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# BENZIMIDAZOLE ANALOGUES AS POTENTIAL PHARMACOLOGICAL AGENTS: A BRIEF REVIEW

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## ABSTRACT

Benzimidazole has several pharmacological actions that make it a crucial anchor for the development of novel therapeutic agents in medicinal chemistry and drug discovery. Replacement of the benzimidazole nucleus is an essential synthetic method used in drug discovery. The therapeutic qualities of benzimidazole-related medicines have prompted medicinal chemists to create novel therapeutic agents. To comprehend the current position of the benzimidazole nucleus in drug discovery, it is necessary to combine the most recent information with the earliest knowledge. In this review, benzimidazole derivatives with various pharmacological activities are described on the basis of substitution patterns around the nucleus, with the goal of assisting medicinal chemists in the creation of SAR on benzimidazoles for each activity. This article seeks to discuss the chemistry and pharmacological activity of benzimidazole derivatives that have been published in previous years.

**KEYWORDS:** Benzimidazole, antioxidant, anti-inflammatory, pharmacological activity, anti-depressant.

## 1. INTRODUCTION

In the field of research and the synthesis of the new bioactive molecule, heterocyclic chemistry plays the most molecules containing nitrogen and oxygen. Many different important roles. The most active biological activities have been shown among these

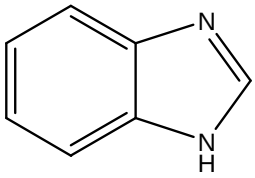
heterocyclic compounds have been prepared and exhibit different types of useful pharmacological activity.[1]

Benzimidazole is a heterocyclic aromatic organic compound. It is an important pharmacophore and a privileged structure in medicinal chemistry. This compound is bicyclic in nature which consists of the fusion of benzene and imidazole. Nowadays is a moiety of choice that possesses many pharmacological properties.[2] Benzimidazole may be considered a common pharmacophore found in numerous natural compounds such as purines, vitamin B 12, and histidine. These fused hetero-aromatic ring structures possess an extensive variety of pharmacological activities such as hypertension, malaria, cancer, microbial diseases, inflammatory disorders, etc. therefore, many efforts have been made by the research community to explore the therapeutic benzimidazole analogues. potential of benzimidazole analogues. Under these conditions, benzimidazole-based fused derivatives have been reported for the treatment of multifactorial diseases and create a scaffold of therapeutic interest for multinational pharmaceutical companies and research groups. In this review, we are focusing on the chemistry and recent biological activities, designing approaches, and SAR (structure-activity relationship) data of different benzimidazole-based analogues during the past years. The benzimidazoles (1) have a phenyl that is fused to an imidazole ring.[3]

## 2. CHEMISTRY OF BENZIMIDAZOLE

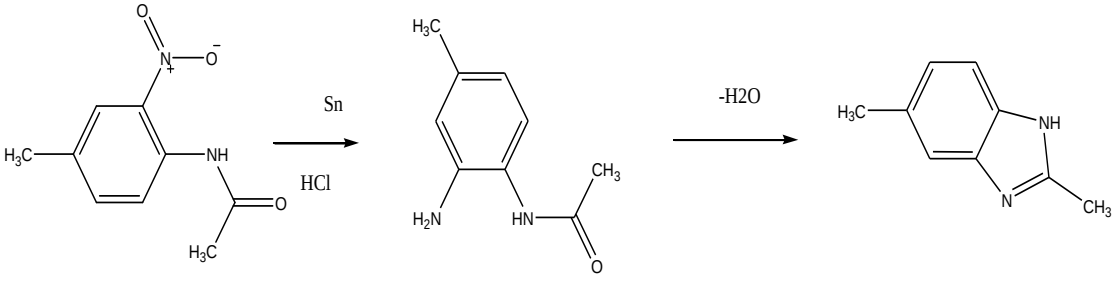
Benzimidazoles are the benzo derivatives of imidazole which contains imidazole heterocycle. They are well-known heterocyclic compounds that have common and characteristic features of a variety of medicinal agents. It is soluble in water and other polar solvents. It exists in two equivalent tautomeric forms because the hydrogen atom can be located on either of the two nitrogen atoms. It is also a highly polar compound. It is classified as aromatic due to the presence of a sextet of electrons, consisting of a pair of electrons from the protonated nitrogen atom and one from each of the remaining four atoms of the ring. It can function as both an acid and as a base.[4]

