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Mannich Base derivatives of Benzimidazole: Synthesis & Antimicrobial properties – A Short Review

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Abstract: Mannich reaction is one of the versatile reaction widely used in organic synthesis. This reaction is useful for synthesizing N-methyl derivatives and many drug molecules. Mannich base derivatives of Benzimidazoles play an important role in medical field with so many pharmaceutical importance such as antibacterial, anthelmintic, antifungal, anti-inflammatory, antiviral and analgesic properties. The potency of these clinically useful drugs encouraged the synthetic chemists for the synthesis of some more potent and significant compounds. This review is summarized to know about Mannich Base derivatives of benzimidazoles along with their anti-microbial properties.

Keywords: Benzimidazole, Mannich Bases, Antimicrobial

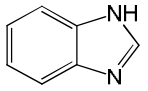
I. INTRODUCTION

Antimicrobial drugs or chemicals are the substances used to kill or slow down the growth of microorganisms. They include antibiotics, antiviral, antifungal and anti-parasitic agents.[1] Antimicrobial chemotherapy has been used from last six decades against infectious diseases caused by a variety of pathogens. Since then, many antimicrobial drugs were discovered, hundreds of drugs using now a days. Anti-microbial drugs are most commonly available today.[2] Since the introduction of penicillin as antibiotics in the control of infectious diseases, frequent use of antimicrobial drugs cause a variety of problems, such as drug resistance, allergic reactions, nutritional loss, toxicity and much more. Almost all of the major categories of antibiotics in the clinical application showed resistance to microorganism specially β- lactam, macrolides, vancomycin and quinolones derived bacterial drug's resistance is a source of concern for healthcare officials. The effective treatment against microbial agents is limiting day by day.[3,4] Many other antimicrobial drugs are toxic too. So, there is a real need to discover new compounds with high efficiency towards pathogens and less toxicity, which may be different from available resistant drugs. This provides a great opportunity to synthetic chemists for the synthesis of such new compounds having lower cytotoxicity and better antimicrobial properties.

The biological activity of the compounds depends on structure of molecule.[5] It has been shown that heterocyclic compounds are more biological active as compared to others.[6] Heterocyclic compounds particularly five and six member heterocycles have attracted the attention of pharmaceutical community over the years due to their therapeutic value.[7] Polyfunctionalized heterocyclic compounds containing Nitrogen, sulphur, oxygen as heteroatoms play important roles in the drug discovery process.[8] Benzimidazole is one such compound which attract attention of synthetic chemists for the synthesis of antimicrobial drugs.[9] The benzimidazoles contain a phenyl ring fused with imidazole ring.[10] This compound has various applications in a number of fields. Benzimidazole contain nucleus plays an important role in various medicines.[11] The role of purines in biological systems is well known and it was discovered that 5, 6-dimethyl-1-(α-Dribofuranosyl)benzimidazole is an important part of Vitamin B^{12} structure, which leads a massive research on benzimidazoles especially for the synthesizing new such compounds having biological applications. This stimulated great interest in the structural study of Benzimidazole and related compounds and much success was made in pharmaceutical industry. Some commercially used Benzimidazole based drugs are; azomycin, metronidazole, thiabendazole, benomyl, clemizole, enviroxime, irtemazole, astemizole, omeprazole, pentoprazole, thiabendazole and nocodazole.[12] Benzimidazole undergoes different reactions i.e. electrophilic and nucleophilic addition, electrocyclic reactions and thermal oxidation.

II. MANNICH BASE DERIVATIVES OF BENZIMIDAZOLE

Benzimidazole **(1)** is a heterocyclic organic compound containing a phenyl and imidazole ring. Benzimidazole derived structures have applications in a number of fields.[13-16] Recently, the interest in benzimidazole chemistry is very high for chemists because of the discovery that vitamin B^{12} contains 5, 6-dimethylbenzimidazole moiety **(2)** as a part of its chemical structure.



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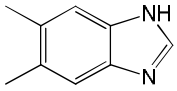

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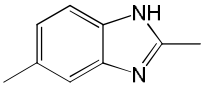
Hoebrecker[17] in 1872 firstly prepared benzimidazole by the reduction of 2-nitro-4-methylacetanilide and obtained 2,5(or 2,6)-dimethylbenzimidazole **(3), (4)**.



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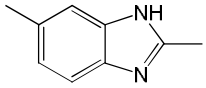

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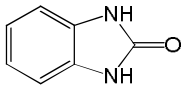
After few years Ladenburg[18] synthesized the same compound by the reaction of 3,4-diaminotoluene with acetic acid under reflux conditions.

