Benzimidazolederivatives and its biological significance- a review

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Abstract: The heterocyclic aromatic chemical benzimidazole is created by joining a six-membered benzene ring with a five-membered imidazole ring. It has a variety of biological and therapeutic uses. Numerous investigations have demonstrated that different substituents placed all around the benzimidazole nucleus produce therapeutically valuable molecules that are pharmacologically active. This moiety is a preferred option of interest in the design and synthesis of novel medicinal compounds due to its variety of pharmacological characteristics. The benzimidazole core, which is present in many different biological agent classes, including anti-bacterial, anti-viral, anti-parasitic, anti-hypertensive, anti-cancer, anti-inflammatory, anticonvulsant, CNS stimulat and depressants has served as a crucial framework for the creation of countless newer therapeutic compounds. Understanding the synthesis and related functions of compounds produced from benzimidazoles in various disorders is crucial.Therefore, in this study, we make an effort to explore several benzimidazole nucleus derivatives with a variety of pharmacological actions.

Keywords: Benzimidazole, Medicinal compounds, anti-bacterial, anti-viral, anti-cancer, anti-inflammatory and anti-convulsant.

1. Introduction

Heterocyclic compounds are well known for their different biological activity. The heterocyclic analogs are the building blocks for synthesis of the pharmaceutical active compounds in the organic chemistry. These derivatives show various type of biological activity like anticancer, antiinflammatory, anti-microbial, anti-convulsant, anti-malarial, anti-hypertensive, etc. From the last decade research showed that the benzimidazole analogs plays a vital role in the development of newer medicinal active compounds for treating various type of disease. Benzimidazole, alternatively know as 1*H*- benzimidazole and 1,3-benzodiazole, consist of benzene ring fused with a five membered imidazole ring and is an important heterocylicpharmacophore (Figure 1). It is regarded as a privileged structure in heterocyclic chemistry due to its association with a wide range of biological activities.[1,2]Benzimidazole moiety act similarly as purines to provide biological respose and the first investigation on biological activity of benzimidazole nucleus was reported in 1944[3].Benzimidazole ring contains two nitrogen atoms placed at position 1 and 3 which exhibit amphoteric nature, possessing both acidic and basic characteristics. Benzimidazole can be synthesized from a variety of starting materials, including aniline, nitrobenzene, and benzamide,common synthesis methods include the Sandmeyer reaction and the Biginelli reaction. Benzimidazoles can exist in several different isomeric forms, including meta- and para-isomers, which can have different properties and reactivity. As a result of changing substituents around the core structure of benzimidazoles, many drugs of a wide variety of therapeutic lies have been developed such as Albendazole, Mebendazole, Thiabendazole as anthelmintics, Eniradine as antiviral, Carbedazim as fungicidal, Omeprazole, Lansoprazole, Pantoprazole as proton pump inhibitors, Candesartan, Cilexitil and Telmisartan as antihypertensive and Astemizole as anti-histaminic agent.[4] (Figure 2)

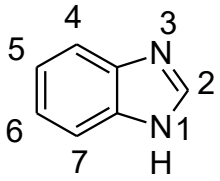


Figure 1

Benziminazoles plays a very important role with plenty of useful pharmacological activities such as: - Antibacterial (2.1), Antifungal (2.2), Analgesic (2.3), Antimicrobial (2.4), Antiulcer (2.5), Anticancer (2.6), Anticonvulsant (2.7), Anti-inflammatory (2.8), Anti-helminthic (2.9). Despite their numerous benefits, benzimidazoles have also been associated with toxic effects, such as carcinogenicity and genotoxicity, which highlights the need for careful regulation and monitoring of their use. Benzimidazole nucleus-containing therapeutic medicines are used to create medications that are a current research topic. This review article is précised to know about the chemistry of different derivatives of substituted benzimidazoles along with their pharmacological activities.