As shown in the structure of benzimidazole (1), the benzimidazoles have a phenyl ring which is fused to an imidazole ring.[5]



(1)

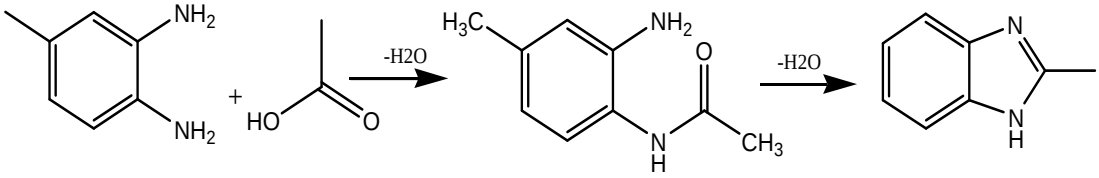
Hoebrecker *et al*, synthesized first benzimidazole in 1872 through the reduction of 2- nitro-4-methylacetanilide.[6]




(2a) (2b) (2)

**Scheme 1.**

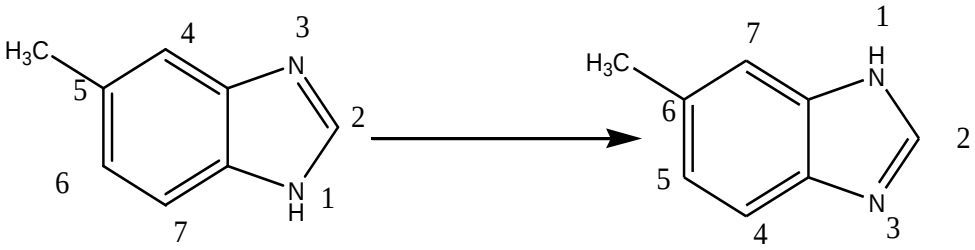
Ladenburg *et al*, synthesized the same compound by refluxing 3,4-diamino toluene with acetic acid.[7]




(3a) (3b) (3c) (3)

**Scheme 2.**

Hydrogen atom attached to N-1 of the nucleus readily tautomerises which is responsible for isomerisation in the derived compounds. Two numbers or sets of numbers are usually given to designate the position of the substituent group (or groups) and the second number or groups of numbers being placed in parenthesis for the designating such tautomeric compounds.[8]



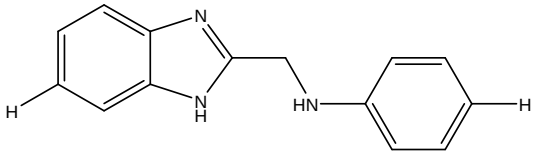
(4a) (4b)

**Scheme 3.**

## 3. BIOLOGICAL ACTIVITIES

### 3.1. Anti-inflammatory

K.C.S. Achar *et al*, prepared A series of 2-methylamino benzimidazole derivatives by the reaction of 2-(chloromethyl)-1H-benzimidazole derivatives with primary aromatic amines and analogs were screened for in vivo anti-inflammatory studies using carrageenan-induced rat paw edema model. Among them, Compounds (5) and (6) showed potent anti-inflammatory activities compared with the standard drug Nimesulide.[9]



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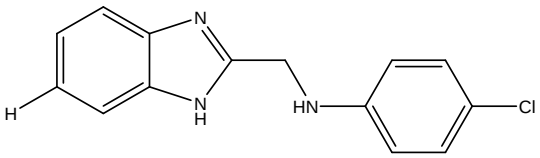
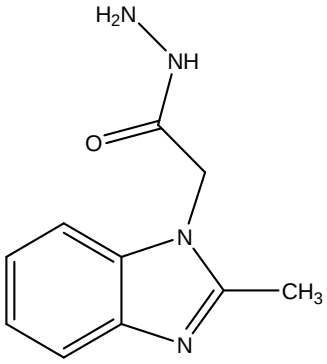


(6)

Alok *et al*, prepared a novel series of benzimidazole analogues and screened for in vivo anti-inflammatory studies using carrageenan-induced rat paw edema model. Analogues 2-(2-

methyl-1H-benzimidazol-1-yl)-N- phenylacetohydrazide (7) and 2-(2-methyl-1H-benzimidazol-1-yl) acetohydrazide(8) were found to possess significant anti-inflammatory properties. Ibuprofen was used as a reference drug.[10]



