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Synthetic and Biological Aspects of Benzimidazole Derivatives

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Abstract: Benzimidazole is a versatile heterocycle possessing a myriad of biological activities. It bears specified structural properties and an electron rich environment. This moiety is a main component of several compounds and plays an important role in pharmacological sciences. Due to immense therapeutic and medicinal properties, the development of benzimidazole containing drugs has reached immense heights in the field of medicinal chemistry. This review enlightens the synthetic and pharmacological studies of benzimidazole derivatives in current era.

Keywords: Nitrogen heterocycles, Benzimidazole, Synthesis, Biological Potential, Drugs

Introduction

Nitrogen containing heterocyclic compounds is inevitable to our life. Among the nitrogen heterocycles, benzimidazole ring system is considered as very important due to its wide occurrence in drugs, medicines, natural products etc. It is the heterocyclic compound containing benzene ring fused to imidazole ring at 4th and 5th positions. It is an important pharmacophore in the field of medicinal chemistry and possesses a gamut of biologically activities such as anti-helminthic, antihypertensive, antiprotozoal, anti-inflammatory, antihistaminic, antiviral, proton pump inhibitor, antitumor, antioxidant, herbicidal activity, aromatase inhibitor, antimicrobial etc[1-14]. Several important drugs bearing benzimidazole ring are shown in Fig 1. This article relates to the synthetic aspects of benzimidazole derivatives along with its diverse biological properties.

1. Synthetic Aspects of Benzimidazole:

1.1 Hoebrecker Synthesis

The first synthesis of benzimidazole was done by Hoebrecker in 1872 by the reduction of 2-nitro-4-methylacetanilide. 2,5-Dimethylbenzimidazole[15] was obtained in this process (Scheme 1) .

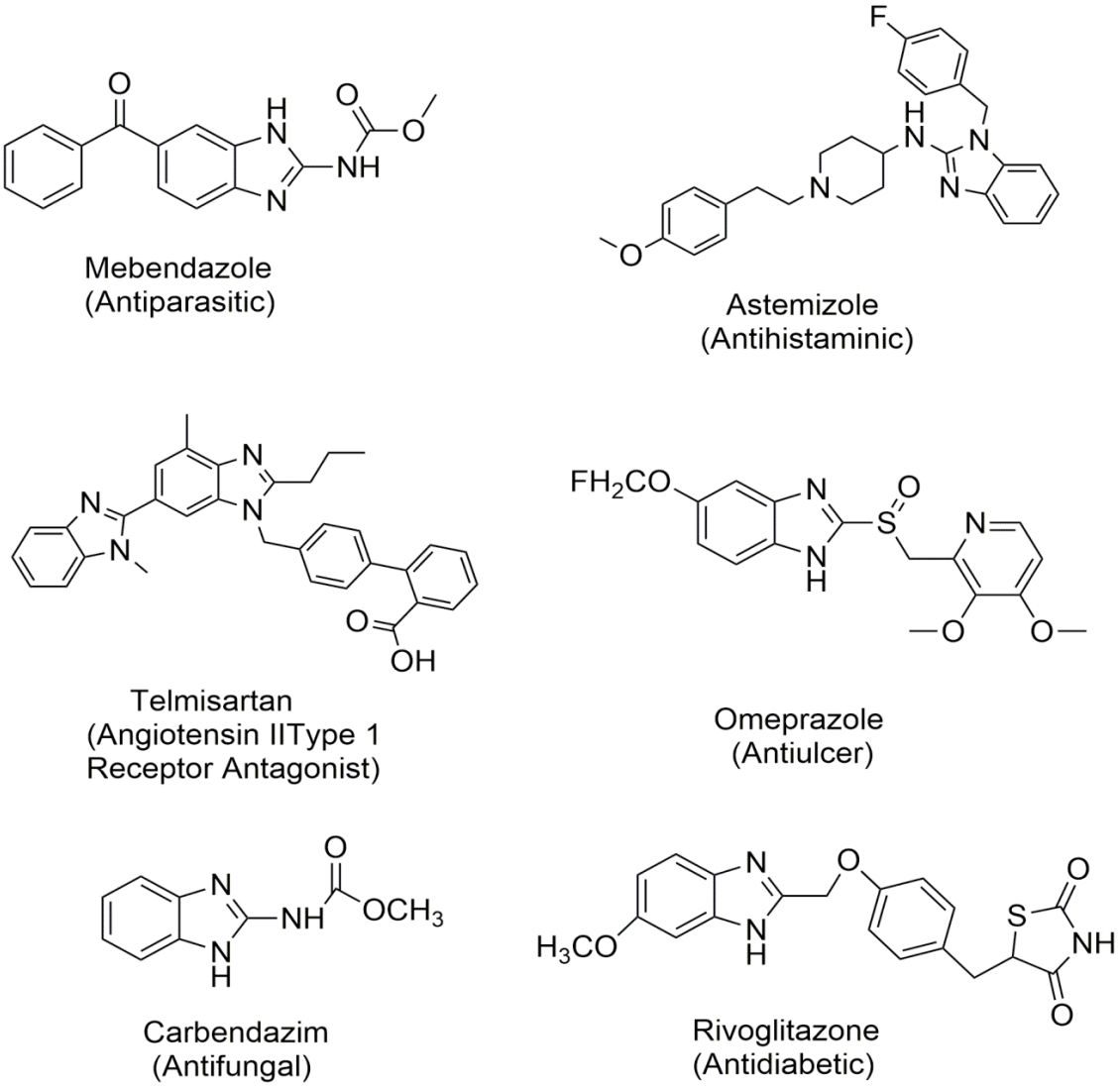
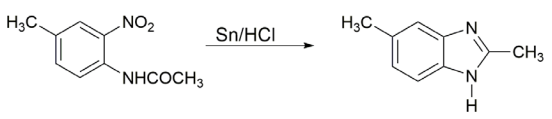