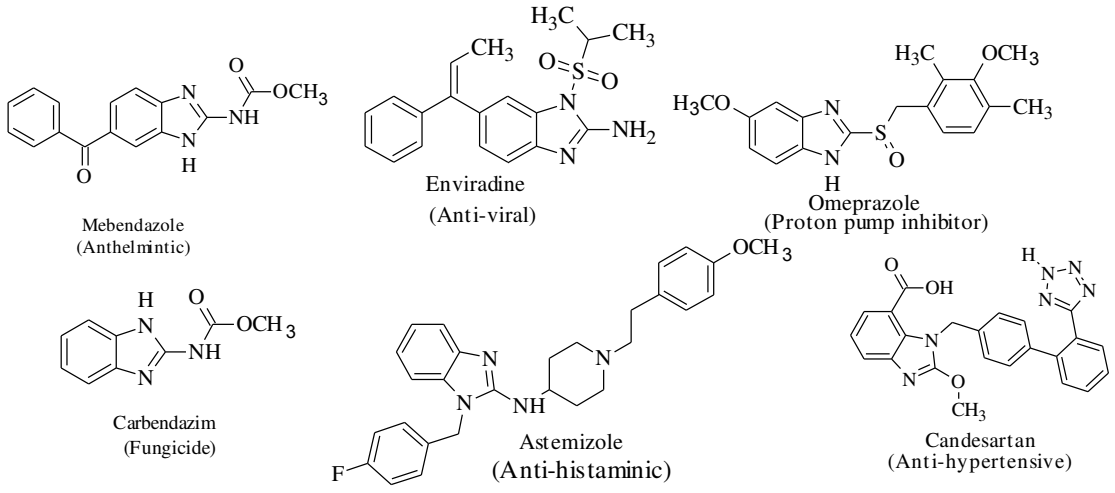
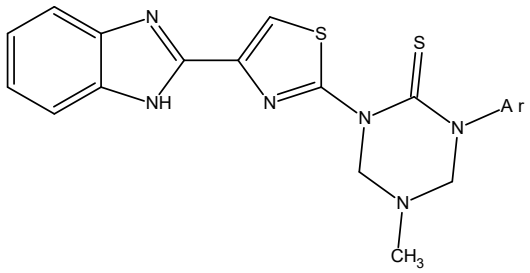


Figure 2: Benzimidazole containing drugs

2. Pharmacological Activities

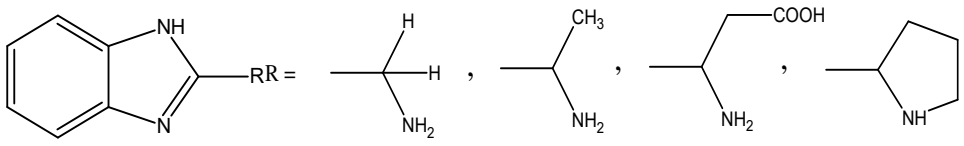
2.1. Anti-bacterial activity

Gullapelli*et al.,* (2017) synthesized new analogs of benzimidazole fused heterocyclic compounds such as triazine andoxadiazinanes **(1)** using amino methylation with different thioureas and were screened for their anti-bacterial activity. The synthesized molecules were subjected to molecular dockingstudies against the targets Topoisomerase II (PDB ID: 1JIJ) and DNA gyrase subunit B (PDB ID:1KZN). The molecular docking studies were supporting the antibacterial activity exhibiting high inhibitionconstant and binding energy.[5]



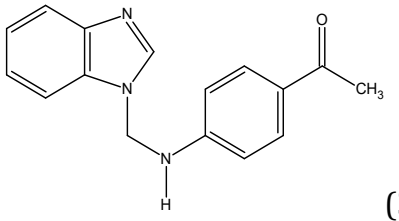
(1)

