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Der Pharmacia Lettre, 2021, 13 (5): 21-27
(http: //scholarsresearchlibrary. com/archive. html)

ISSN 0975-5071
USA CODEN: DPLEB4

An Overview About Synthetic and Biological Profile of Benzimidazole

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ABSTRACT

Medicinal chemistry is a science associated with extraction, analysis and chemical synthesis of newer derivatives which finds applications as medicinal agent in identification and treatment of diseases. In this context, this branch of chemistry is establishing a basis of medicinal molecules in therapeutics. The aim to develop new synthetic compounds to be used as drugs requires combined approach of many disciplines such as chemistry of biomolecules and also of biology at molecular level with medicinal chemistry. The chemists and the biologists are working in collaboration in the search of a lead compound for the new medicines or drug molecules or also in case of an on-going research on a pre-clinical drug molecule. The various other disciplines working in collaboration includes biology, CADD and X-ray crystallography. This team of collaborators discovered various biologically important compounds, one of them is Benzimidazole. Benzimidazoles and the compounds derived from it represent as an active class of biological literature. Following the discovery of benzimidazole, several structural modifications have been included in the benzimidazoles nucleus to increase its biological activity. In this review we are focusing on various synthetic strategies and biological activities of Benzimidazole nucleus.

Keywords: Benzimidazoles, Synthetic strategies, Alkylating agents, Topoisomerase inhibitors, Folate reductase.

INTRODUCTION

Benzimidazole, a heterocyclic compound is a part of many natural and non-natural products which even include some vitamins [1]. Therefore, benzimidazole substitutes took the attention of different researchers, mostly as a substituent or as a replacement. The most important positions or sites effecting drug actin of benzimidazole substituents is 1st and 2nd position [2] (Figure 1).

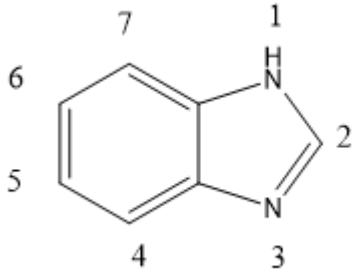

Figure 1: Benzimadazole.

Benzimidazole is also known as benziminazoles or benzoglyoxalines or o-phenylene formamidine. In this review, we focused on few methods to synthesize benzimidazole 2-substitutents because of the importance of the benzimidazole molecules in pharmacology specially as antibiotics, anticancer agents, angiotensin-II receptor antagonists and also possess antimicrobial properties [2], antifungal, antiparkinsonian, etc [3]. The molecules containing -NH group undergo N-alkylation and N-acylation reaction as per Mannich reaction and Michael reaction in case of Isatin compounds [4], possess properties almost similar to benzimidazoles [5]. Benzimidazole is usually soluble in H_2O and also in polar solvents [6]. The benzimidazole molecule exists in 2 tautomeric forms which are equivalent and the existence of tautomeric forms is due to the hydrogen atom which can be present among any one of the two nitrogen atoms present in ring. It is having a dipole moment of 3.61 D thus acts as a polar molecule and is highly water soluble [7]. The molecule of benzimidazole is considered as an aromatic molecule because it is completing a sextet of π-electrons, one pair of electrons from the -N atom which is protonated and one pair from the rest four other atoms present in the ring. It exists both as an acid as well as a base. Being acidic, its pKa is 14.5 thus its acidity is less than phenol, imides, carboxylic acid but a bit more than alcohols. Being basic, pKa for the conjugated acid is 7 thus benzimidazole is highly basic in comparison to pyridine which is approximately 60 times [8,9].

SYNTHETIC STRATEGIES OF BENZIMIDAZOLE

Benzimidazole falls under the category of heterocyclics having usual properties of common and specific medicinal compounds. The topic of concern from a long time is to establish a library of the derivatives of benzimidazole because of the numerous biological activities and great importance as a synthetic compound. The thorough literature survey on the chemical properties of derivatives of benzimidazole reported the synthesis of 1st benzimidazole molecule by Hoebrecker et al. in 1872 by the reduction of 2-nitro-4-methylacetanilide (Figure 1) [10]**.** Few years after discovery by Hoebrecker et al., Ladenburg et al. worked on the synthesis of same benzimidazole molecule by a reflux reaction of acetic acid and 3, 4-diamino toluene (Figure 2).