Fig. 1 Drugs bearing Benzimidazole Ring

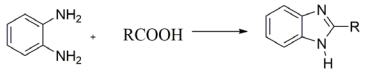


Scheme 1: Synthesis of Benzimidazole using 2-nitro-4-methylacetanilide

Several methods have been reported for the benzimidazole synthesis via condensation of ortho phenylene diamine and aldehyde, nitriles, carboxylic acid, alcohols, amines using various catalysts.

1.2 Synthesis of benzimidazoles using o-phenylene diamine and acids:

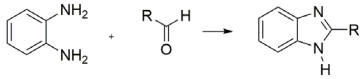
2-Substituted benzimidazoles were obtained by the reaction of o-phenylenediamines and carboxylic acids in high yields by heating under reflux in the presence of conc. HCl, NH_4Cl, alumina, silica gel, zeolite etc.[16-19] (Scheme 2)



Scheme 2: Synthesis of Benzimidazoles using o-phenylenediamine and carboxylic acids

1.3 Synthesis of benzimidazoles using o-phenylene diamine and aldehydes:

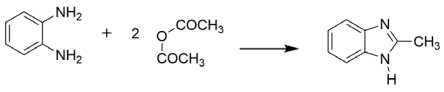
Aldehydes and *o*-phenylene diamines reacted with each other to form 2-substituted benzimidazoles in the presence of different catalysts viz. cupric acetate, nitrobenzene, lanthanum chloride ($LaCl_3$), air, indium triflate, zinc triflate, sodium hexafluoroaluminate (Na_3AlF_6), molecular oxygen and visible light, transition metals , fruit juice, cetyl trimethylammonium bromide (CTAB)-assisted Bi_2WO_6 (CBTH) photocatalyst using tungsten lamp 35 W etc.[16, 20-30] (Scheme 3)