Chintakunta*et al., (2020)* synthesized some novel 2- substituted benzimidazolederivatives**(2)**using o-phenylenediamine and amino acids undergo condensation via Philips's reaction. The synthesized compound showed promising Anti-bacterialactivity against *Bacillus subtilis*and *Pseudomonas aeruginosa*compared with the standard drug Ciprofloxacin[6]



(2)

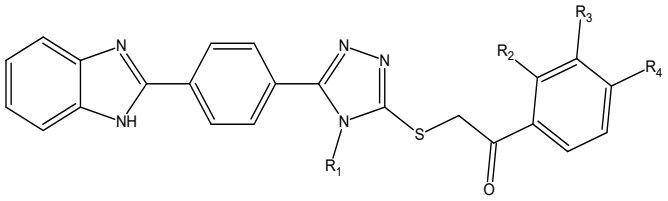
Chandrasekar*et al.,* (2019) synthesized benzimidazole and itsderivatives**(3)**by reflux process. The study was performed to identify a potent antibacterial activity of benzimidazole derivatives. The derivatives are well screened for antibiotic susceptibility (AST) and Minimum inhibitory concentration (MIC) against gram positive and gram-negative bacteria and compared with standard drug Norfloxacin.[7]



(3)

2.2. Anti-fungal Activity

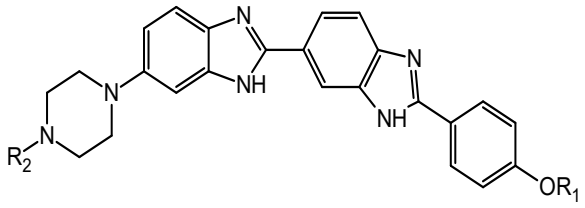
Can*et al*., (2019) reported a new series of benzimidazole-triazole derivatives **(4)** were designed and synthesized as ergosterol inhibitors. The final compounds were screened for antifungal activity against *Candida glabrata, Candida krusei, Candida parapasilosis, Candia albicans.*[8]



R1 : - CH_3 , C_2H_5 ; **R2,R3,R4** : -H, -Cl, -F, -Br, -CN, -OH, -OH, -CH_3

(4)

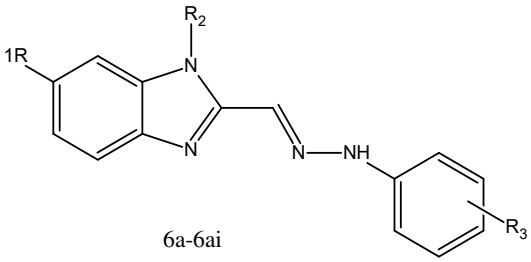
Chandrika*et al.,* (2016) synthesized 18 alkylated mono-, bis-, and tris-benzimidazolederivatives**(5)**. Bis-benzimidazole exhibits moderate to excellent antifungal activities. Synthesized bisbenzimidazole compared with standard drug Amphotericin B, Fluconazole, Itraconazole its activity was found to be equal or superior than standard anti-fungal agents.[9]



2: R1 = H, R2 = CH_3
3: R1 = H, R2 = C_3H_7
4: R1 = H, R2 = $C_{12}H_{25}$
18:R1 = C_3H_3, R2 = CH_3

(5)

Wang*et al.,* (2016) synthesized a series of benzimidazolephenylhydrazone derivatives **(6)**. All the compounds were screened for antifungal activity againstRhizoctoniasolani and Magnaporthe oryzae. Compound 6f shows significant activity.[10]

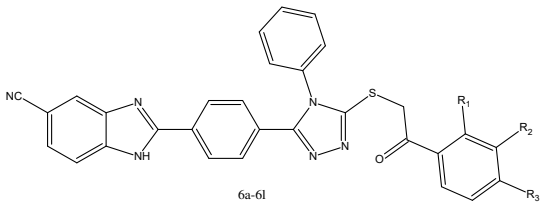


6a-6ai

Compound	R_1	R_2	R_3
6a	H	H	H
6b	H	H	2-F
6f	H	H	3-F

(6)