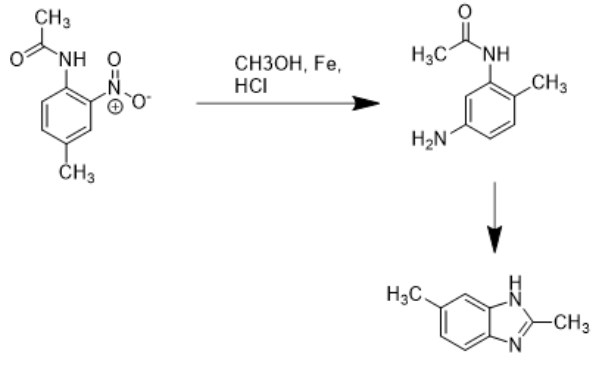

Figure 2: Synthesis of 2, 5-benzimadazole derivatives.

Other name for benzimidazoles are benziminazoles or benzoglyoxalines which are classified as derivatives of o-phenylenediamine such as ethenyl-o-phenylenediamine is also named as methenyl-o-phenylenediamine and 2-methylbenzimidazole. They can be also categorised as derivatives of the compounds possessing imidazole moiety in the ring e.g. o-phenylene formamidine is other name for benzimidazole, 2-(3H)-Benzimidazolone as o-phenyl urea and 2-(3H)-benzimidazolethione as *o*-phenylene thiourea [10,11]. The derivatives in Figure 2 show isomerisation due to the tautomerism by H-atom present on the nitrogen at 1st position in the nucleus [10]. To define the position of a group or groups as substituent, either a set of numbers or two numbers can be given and the other set of number added in parenthesis is usually given to define the tautomeric forms of compound. So, based on this criterion, the mentioned compounds have been named as 5(or 6) methyl benzimidazole [10,11] (Figure 3).

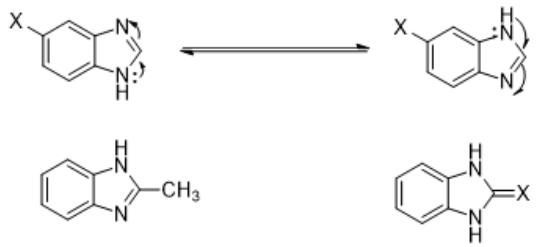

Figure 3: Tautomerization in benzimadazole**.**

The compounds under study are based on the derivatives of Benzimidazole. A great variety of potent microbial inhibitors can be designed just by substituting the position of hydrogen atom on the ring under study i.e. Benzimidazole with various functional groups. The substitutions at 1-, 2- and 5th position are highly feasible and easy. To explain the feasibility of synthesis of specifically substituted benzimidazoles, retrosynthetic analysis was studied for 2,5-disubstituted benzimidazoles which resulted in the formation of two small fractions (Figure 4).

