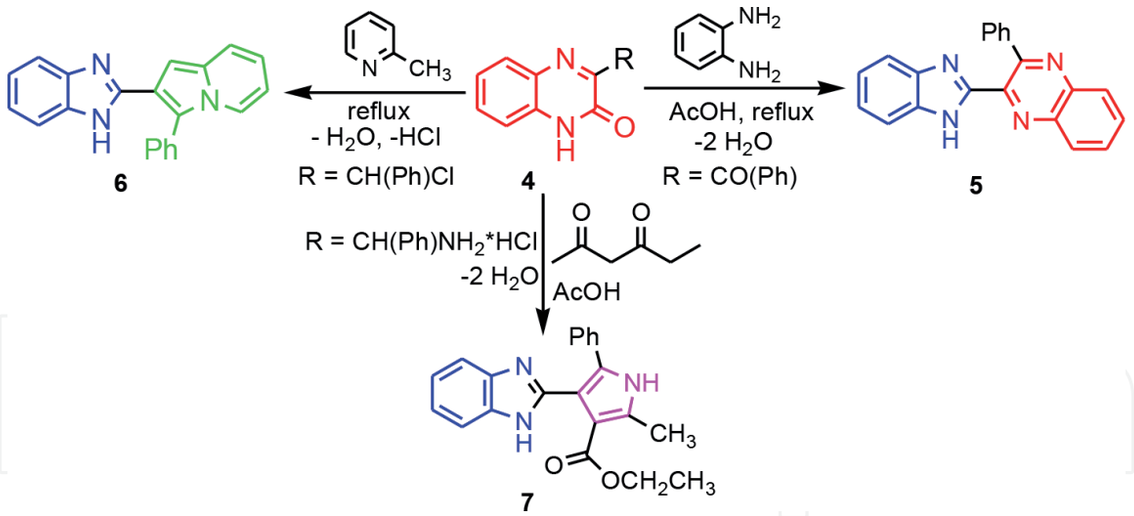

Figure 2.
Synthesis of 2-heteroaryl benzimidazoles by rearranging the quinoxalinones.

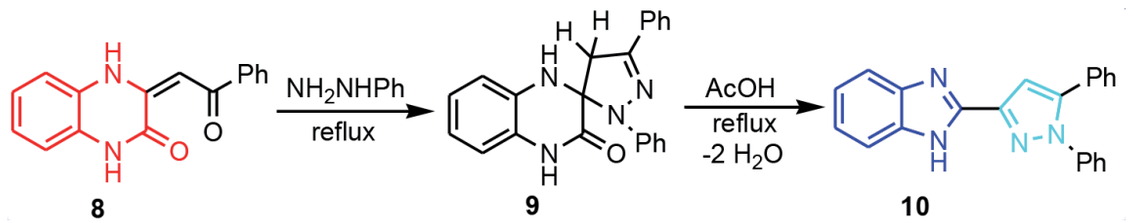

Figure 3.
Synthesis of 2-(1,5-diphenyl-1H-pyrazol-3-yl)-1H-benzo[d]imidazole ***10****.*

Rearrangements of quinoxalinones represent the most advantageous methods of synthesis currently reported [26, 36]. Hereinafter, some newer syntheses of benzimidazole derivatives are presented by quinoxalinone rearrangements. These new syntheses represent a combination of rearrangements, multicomponent reactions, and tandem sequences [26].

Thus, synthesis of benzimidazoles by the Hinsberg reaction implies condensation between 1,2-diaminobenzene and quinoxalin-2-one **4** to afford 2-benzimidazolylquinoxaline **5** in a 97% yield (see **Figure 2**). 2-(Indolizinyl)benzimidazoles **6** were obtained in high yields using a Chichibabin reaction, by refluxing quinoxalin-2-one **4** with α-picoline [37].

2-(Pyrol-3-yl)benzimidazole **7** was synthesized by a Knorr reaction between α-aminoketone of quinoxalinone **4** and ethyl acetoacetate [37].

Reaction of phenylhydrazine with 3-arylacylidene-3,4-dihydroquinoxalin-2(1H)-one **8** in boiling acetic acid implies the formation of spiro-compound **9**, which rearranges into pyrazolylbenzimidazole **10** (see **Figure 3**) [26].

3. Applications of benzimidazole derivatives in other fields than medicinal and pharmaceutical chemistry

There are a large number of published scientific papers that refer to the synthesis, properties, and applications of benzimidazoles. Thus, if we search the keyword "benzimidazole" on Science Direct, we get 26,386 results, of which 915 are published in the last 4 months.

Particular attention has been paid to improving the synthesis of chiral benzimidazoles, a relatively young branch of chiral chemistry, due to their importance in the field of therapeutic agents [38]. Also, chiral benzimidazoles were

used as organocatalysts in Diels-Alder reaction, asymmetric aldol type reactions, asymmetric Michael addition, or enantioselective α-chlorination reactions as well as in palladium and rhodium benzimidazole complexes used as catalysts in Mizoroki-Heck [39] and Suzuki-Miyaura coupling reactions or in reduction reactions [40].