Guzel*et al.,* (2023) synthesized a series of benzimidazole – 1,2,4- triazole derivatives **(7)**. The synthesized compounds were screened for antifungal activity against 4 fungal strains namely *Candida albicans, Candida glabrata, Candida krusei*and *Candida parapsilopsis*. Synthesized compounds can be used as new fungicidal lead targeting 14α – demethylase.[11]



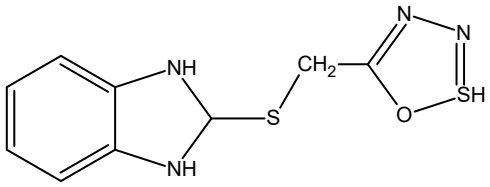
6a-6l

6a: R1=-NO2, R2 =-H, R3 =-H 6b: R_1= -OCH3, R_2= -H, R_3= -H

(7)

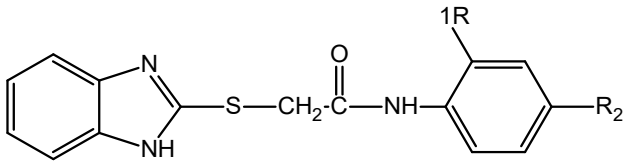
2.3. Analgesic Activity

Sakr*et al.,*(2021)synthesized new derivativesofbenzimidazole**(8)** by condensation of o-phenylenediamine and carbon disulfide resulting in 2-mercapto-benzimidazolewhich is treated with alcoholic KOH forming potassium salt of 2-mercapto benzimidazole, final compound is screened for analgesic and anticancer activity.[12]



(8)

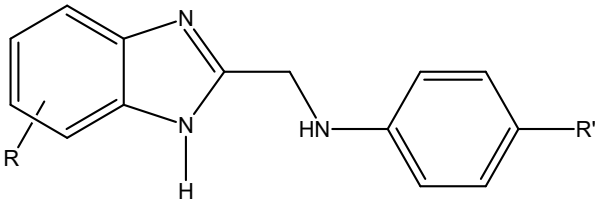
Goud*et al.,* (2011) synthesized new series of benzimidazolederivatives**(9)** and the structures of the compounds were confirmed by IR, HNMR, and Mass spectroscopy. The final compounds were screened for analgesic and anti-inflammatory activities.[13]



R1 = CH3 , NO2 , Cl , CH3
R2 = OH , NH2

(9)

Achar*et al.,* (2010) synthesized a series of 2-methylaminobenzimidazole derivatives **(10)**. The compounds were screened for analgesic and anti-inflammatory activity. All these compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR and elemental analysis.[14]

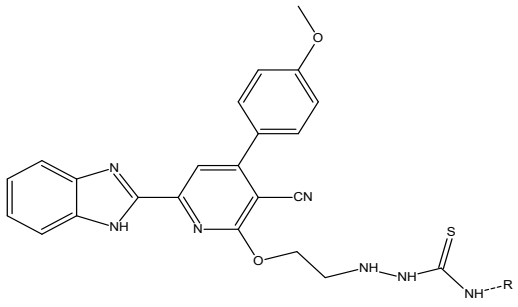


R = H , Br , NO_2
R' = H , Cl , CH_3 , OCH_3

(10)

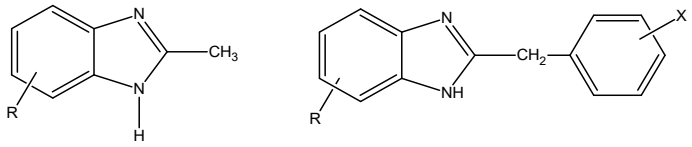
2.4. Anti-microbial Activity:

Zaghary*et al.,* (2021) synthesized new series of benzimidazolederivatives**(11).** The compound is screened for antimicrobial activity and antifungal activity. Molecular docking was performed with amino acid residues of DNA gyrase and topoisomerase IV using MOE software.[15]