The benzimidazoles are also called as benzoglyoxalines or benziminazoles. As they have an imidazole portion in the ring so they are named as derivatives of the imidazoles. Thus, benzimidazole, 2(3H)-benzimidazolone **(5)** and 2(3H)-benzimidazolethione **(6)** are also known as o-phenyleneformamidine, o-phenyleneurea and o-phenylenethiourea, respectively.[19]



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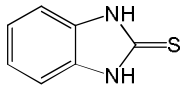
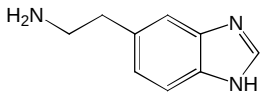


6

The benzimidazole compounds are not very widespread in nature. Benzimidazole and its derivatives have remarkable biological actions against different pathogens.

Auvermann[20] studied biological activities of Benzimidazole, 2-methylbenzimidazole and 2-phenylbenzimidazole. Benzimidazole is less toxic and has negligible effects on blood pressure. It was reported that β-aminoethyl derivatives of benzimidazole (5(or 6)-3-Aminoethylbenzimidazole **(7),** 2-methyl-5(or 6)-β-aminoethylbenzimidazole) which have close relation with histamine, cause a rise in blood pressure[21] but



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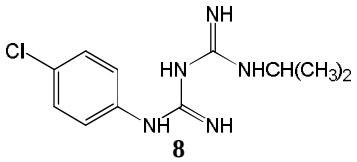
2-β-Aminoethylbenzimidazole dihydrochloride is stated to have no such effects even in high doses[22] and does not show histamine-like activity on the guinea-pig ileum[23].

Benzimidazole and its derivatives have been synthesized and evaluated as antimalarials. In most of these compounds diethylaminoalkyl group is at 1-position and other substituent groups in different positions of the benzimidazole ring[24-29]. It was quite interesting that 2-piperidinomethyl-5(or6)-chlorobenzimidazole and 2-Diethylaminomethyl-5(or6)-chlorobenzimidazole does not show antimalarial activity[30].

Paludrine **(8)** related active antimalarial benzimidazole compounds which look like closed-ring analogs of Paludrine have been prepared[31,32].

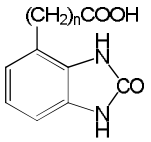


8

Benzimidazoles derivatives with anesthetic properties have also been prepared and tested. There are number of local anesthetics including 2-alkylaminomethylbenzimidazoles[33], 2-(a-alkylaminoethyl)benzimidazoles[34] and 2-Diethylaminopropyl-5(or 6)-phenoxybenzimidazole[35] have been prepared and widely ued. It is also reported that 2-Methyl-5(or 6)-ethoxybenzimidazole does not show anesthetic properties[36].

A number of compounds related to 1-Dimethylaminoethylbenzimidazole containing substituent groups in the 2-position of the benzimidazole ring have shown only slight antihistaminic activity[37]. It was observed that

Benzimidazole compounds when administered in large doses shows anticonvulsant activity. N-Benzoylbenzimidazole shows significant anticonvulsant activity, but 2-aminobenzimidazole was almost inactive[38]. Many benzimidazole derivatives have been reported with prominent goitrogenic activity[39-43]. It has been investigated that hexahydro derivatives of 2(3H)-Benzimidazolonecarboxylic acids **(9** and **10**, Where n = 0, 3, 4**)**,



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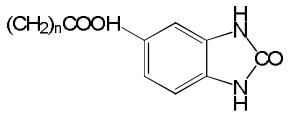
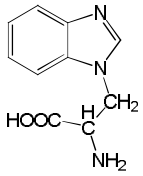


10

which were obtained by the reduction of benzene, show antibiotic activity[44-51].

Yeasts and bacterial growth have been inhibited by certain benzimidazole compounds. Growth inhibition was stoped by the addition of certain purines[52], and yeast nucleic acid[53]. It was also found that benzimidazole also prevents the production of vaccinia virus[54]. Mamalis and Sturgeon[55] have reported some benzimidazole drivatives of the general type **(11)** and **(12)**. These compounds were almost inactive against variety of organisms.