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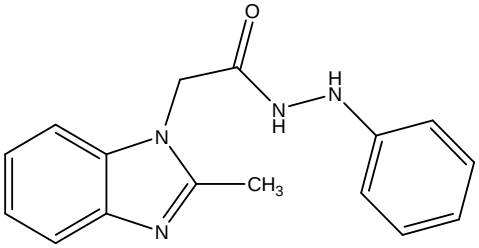
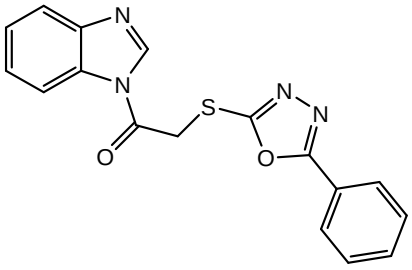


(8)

S. Rajasekaran *et al*, synthesized a series of benzimidazole derivatives fused with an oxadiazole ring system and these compounds were screened for their in-vitro anti-inflammatory activity, it was observed that the compounds (9,10,11) with phenyl or pyridyl substituted oxadiazole ring fused to benzimidazole moiety through thioacetamide linkage have shown good anti-inflammatory activity.[11]



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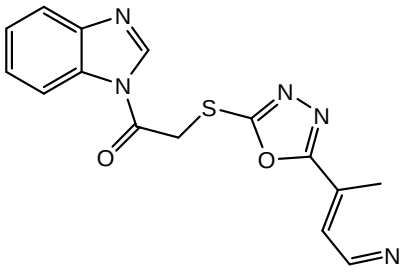

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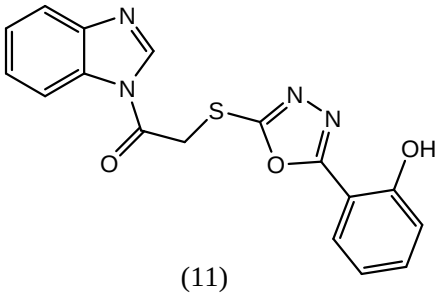
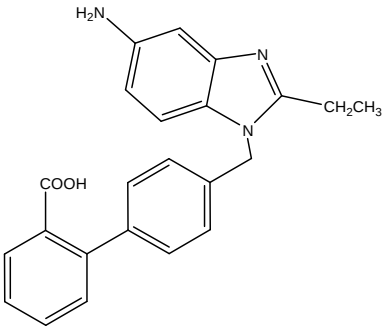


(11)

### 3.2. Anti-hypertensive

Rakesh Kumar *et al*, prepared 5-substituted (amino) -2- phenyl-1-(2'carboxy biphenyl-4-yl) benzimidazoles and these compounds showed a potent hypertensive effect upon oral administration. Among them, compound (12) & (13) has shown better result.[12]

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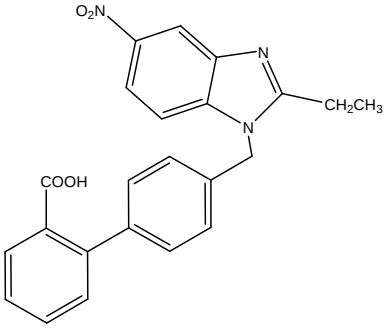
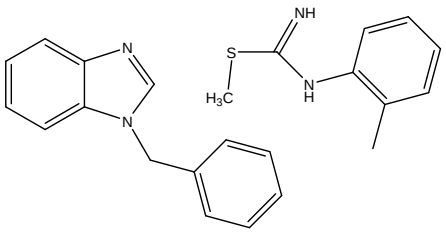



(13)

### 3.3. Anti-depressant

Nadeem Siddiqui *et al*, identified a series of benzimidazole derivatives which were evaluated for their antidepressant activity. Compounds (14),(15) and (16) were found to possess better CNS activity against standard drugs. Fluoxetine was used as a standard drug.[13]

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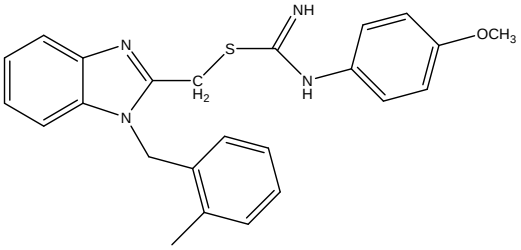