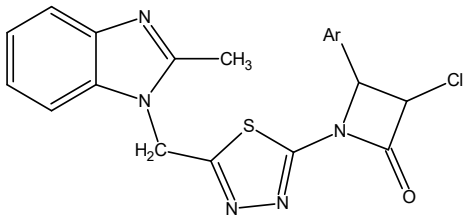
(11)

Rathee*et al.,* (2011) synthesized series of two novel benzimidazolederivatives**(12)**. The first one comprises of 2-methyl, the second one comprises of 2-phenyl substitution on benzimidazole moiety. The synthesized compounds were screened for antimicrobial activity (anti-bacterial and anti-fungal activity) by tube dilution method.[16]



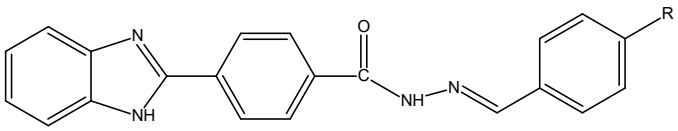
(12)

Ansari *et al.,* (2009) synthesized novel azetidine-2-one of benzimidazolederivatives**(13)**. The synthesized compounds were screened for their anti-microbial activity. Synthesized compounds were analyzed by elemental and spectral data.[17]



(13)

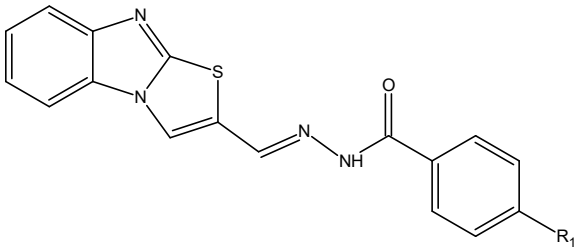
Özkay*et al.,* (2010) synthesized 12 novel benzimidazolecompounds**(14)** bearing hydrazone moiety and shows their possible antibacterial and antifungal activity. The synthesized compounds were found to be significantly effective against *Proteus vulgaris, Staphylococcus typhimurium, Klebsiellapneumoniae*and *Pseudomonas aeruginosa gram-negative bacterial strains.*[18]



R: -H, -OH, -N(CH3)2, -Cl, Br, -F, -CH, -OCH, -NO2, -CF, COOH, CN

(14)

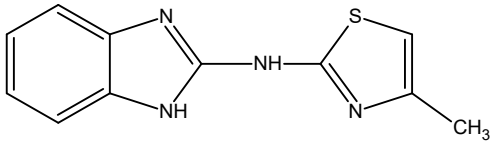
Kamat*et al.,* (2020) reported the synthesis of benzimidazole**(15)**containing tricyclic systems and screened for their antimicrobial activity and it's alsoexhibiting anti-inflammatory property. **5b** compound has a significant IC_{50} value.[19]



(15)

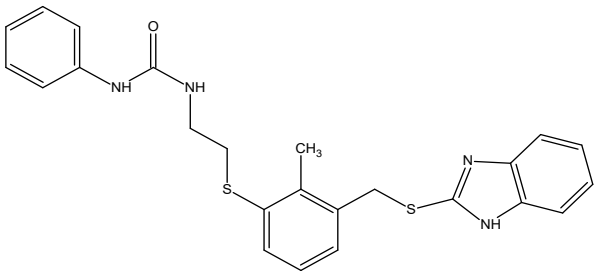
2.5.Anti-ulcer Activity

Grassi*et al.,* (1991) studied antiulcer activity of BAY P 14551 a thiazolylaminobenzimidazolederivatives**(16)**. Antiulcer activity was compared with that of reference drugs such as cimetidine, pirenzepine and carbenoxolone.[20]



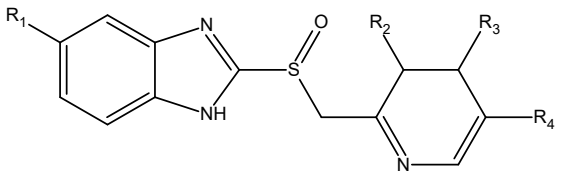
(16)