Scheme 3: Synthesis of benzimidazoles using o-phenylene diamine and aldehydes

1.4 Synthesis of benzimidazoles using o-phenylene diamine and acid anhydride:

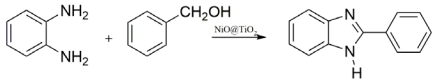
O-phenylenediamines when heated under reflux for several hours with acetic anhydride got completely converted to 2-methylbenzimidazole.[16] (Scheme 4)



Scheme 4: Synthesis of benzimidazoles using o-phenylene diamine and acid anhydride

1.5 Synthesis of benzimidazoles using o-phenylene diamine and alcohols:

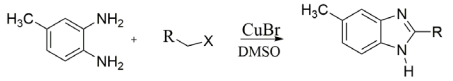
Benzylalcoholreactedwith*o*-phenylenediamines to yield 2-aminobenzimidazoles in high yields via ultrasonication and photoradiation for five minutes in the presence of niobium oxide (NiO) @ anatase/rutile-TiO_2 nanoparticles.[31] (Scheme 5)



Scheme 5: Synthesis of benzimidazoles using o-phenylene diamine and alcohols

1.6 Synthesis of benzimidazoles using o-phenylene diamine and alkyl halides:

Qiu and co-authors[32] synthesized 2-arylbenzimidazoles using arylmethyl halides and o-phenylenediamine in high yields using copper bromide (CuBr) under aerobic oxidation reaction. (Scheme 6)



Scheme 6: Synthesis of benzimidazoles using o-phenylene diamine and alkyl halides

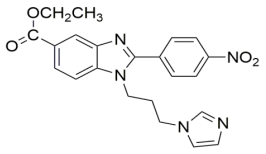
2. Biological Profile of Benzimidazole Derivatives:

Several important drugs like albendazole, thiabendazole etc. contain benzimidazole nucleus. 2- or 1,2-disubstituted benzimidazoles possess promising pharmacophoric behavior that has led to a huge upsurge for the exponential development of its synthetic methods.

Yoon *et al.*[33] synthesized benzimidazole derivatives and studied their acetylcholinesterase and butyrylcholinesterase inhibitory activity. Rivastigmine and donepezil were used as standard drugs for butyrylcholinesterase and acetylcholinesterase respectively. Compound **1** showed promising inhibitory activity with **IC_{50} = 8.63 µM** for AChE and **IC_{50} = 5.12 µM** for BChE. Diaz-Chiguer *et al.*[34] developed benzimidazole derivatives and evaluated their vitro and in vivo trypanocidal activity against

Trypanosoma cruzi (NINOA and INC5). Compound **2** showed promising in vitro and in vivo **[INC5: 68.4 (% lysis); NINOA: 46.4 (% lysis)]** trypanocidal activity.

Hernandez-Luis and co authors[35] synthesized a series of benzimidazole derivatives and studied their in vitro antiparasitic activity against various protozoan parasites viz. *G. intestinalis, T. vaginalis*, *E. histolytica* and *L. mexicana.* Albendazole, mebendazole and pentamidine were used as standard drugs and the *in vivo* antiparasitic study was done towards *Trichinella spiralis* using albendazole , triclabendazole and pentamidine as standard drugs. Compounds **3, 4** and **5** exhibited good antiparasitic activity.



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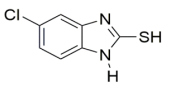

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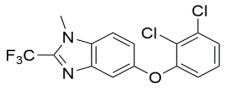

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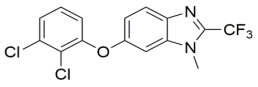

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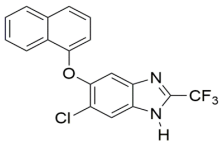

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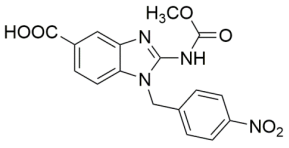
Oh *et al.*[36] synthesized a new series of imidazo benzimidazoles and screened their anti-leishmanial and anti-trypanosomal activities towards *Leishmania donovani* and *Trypanosoma cruzi.* Miltefosine, benznidazole and amphotericin B were used as standards. Most of the compounds showed promising antiprotozoal activity. Palomares-Alonso *et al.* synthesized new substituted benzimidazole derivatives and assessed them for their cysticidal activity against *Taenia crassiceps* cysts (ORF and WFU strain) using albendazole sulfoxide as a control drug. Compounds **6** and **7** displayed superior cysticidal activity.