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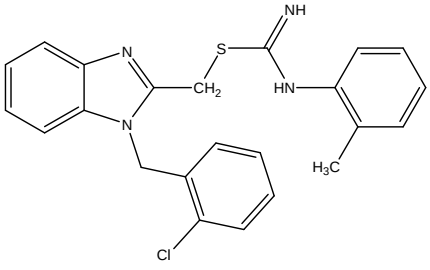
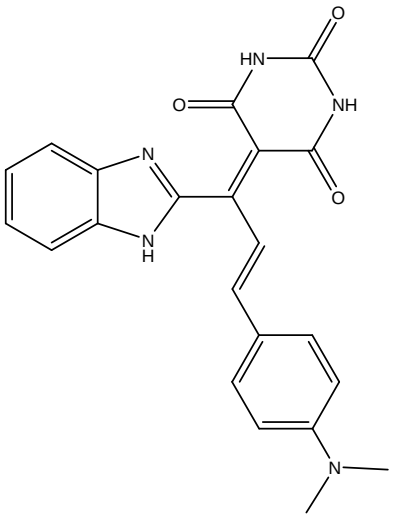



(16)

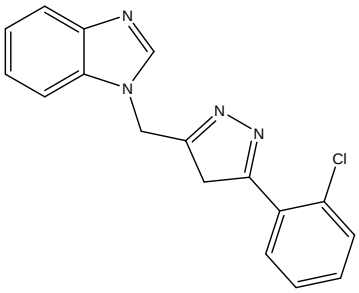
B. Mathew *et al*, synthesized some novel 5-[(2E)-1-(1H-benzimidazol-2-yl)-3-phenylprop-2-en-1-ylidene] pyrimidine-2,4,6 (1H,3H,5H)-triones from benzimidazole chalcones by conventional method. All the synthesized derivatives showed good antidepressant activity when compared to the standard clomipramine. among them, The compound (17) 5-{(2E)-1-(1H-benzimidazol-2-yl)-3-[4-(dimethylamino)phenyl] prop-2-en-1-ylidene} pyrimidine-2, 4, 6(1H,3H,5H)-trione has shown highest activity.[14]




(17)

### 3.4. Anti-microbial

Ansari *et al*, prepared a series of 2-substituted benzimidazole derivatives and screened them for their antimicrobial activity against Gram-positive bacteria, and, Gram-negative bacteria. All the synthesized compounds showed significant antibacterial activity against all the Gram-positive strains of bacteria. Among them compounds (18),(19) and (20) were found to be more potent.[15]

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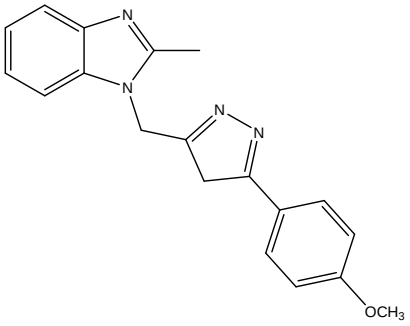


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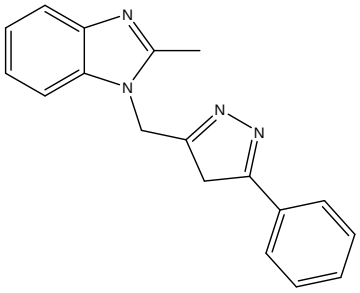
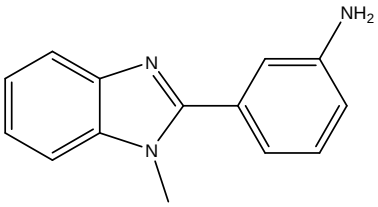


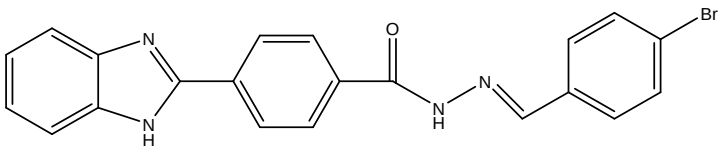

(20)