Carcanague*et al.,* (2002) successfully provided a set of 2-({3-[(1*H*-benzimidazol-2-ylsulfanyl) methyl]-2-methylphenyl} sulfanyl) ethyl carbamates**(17)**with the generic structure, the synthesized compound selectively acts against gastric pathogen *Helicobacterpylori*.[21]



(17)

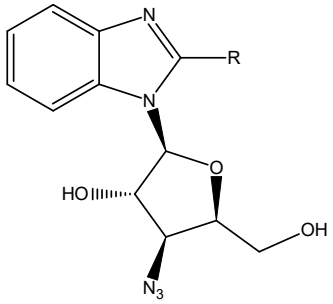
Shin *et al.,* (2009) synthesized new aryl sulfonyl proton pump inhibitor (PPI)**(18)**prodrug forms were synthesized. These prodrugs provided longer residence time of an effective PPI plasma concentration resulting in better gastric acid inhibition.[22]



(18)

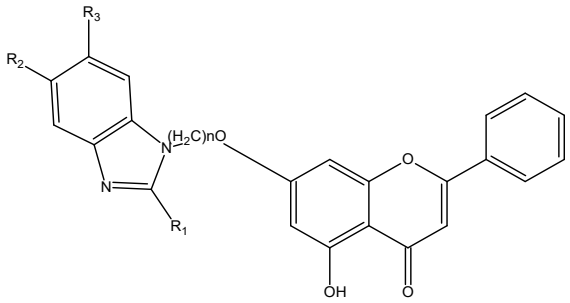
2.6.Anti-cancer Activity

Shinde*et al.,* (2020) synthesized benzimidazole nucleosides 1-8 from readily available D-glucose **(19)**. Newly synthesized analogs were evaluated for anticancer activity using MDA-MB-231 cell line. Among 3'- azide substituted nucleosides are more potent.[23]



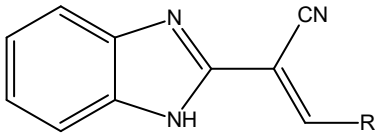
(19)

Wang *et al.,* (2018) synthesized a series of chrysinbenzimidazole derivatives **(20)** and evaluated for anticancer activity and it was found to be potential anticancer activity.[24]



(20)

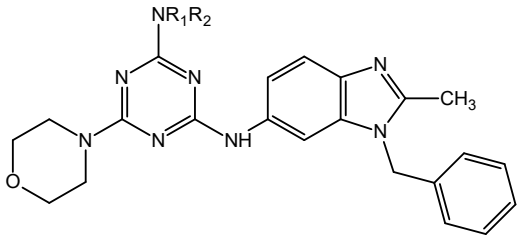
Refaat*et al.,* (2010) synthesized the various series of 2-substitued benzimidazoles**(21)**. 2-[(4-oxothiazolidin-2-ylidene) methyl and (4-amino-2-thioxothiazol-5-yl) benzimidazoles**.**The synthesized products were screened for anticancer activity.[25]



R = different aryl or heteroaryl

(21)

Singla*et al.,* (2015) synthesized a new series of trazine-benzimidazole hybrids **(22)** with different substitution of primary and secondary amines at one of the positions of trazine in moderate to good yields. These synthesized compounds show inhibitory activities over 60 human tumor cell lines at one dose and 5 doses concentration and it also inhibits DHFR (Dihydrofolatereductase).[26]

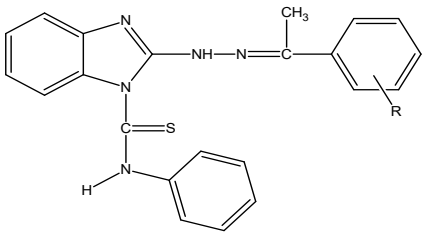


NR^1R^2 = 15; morpholine
16; piperidine
17; pyrrolidine
18; N-methylpiperazine

(22)