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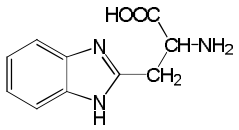
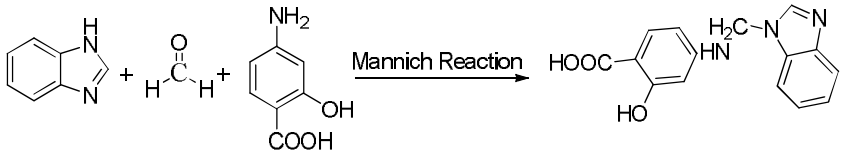


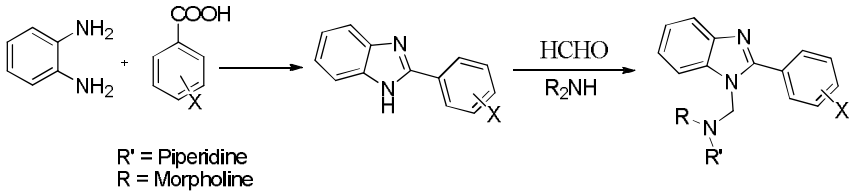
12

Several benzimidazole compounds are used for the preparation of sun-burn preventatives which protect the skin by UV rays. Salts of benzimidazole sulfonic acid are also valuable in the preparation of mouth and teeth care products. Here is an overview of so far synthesized Mannich base derivatives. Their synthesis route, reaction conditions and applications are discussed.

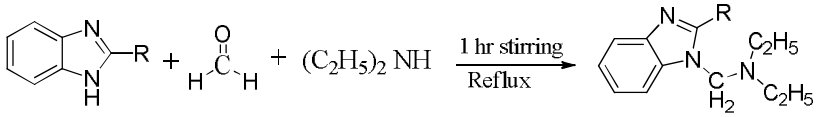
In 2009 Kamlesh and Arun[56], synthesized Benzimidazole-Salicylic Acid by the reaction of benzimidazole (0.02 mole), 4-aminosalicylic acid (0.02 mole), formaldehyde (0.02 mole). Complexes of Mannich bases with transition metal were also prepared and studied.



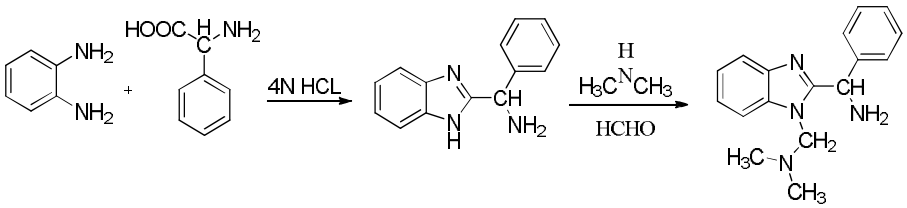
Mohamed G. Elerafi and Mohamed N. Ibrahim[57] in 2010 synthesized Mannich bases derived from 2-Substituted Benzimidazoles by reacting 2- Substituted phenyl benzimidazoles, formaldehyde and sec. amine.



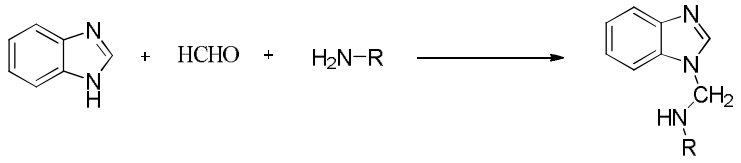
Murugesan and Sathiyamoorthy[58] in 2011 have Synthesis Mannich bases of 2-Substituted benzimidazole by 1st reacting 0.25 mole of o-Phenylene diamine with 0.34 mole of carboxylic acid on a water bath at 100 ^{0}C for 6-8 hours and subsequently gives 2-substituted benzimidazole which then react with Diethylamine and formaldehyde, product formed was filtered, dried and recrystallized from DMF.



Anil R. [59] in 2010 synthesized 1, 2- Disubstituted Benzimidazole derived compounds using Mannich base reaction. The product prepared by 1st reacting diamine and glycine in acedified ethanol then substituted benzimidazole dissolved in sec. amine and formaldehyde.

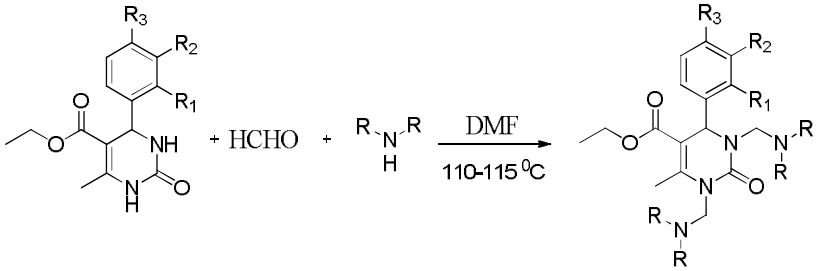


P. Selvam[60] *et al.,* in 2010 have synthesized some N-substituted benzimidazole derivatives by the reaction of formaldehyde, benzimidazole and active hydrogen compounds (sulphanilamide, sulphadimidine, sulphamethoxazole, 2-aminopyrimidine, phthalimide, anthranilc acid, 2-mercaptobenzimidazole and benzamide). The anti-HIV and in vitro anti-viral activities of the new compounds were also screened and all the compounds showed good potency.