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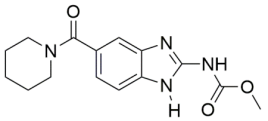

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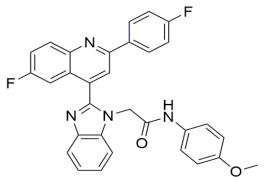
El-Feky *et al.*[38] synthesized some fluorinated quinoline incorporated benzimidazoles and assessed their in vivo anti-inflammatory activity using carrageenin induced edema bioassay method in rats. Celecoxib was used as a reference. Compound **8** demonstrated excellent anti-inflammatory activity and showed best binding profiles into COX-2 binding site.

Paramashivappa *et al.*[39] developed a series of substituted benzimidazoles and examined for its human cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) and enzyme inhibition activity in human whole blood assay. Rofecoxib was used as a reference. Compounds **9** and **10** were found as the most active agents.



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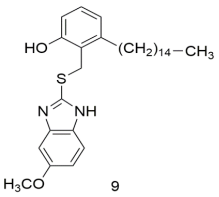

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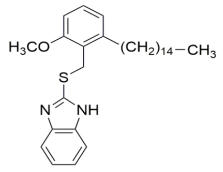
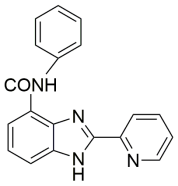


10

Camacho *et al.*[40] synthesized some novel *N′*-substituted benzo[*d*]imidazole-5-carbohydrazide derivatives and studied their antitubercular potency against multidrug resistant MDR-MTB and MTB H37Rv strains. Compounds **10** exhibited good anti-mycobacterial activity **(MIC = 12.5 µg/mL)** against sensitive *M. tuberculosis* H37Rv and MDR-MTB **(MIC = 6.25 µg/mL)** strains as

compared to isoniazid **(MIC = 0.063 µg/mL)** and rifampin **(MIC = 32 µg/mL)**.

Gong *et al.*[41] reported substituted benzimidazole compounds and investigated their antitubercular potency against *M. tuberculosis* in a replicating state (R-*Mtb*), a physiologically-induced non-replicating state (NR-*Mtb*). Cheng *et al*.[42] synthesized some novel benzimidazole derivatives and assessed their antiviral activity against Coxsackie virus B3 in VERO cells. Ribavirin was used as a reference. Compounds **11** and **12** (Fig. 8) exhibited significant activity with half maximal inhibitory concentration (IC_{50}) values **(1.43 and 0.54 µg/mL)** as compared to ribavirin.



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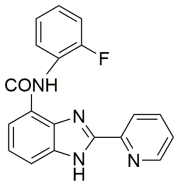
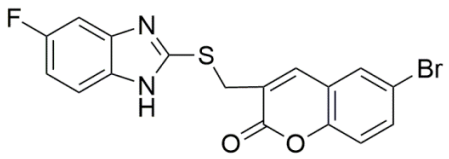


12

Hwu *et al.*[43] developed some new benzimidazole derivatives bearing coumarin ring and evaluated them for their antiviral activity against hepatitis C virus. Compounds **13** and **14** (Fig. 8) were found to be most active and showed half maximal effective concentration (EC_{50}) values **(3.4 µM and 4.1 µM).**



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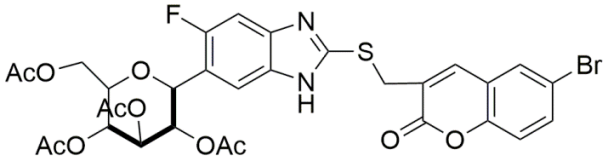
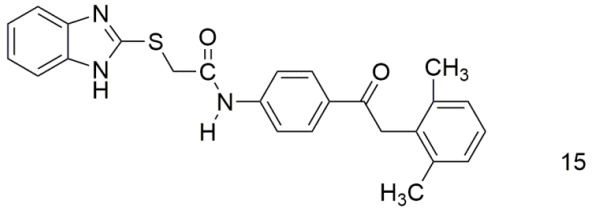


