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ORIGINAL ARTICLE

Synthetic approaches to benzimidazoles from *o*-phenylenediamine: A literature review

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KEYWORDS

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Abstract The methods for the synthesis of benzimidazoles have become a focus of synthetic organic chemists, as they are useful building blocks for the development of important therapeutic compounds in medicine. Benzimidazole nucleus plays a very important role as a therapeutic agent e.g. antiulcer and anthelmintic drugs. Other benzimidazole derivatives exhibit pharmacological activities such as antimicrobial, antiviral, anticancer, anti-inflammatory and analgesic.

1. Introduction

Among heterocyclic pharmacophores, the benzimidazole ring system is quite common. These substructures are often called 'privileged' due to their wide recurrence in bioactive compounds. Although there is great interest in benzimidazole ligands and structural chemistry, the main interest is in their biological activities.

The early 1950s was an important period regarding discovery of the biological significance of benzimidazole-containing structures and the closely-related purines (Fig. 1). The 5,6-di methyl-1-(α-D-ribofuranosyl)benzimidazole ring system was discovered in 1948 as an integral part of the structure of vitamin B12 [1] (Fig. 1).

Subsequently pharmaceutical, veterinary and agrochemical products were discovered including thiabendazole, cimetidine, azomycin, metronidazole, misonidazole, and chlotrimazole, antihistamines, astemizole and the anti-ulcerative omeprazole) [2].

Benzimidazole-based drugs exhibit a wide range of different biological activities as a result of changing the groups on the core structure, as shown in Fig. 2. These biological activities include anti-cancer (1) [3], bactericidal (2), [4], fungicidal (3) [5] and [6], analgesic (4) [7] and anti-viral properties (5) [8]. Some have cardiovascular applications (6) [9] while some derivatives have been synthesized and evaluated for inhibition of HIV-1 infectivity [10].

2. Synthesis of benzimidazoles

The first benzimidazole was prepared by Hoebrecker [11], who obtained 2,5-dimethylbenzimidazole by the reduction and dehydration of 2-nitro-4-methylacetanilide (Scheme 1).

Almost all syntheses of benzimidazoles start with benzene derivatives possessing nitrogen-containing functions ortho to each other (Fig. 3) that is, the starting material possesses the function designated by formula many methods have been reported for the synthesis of benzimidazols. Most of these methods involve the condensation of ortho-

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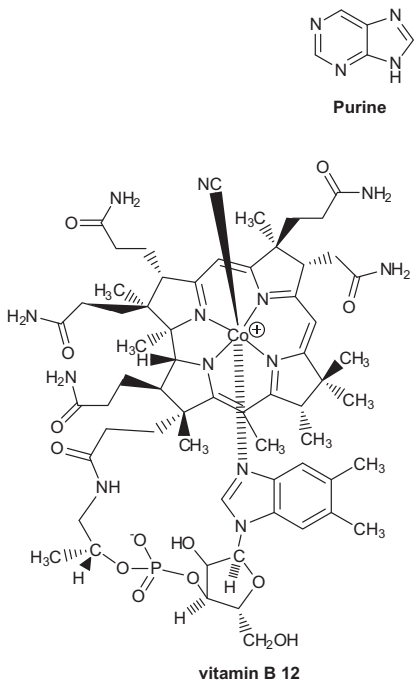

Figure 1 Some imidazole containing bioactive compounds.

phenylenediamine, and its derivatives with carboxylic acids, or aldehydes.

Various catalyzed synthesis of benzimidazole derivatives are known condensation of *o*-phenylenediamine with ortho esters in the presence of various lewis acid catalyst is also known such as $ZrCl_4$, $SnCl_4$, $TiCl_4$, $ZrOCl_2{\cdot}9H_2O$ and $HFCl_4$.

Here a number of different synthetic methods for benzimidazoles have been grouped according to the starting material of *o*-phenylene diamines [12].

2.1. By reaction with carboxylic acids

Literature survey has revealed that *o*-phenylenediamines react readily with most carboxylic acids to give 2-substituted benzimidazoles, usually in very good yields. The reaction is carried out usually by heating the reactants together on a steam bath, by heating together under reflux or at an elevated temperature, or by heating in a sealed tube [13] (Scheme 2).

The most commonly used (Phillip's method [14], involves the condensation of *o*-diaminobenzenes with carboxylic acids or its derivatives, including heating the reagents together in the presence of concentrated hydrochloric acid (Scheme 3), this is the most common synthetic method for preparation of a wide range of benzimidazoles.

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 (Scheme 4) only at room temperature, and this is an important precursor for 2-carboxylic benzimidazoles [15].

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 (Scheme 5). The reaction is green and economically viable [16].

Recently Saberi has reported synthesis of 2-benzimidazoles under microwave irradiation and solvent-free conditions which is catalyzed by alumina, silica gel and zeolite HY As shown in Scheme 6, *o*-phenylenediamine (2 mmol) with aromatic, aliphatic and heterocyclic carboxylic (2 mmol) and 50 mg of Alumina or Silica gel or Zeolite were mixed thoroughly in a mortar. The reaction mixture was then irradiated in a domestic microwave oven for 5–9 min at 160–560 W [17].

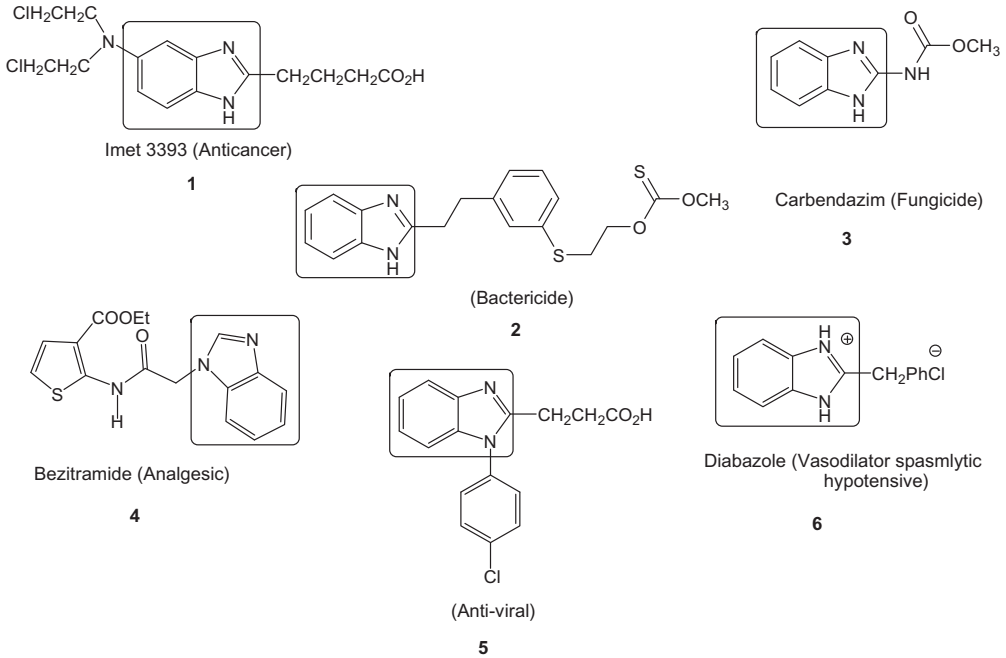

Figure 2 Some benzimidazole containing drugs.