R = Sulphanilamide, Sulphadimidine, Sulphamethoxazole, 2-aminopyrimidine, Phthalimide, Anthranilc acid, 2-mercaptobenzimidazole and Benzamide

In 2009 T. B. Shah[61] *et al.,* have synthesized a series of N-Mannich base derivatives of 3,4-dihydropyrimidine-2(1H)-one with some heterocyclic amines and formaldehyde. The structure of these compounds was characterized through different technical analysis. All the compounds showed good biological activities against two bacterial (E. Coli, B. Subtilis) and two fungal (C. Albicans, A. Niger) strains.

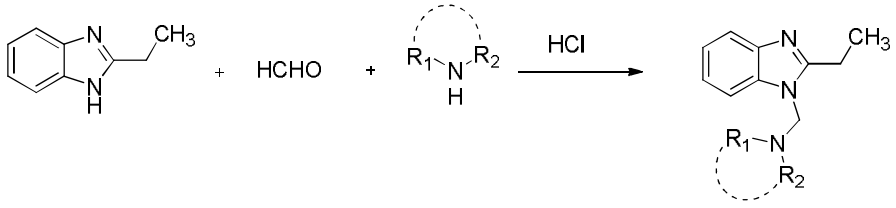


R_1 = OH

R_2 , R_3 = H

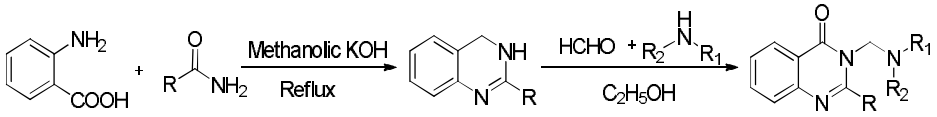
R = Benzimidazole, 2-methyl benzimidazole, 2-phenyl benzimidazole, Benzotriazole, Phthalimide, Morphiline, Tetrahydrocarbazole

A series of 2-ethyl benzimidazole derivatives have been prepared by G. Mariappan[62] *et al.,* in 2011 by the condensation reaction of 2-ethyl benzimidazole, primary and secondary amine and formaldehyde.



-NR_1R_2 = Diethylamino, piperidino, morpholino, diethanolamino, 2-chloroanilino, 3-chloroanilino, 2,3-dichloroanilino, 3,4-dichloroanilino, 4-fluoroanilino, 4-bromoanilino

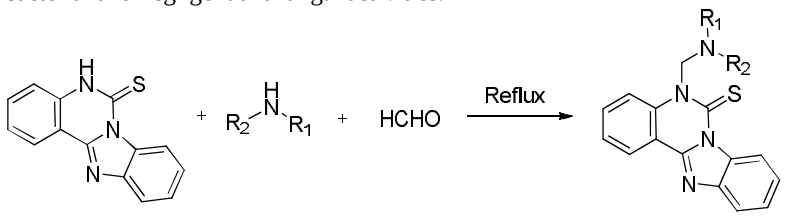
P. S. Misra[63] *et. al.,* in 2010 synthesized Mannich Schiff base derivatives of 2-Phenyl Benzimidazole. Anthranilic acid reacts with alkyl amide under reflux conditions to form 2-alkyl-4(3H)-quinazolinone which further underwent Mannich reaction in the presence of formaldehyde and amine. Antibacterial and antifungal activities checked by using Norfloxacin and Fluconazole standard drug. All compounds showed good potency towards antimicrobial agents.



R = H, CH_3, C_6H_5

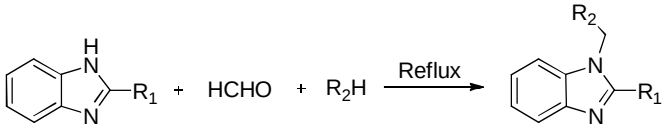
R_1, R_2 = CH_3, C_6H_5

Mannich base derivatives of Benzimidazo compound were synthesized in 2010 by A. M. Saraswa[64] et. al., through the cyclization reaction. All the compounds were seen for biological activities and some of the compounds showed moderate antibacterial and negligent antifungal activities.