But recent research shows that benzimidazole scaffold is important not only for its therapeutic applications but also for its different uses in (nano) materials chemistry as optical chemical sensors [41], with special applications in medicine, environmental science, and chemical technology and has obvious advantage over other sensing devices, such as ease of operation and low cost (see **Figure 4**).

Supramolecular assemblies with interesting properties and with a wide range of applications like adsorbent materials, thermostable polymers, nanocontainers for small molecules, or liquid crystals for electronic conduction make up another use of benzimidazole and its derivatives [42–45].

Polybenzimidazole (PBI) derivatives: solid electrolyte for fuel cells [46], fibers [47], thin coatings [48], protective coatings for aerospace applications [49], or for the removal of uranium, thorium, and palladium from aqueous medium [50] are intensively studied in recent years. With an experience of 32 years, PBI Performance Products from Charlotte, North Carolina, is the leader in firefighter safety in Europe, USA, and the Middle East. PBI fabrics protect firefighters in a number of fire services, being renowned for their proven protection from heat and flame [51]. Another use of polybenzimidazoles is as PBI-based mixed matrix membranes with exceptional high water vapor permeability and selectivity [52].

In addition, the organic compounds are the most preferred for future photonic technology. Thus, several benzimidazoles with very good non-linear optic (NLO) properties, from very small molecules, such as 2-mercaptobenzimidazole, 2-phenyl benzimidazole, and 2-hydroxybenzimidazole [53], till molecules with more complicated structures [54], were studied.

Benomyl and carbendazim are recommended as benzimidazole fungicides having low toxicities in low doses and also are not carcinogenic, mutagenic, or teratogenic [55].

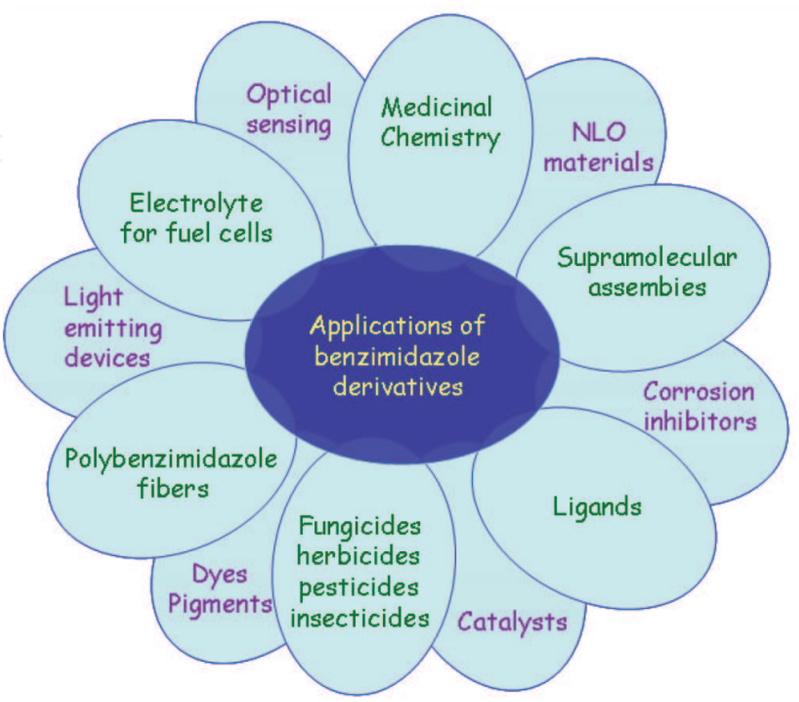

Figure 4.
Applications of benzimidazole derivatives.

The literature shows the conditions of using common benzimidazole pesticides and reported the use of benzimidazoles as herbicides and insecticides [56].

More and more research is being reported on the use of benzimidazoles as corrosion inhibitors for various metals (Cu, Fe, and Zn) under acidic conditions [57–58].

Other authors have shown that benzimidazole is a versatile and essential chromophore for organic dyes with photophysical, electrochemical, and photovoltaic properties due to the position of donors, acceptors, and π-linkers in the benzene ring [59]. A broad range of nuances in watercolor painting and electrophotographic developer toner has been made over three decades using benzimidazol-2-one derivatives, highly appreciated for their durability and light resistance [36]. Benzimidazole proved to be an essential core for organic light emitting devices (OLEDs) with superior phosphorescence, thermal properties, and morphological stabilities [60].

4. Conclusion

Benzimidazole occupies a central place in the class of heterocyclic compounds used in pharmaceutical and medicinal chemistry. The chemistry and applications of benzimidazole and its derivatives are in continuous development, especially in the last decades. In the coming years, we expect new synthesis strategies and more exciting applications to meet world market requirements.

Conflict of interest

There is no 'conflict of interest' in writing this chapter.

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