Ayhan-Kilcigil *et al*, synthesized benzimidazolylbenzamides derivatives and screened for antimicrobial activities against Staphylococcus aureus, Streptococcus faecalis, Bacillus subtilis, Escherichia coli, Pseudomonas aeruginosa and Candida albicans. It was shown that the compound (21) exhibited the best activity against B. subtilis, P. aeruginosa and C. albicans.[16]




(21)

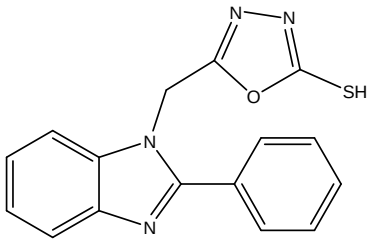
Ozkay *et al*, prepared novel benzimidazole compounds bearing hydrazone moiety and screened them for their antimicrobial activity. among them, The compound (22) was more potent than reference against P. vulgaris and P. aeruginosa, respectively. Chloramphenicol was used as reference drug.[17]




(22)

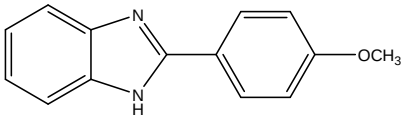
### 3.5. Antioxidant

Ayhan-Kilcigil *et al*, prepared some novel oxadiazolyl benzimidazole derivatives and screened for their antioxidant activity. All of the screened compounds have shown high antioxidant activity and compound (23) has shown promising antioxidant activity than caffeine.[18]




(23)

Brishty *et al*, prepared N-substituted pyrazole-containing benzimidazoles and investigated their antioxidant properties by assessing their radical scavenging ability against DPPH and H2O2. Results showed that compounds (24) and (25) with benzyl groups attached to the nitrogen of imidazole exhibited strong antioxidant activity.[19]

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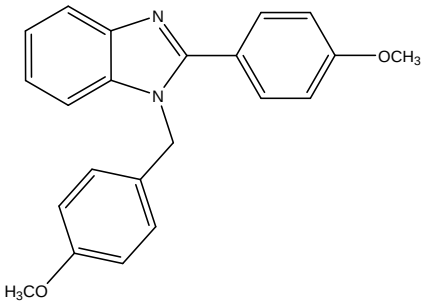
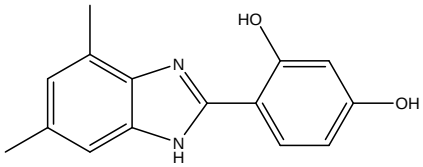



(25)

Taha *et al*, synthesized new Benzimidazole derivatives and evaluated them for their antioxidant activity. Among them, Compound (26),(27) and (28) showed potent antioxidant activity when compare with standard Propyl gallate[20]

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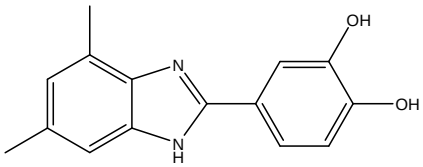


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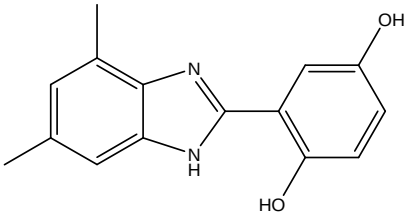
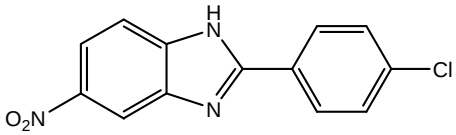



(28)

### 3.6. Anticancer

Baszczak-Swiatkiewicz *et al*, prepared a series of new benzimidazole derivatives and all synthesized compounds were screened for their anticancer activity against human lung adenocarcinoma A549 cell line. Among them, Four of the examined compounds (29) and (30) showed a very good antiproliferative effect.[21]

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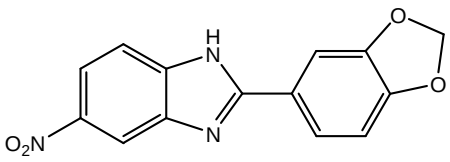
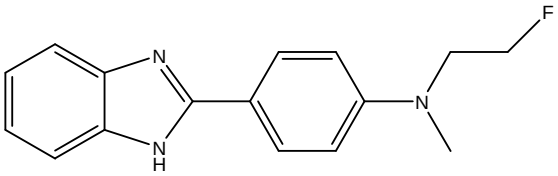