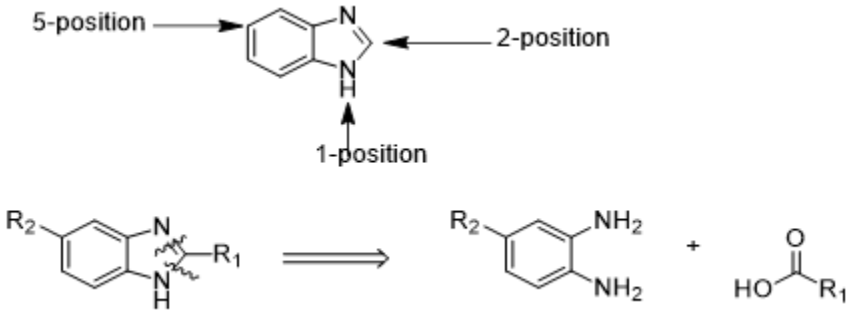

Figure 4: Retrosynthetic analysis of benzimadazole**.**

Another method contributing towards the library of benzimidazole derivatives is the reaction of carboxylic acids with substituted 1,2-phenylenediamines. This process involved designing such inhibitors which had taken into account the synthesis of 5-substituted benzimidazoles and 2,5-disubstituted analogues based on (1H-benzimidazole-2-yl) alkylamines derivatives 9-19, (1H-benzimidazole-2-yl)-ethyl derivatives and (1H-benzimidazole-2-yl)-methanethiol derivatives 22,23 and (1H-benzimidazole-2-yl) methanol derivatives 24-31. The most common method for the synthesis of such benzimidazole derivatives i.e. 1-31 followed the general Phillips procedure [12] (Figure 5).

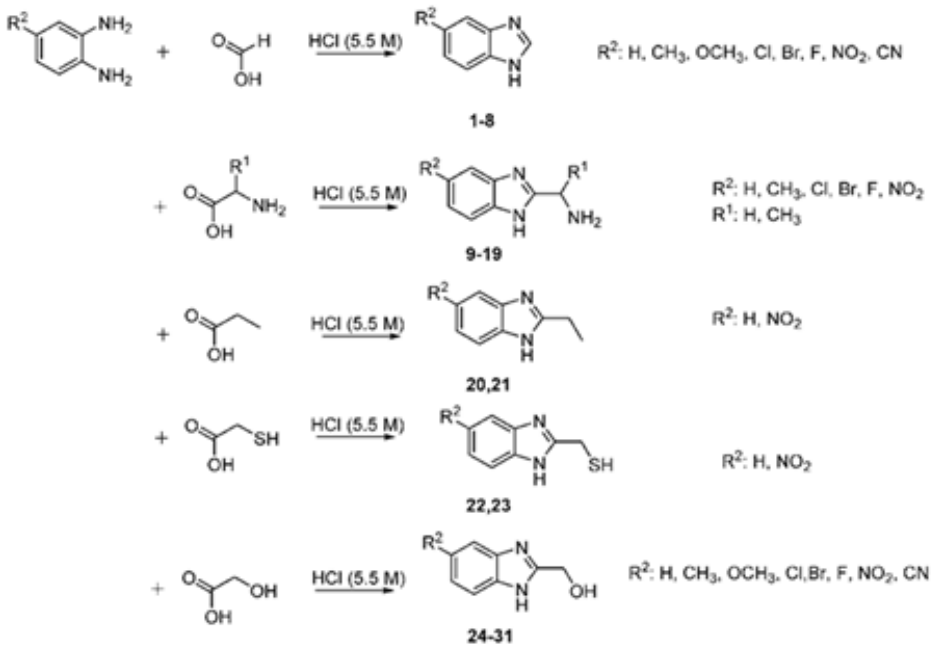

Figure 5: 2, 5 Substituted benzimidazole derivatives.

The (1H-benzimidazole-2-yl) methanol derivatives 24-31 has been synthesized as per the procedure given in Figure 5. The (1H-benzimidazole-2-yl) methanol contains hydroxyl group which was allowed to react with thionyl chloride thus converted into chloromethyl giving 2-(chloromethyl)-1H-benzimidazole derivatives, IX-XVI. These 2-(chloromethyl)-1H-benzimidazole derivatives were compared with other derivatives of benzimidazole containing substitution at 2nd position with the help of biological studies [13]. Further reaction of (1H-benzimidazole-2-yl) methanol derivatives, I-VIII with $KMnO_4$ resulted in Benzimidazole-2-carboxylic acid derivatives, XVII-XXIII. The N-methylation reaction of I-VIII, benzimidazole derivatives resulted in the synthesis of N-methyl-5-substituted (1H-benzimidazole-2-yl) methanol derivatives, XXIV-XXX (Figure 6).