R_1, R_2 = CH_3, C_6H_5, 4-methylmorpholine, 1-methylpiperidine

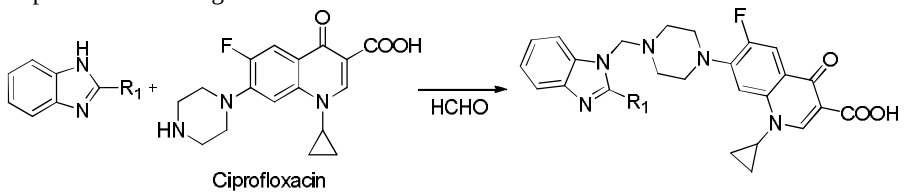
E. P. Jesudason[65] et. al., in 2009 synthesized N-Mannich bases of benzimidazole through Mannich base reaction and characterized by elemental analysis, MS, ^{1}HNMR and IR spectroscopic studies. All the synthesized compounds were checked for anti-inflammatory and analgesic properties. Some of the compounds were more potent than paracetamol and Diclofenac and almost all the compounds exhibit good corneal penetration.



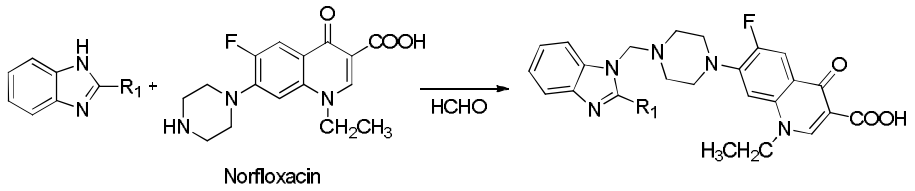
R_1 = H, CH_3, -CH=CH-C_6H_5

R_2 = -N(CH_3)$_2$, -N(C_2H_5)$_2$, 1-methylpiperidine, 4-methylmorpholine

In 2010 S. Jubie[66] et. al., synthesized microwave assisted benzimidazole derivatives by the reaction of benzimidazole, ciprofloxacin, norfloxacin and formaldehyde. Synthesized compounds were confirmed by physical, chromatographic and spectroscopic methods. All the compounds were checked for activities against microbial agents and almost all the compounds showed significant activities.



Ciprofloxacin

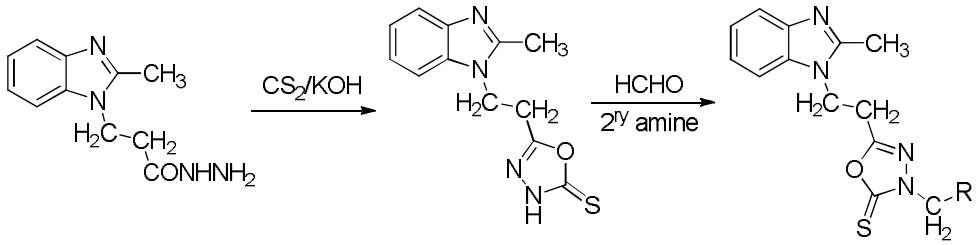


Norfloxacin

R = H, CH_2CH_3, $CH_2CH_2CH_3$

A. H. El-masry[67] et. al., in 2000 synthesized Mannich base derivatives of a benzimidazole derived compound by using some secondary amines (4-methylmorpholine, diethylamine, 1,4-dimethylpiperazine) and formaldehyde. Compounds

checked for Gram positive, Gram negetive bacterial strains, (*Bacillus cereus*, *Escherichia coli*) Yeast and a Fungai (*Saccharomyces cerevisae, Aspergillus niger*) inhibition. Some of the compounds showerd activities against bacterial strains but none of the compound was active against Yeast and Fungai.



R = -N(C2H5)2, 4-methylmorpholine, 1,4-dimethylpiperazine

III. CONCLUSION

Benzimidazole is very important molecule made up of imidazole and phenyl ring, with extensive antimicrobial properties. Synthesis of Mannich base derivatives provides a good opportunity to pharmaceuticals chemists for evolving better antimicrobial drugs with lower cytotoxicity and better results. Mannich base derivatives could easily replace the existing pathogenic resistant drugs. This review gives an overview to Manich base derivatives of Benzimidazole and highlights their antimicrobial properties.

ACKNOWLEDGEMENTS

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