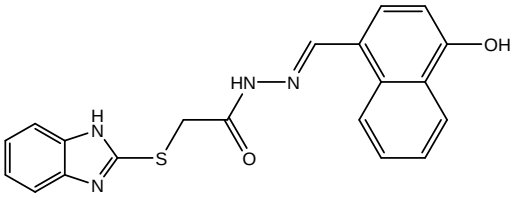

(30)

Goreti Ribeiro Morais *et al*, developed a number of new benzimidazole analogues with fluorinated or hydroxylated alkyl substituents and screened their anticancer activity. The findings showed that the compound 2-[N-methyl-N-(2′-fluoroethyl)-4′-aminophenyl] -1H-benzo [d]imidazole (31) displayed the most promising anticancer activity.[22]



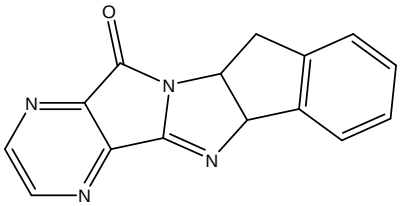

(31)

Yadav *et al*, Prepared series of benzimidazole derivatives and screened for anticancer activity against breast cancercell line (MCF 7). among the synthesized compounds, compound (32) has shown potent anticancer activity than 5-fluorouracil.[23]



(32)

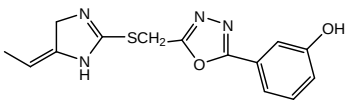
Sondhi *et al*, prepared a series of Heterocyclic benzimidazole derivatives. All these compounds were screened for anticancer activities. Among them, compound (33) exhibit good anticancer activity against ovary (IGR-OV-1), breast (MCF-7) and CNS(SF-295) human cancer cell lines.[24]



(33)

### 3.7. Antidiabetic

Shingalapur *et.al*, prepared novel benzimidazole analouges and screened them for antidiabetic activity using Oral Glucose Tolerance Test (OGTT). Among them, compounds (34),(35),(36) and (37) showed excellent antidiabetic activities.[25]



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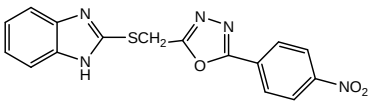

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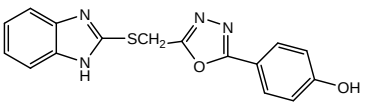

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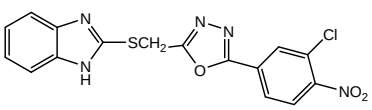
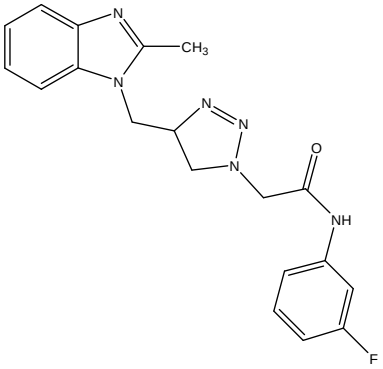


(37)

Laxmi Deswal *et al*, prepared a series of novel benzimidazole-tethered 1,2,3-triazole derivatives and the synthesized compounds were evaluated for their antidiabetic activity. Among them, Compounds (38), (39) and (40) were found to be the most active.[26]



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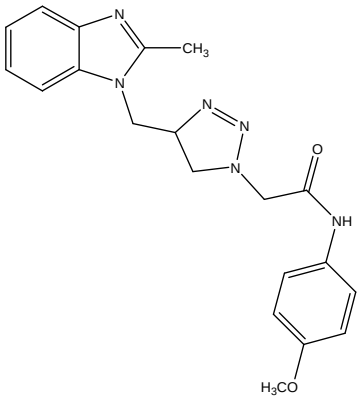
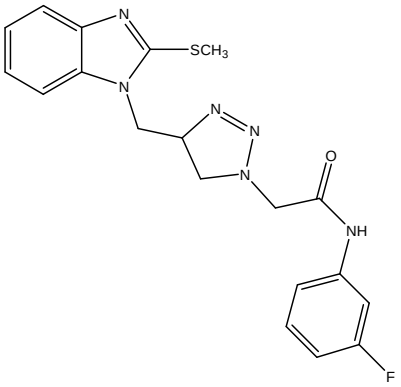
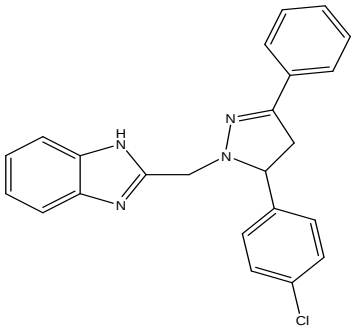