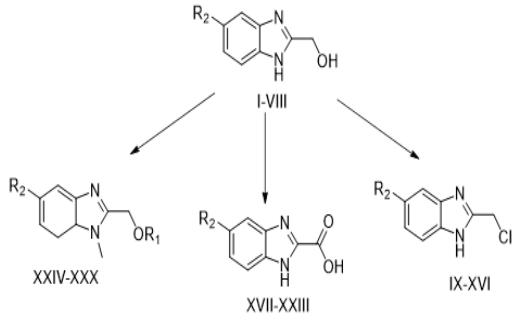

Figure 6: Conversion 2-methanol benzimadazole derivatives.

R_2: H, CH_3, OCH_3, Cl, Br, F, NO_2, CN.

R1: H, CH_3.

Some of the benzimidazole derivatives are also under study using microwave radiations. The reported method involves the synthesis of 1H,3H-thiazolo [3,4-a] benzimidazoles (A), 2-aryl-1-benzylbenzimidazoles (B) and 2,3-diaryl-1,3-thiazolidin-4-ones (C) as microwave

assisted synthesis. The advantages of microwave assisted synthesis includes more yield, less reaction time, less or no side products and eco-friendly because it is achieved usually without the use of any solvent which is practically the environmentally friendly as compared to other conventional methods. This type of reaction usually occurs as one pot synthesis as given below:

1H,3H-thiazolo [3,4-a] benzimidazoles (A) can be synthesized by the condensation followed by cyclization of 1,2-phenylendiamine, an aromatic aldehyde which is substituted and 2-mercaptoacetic acid while the normal conventional method for such synthesis involved refluxing all the substrates using dry benzene as solvent for almost 2 days but still associated with degradation products and low yield. The microwave assisted synthesis had reduced the time to only 12 minutes and the product so obtained showed satisfactory yield almost 92% (more than conventional method i.e. 60%). Also, use of toluene in place of dry benzene proved eco-friendly as it is less toxic compared to benzene and is transparent to microwaves. The use of microwaves in this reaction results in transfer of energy from polar reactants to the non-toxic solvent so the associated side products so obtained in normal refluxing, not formed with microwaves resulting high yield of final product (Figure 7).

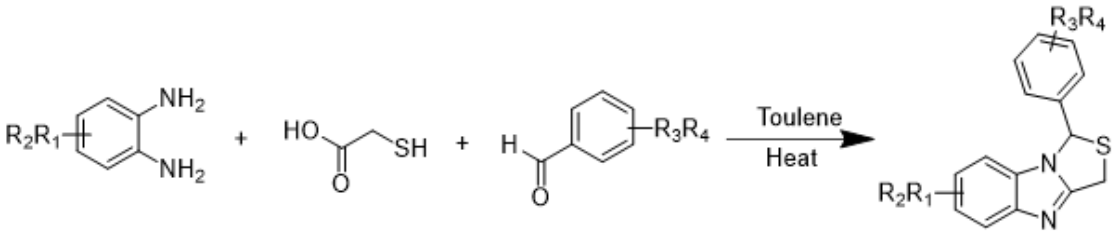

Figure 7: Pharmacological activities of various benzimidazole derivatives.

BIOLOGICAL PROFILE OF BENZIMIDAZOLE

Benzimidazole molecule possesses a wide diversity in terms of its biological profile. Benzimidazole and its derivatives acts as antiviral agents, antimicrobial agents, topoisomerase inhibitors, alkylating agents, androgen receptor antagonists, kinase inhibitors etc. Some of the activities are summarized in the (Figure 8).