14

Tahlan *et al.*[44] developed a new class of benzimidazole benzamide compounds and demonstrated their anticancer activity against cancer cell line (HCT116) by SRB method with the standard drug, 5-fluorouracil. Compound **15** and **16** showed significant anticancer activity.



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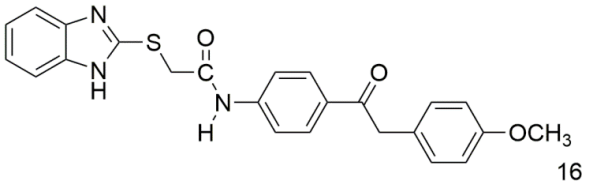
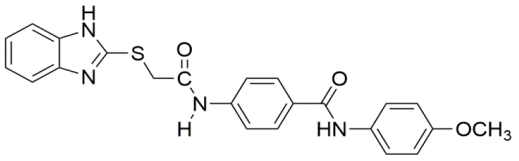


16

Tahlan *et al.*[45] synthesized a novel series of benzimidazole derivatives and evaluated their anticancer potency towards cancer cell line (HCT116) by sulforhodamine B (SRB) assay. Compound **17** showed promising anticancer activity.



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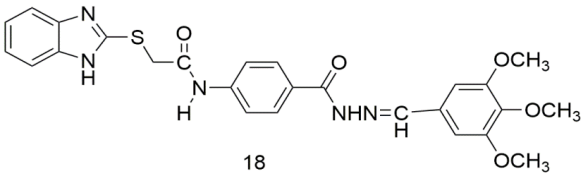

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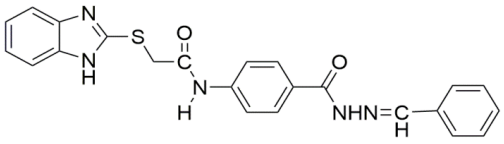
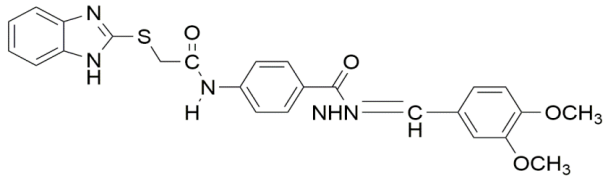


19

Novel class of benzimidazole Schiff base derivatives were synthesized by Tahlan *et al.*[46] and evaluated them for their antimicrobial activity against several bacterial and fungal species by tube dilution method. In this

series, compounds **18** and **19** displayed potent antifungal activity against *A. niger* and *C. albicans*.

Tahlan *et al.*[47] synthesized a class of benzimidazole Schiff base derivatives and screened them for antimicrobial activity. Compounds **20** and **21** exhibited promising antimicrobial activity towards bacterial and fungal species.



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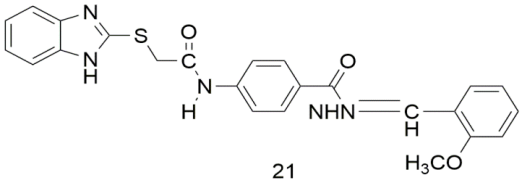

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Conclusion:

Benzimidazoles possess a flurry of biological activities with specified mechanism of action. Literature studies evidenced that benzimidazole based compounds bear high medicinal importance and strong tendency to combat life threatening diseases. Owing to their unique structural, chemical and biological features, they are widely researched and helpful for pharmaceutical companies for rational drug design and discovery. Moreover, it has an outstanding scope for further discovery of new, safe and potent therapeutic agents.

Conflict of interest:

None

Acknowledgement:

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