(39)



(40)

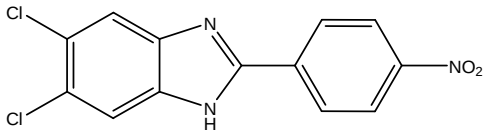
Ahmad *et al*, synthesized a new series of compounds, 2-((3,5-diaryl-4,5-dihydro-1H-pyrazol-1-yl)methyl)-1H-benzo[d]imidazole were synthesized. The antidiabetic potential of these compounds was studied by screening them for their α-glucosidase inhibition activity. Compound (41) appeared as effective.[27]



(41)

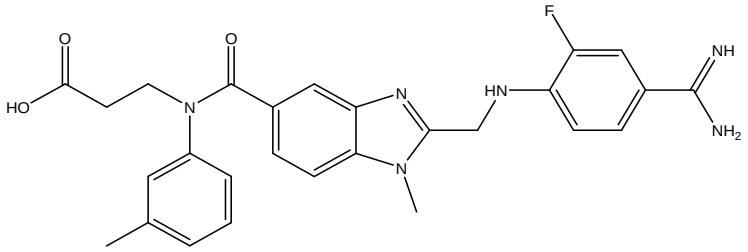
### 3.8. Antiprotozoal

Kazimierczuk *et al*, synthesized two series of benzimidazole derivatives. The first one was based on 5,6-dinitrobenzimidazole, the second one comprises 2-thioalkyl- and thioaryl-substituted modified benzimidazoles. Among the tested compounds, 5,6-dichloro-2-(4-nitrobenzylthio)-benzimidazole (42) showed the most distinct antiprotozoal activity.[28]

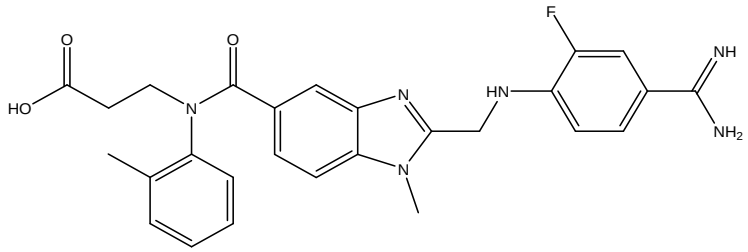



(42)

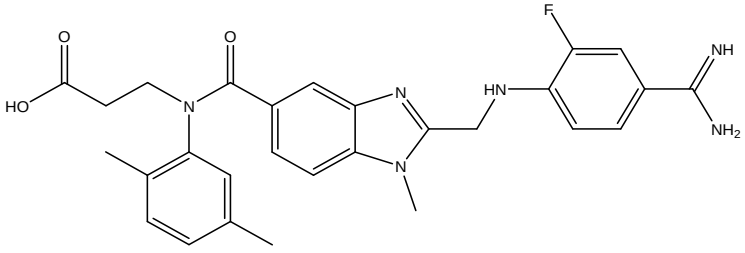
Yang Haoran *et al*, synthesized 1,2,5-trisubstituted benzimidazole fluorinated derivatives and screened for inhibitory activity against thrombin, among which three compounds showed that compounds (43),(44) and (45) exhibited better anticoagulant activity than argatroban.[29]




(43)




(44)




(45)

## 4. CONCLUSION

From the literature review, it is discovered that functional group present on molecule plays vital role in physicochemical properties showing by molecule. To develop a better pharmaceutical drug, researchers must first understand the proportional contributions of each functional group. Being a bioactive and structurally simple heterocyclic compound, the benzimidazole molecule has played a significant role in medicinal chemistry. It has the potential to be used in the development and discovery of novel medications with potential biological activity. Over previous decade attempts have been conducted to synthesis medicinally relevant benzimidazole derivatives and researchers identified several benzimidazole derivatives showing promising biological activity.

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