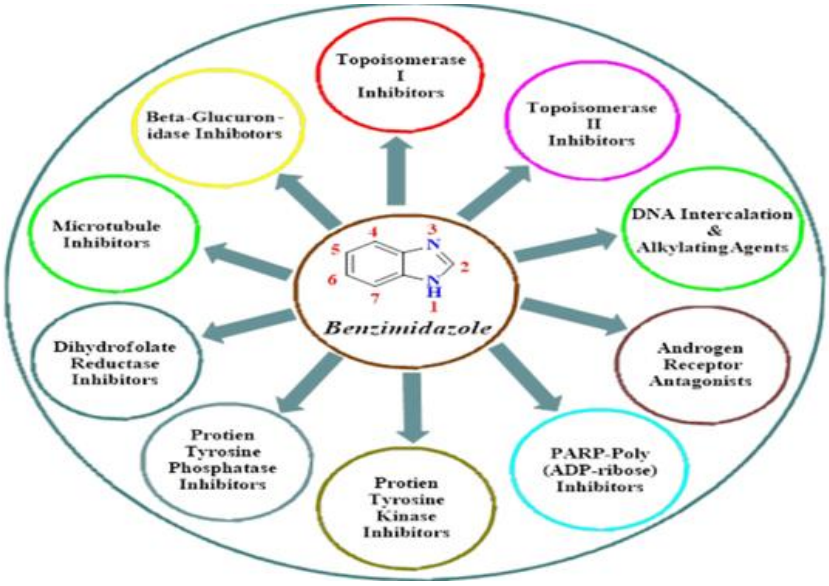

Figure 8: Biological activities of benzimadazole.

Such activity of Benzimidazoles is associated with their action to inhibit microtubules in nematodes, trematode and cystodes. All the sites of Benzimidazoles are active to show pharmacological profile but most of the biologically active benzimidazole based compounds has functional groups at 1-, 2- and/or 5-(or 6-) positions. These compounds may be mono, di or tri-substituted derivatives of the benzimidazole nucleus. A number of benzimidazole derivatives possess various activities such as antimicrobial, antiviral, antiprotozoal, antiulcer, anti-inflammatory, anticonvulsant, HIV inhibitors, anti-tubercular, anti-leishmanial, anti-depressant, antioxidant, antihypertensive, antidiabetic, anticoagulant, anticancer, phosphodiesterase inhibitors, Luteinizing Hormone-Releasing Hormone (LHRH) or gonadotropin releasing hormone antagonists, progesterone receptor antagonist, tissue selective androgen receptor modulator, some of which are summarized in Figure 9.

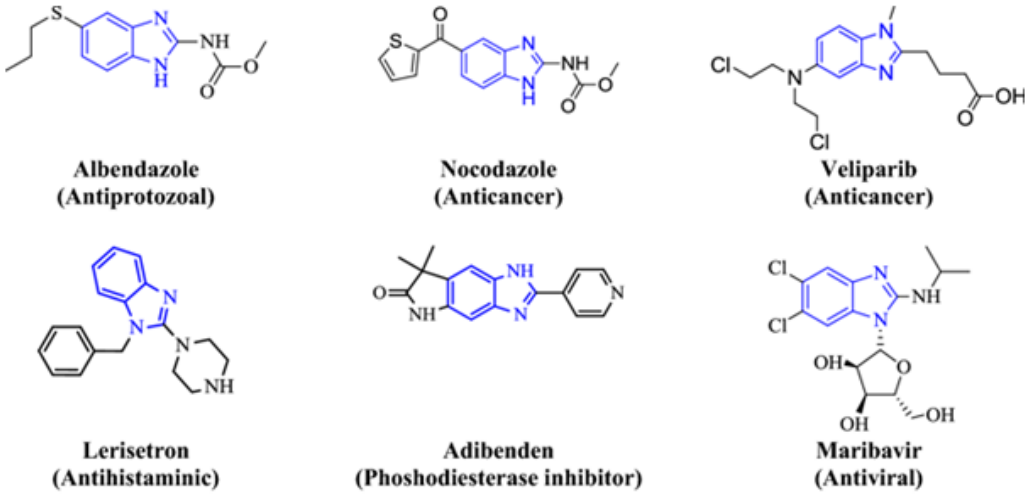

Figure 9: Pharmacological activities of various benzimadazole derivatives.

CONCLUSION

Benzimidazole molecule possess wide range of biological activities. A number of pathways are reported to synthesize benzimidazole molecule and its derivatives but still more approaches are required in this direction to search newer and alternative pathways such as microwave assisted synthesis which is gaining lot of importance these days in organic and medicinal chemistry. Several mechanisms of action are reported to understand the biological profile of benzimidazole. More research is required in this direction also, to come up with a combined action explaining most of the activities.

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