2.7. Anti-convulsant Activity

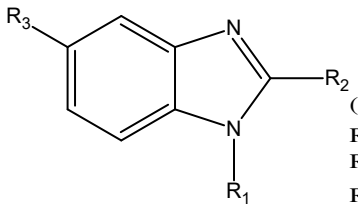
Bhrigu*et al.,* (2012) synthesized a series of new 2- [(1-substituted phenylethylidine) hydrazine]-*N*-phenyl-1*H*-benzo[*d*]imidazole-1-carbothioamides **(23)**and the compound is screened for anticonvulsant activity.[27]



R = H, 4-NH2, 4-OH, 3-OH, 4-Br, 4-F, 2-Cl, 4-NO2.

(23)

Singh *et al.,* (2010) synthesized a series of 1,2,5-trisustituted benzimidazole derivatives **(24)**. The compounds with optimum chain length at position two (R_2) and electron withdrawing group at position five (R_3) showed better anticonvulsant activity.[28]

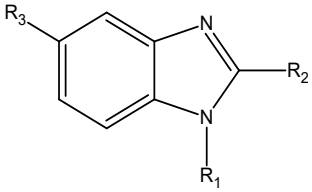


(a)
R1= 1-picoline
R2= H, CH_3,C_2H_5,C_3H_7
R3= H, NO2

(24)

2.8. Anti-Inflammatory Activity

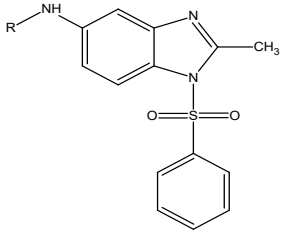
Thakurdesai*et al.,* (2007) studied benzimidazole moiety with carboxylic acid substitution at 2nd position **(25)**, yields anti-inflammatory activity. The compound was screened for acute anti-inflammatory activity and found to be potent anti-inflammatory agent.[29]



R_1= H, CH_2-Ar
R_2= COOH, CH_2COOH, CH_2CH_2COOH
R_3= H, NO_2, Cl, OCH_3, OC_2H5

(25)

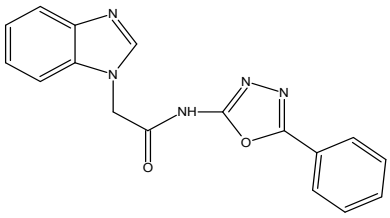
Gaba*et al.,* (2010) synthesized 5-substituted-1-(phenyl sulfonyl)-2-methyl benzimidazole derivative **(26)** and the compound was found to anti-inflammatory and analgesic activity as well as gastric ulcerogenic effects. Compounds have been screened for IR, ^{1}H NMR, ^{13}C NMR, Mass spectral data and elemental analyses.[30]



R = a= p -$NH_2C_6H_4$
b= o -NH_2C6H_4
c= p - $NH2C_7H6$

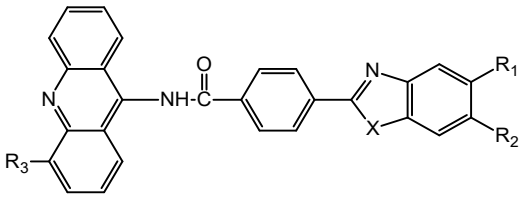
(26)

Rajasekaran*et al.,* (2012) synthesized a series of benzimidazole derivatives **(27)** fused with oxadiazole ring. The five membered heterocyclic moiety 1,3,4-oxadiazole also confers for various biological activity, final compound is screened by UV, IR &^{1}H NMR spectral data and synthesized compound is evaluated for anti-inflammatory and antioxidant activity.[31]



(27)

Sondhi*et al.,* (2006) synthesized a series of N-(acridin-9-yl)-4-(benzo[d]imidazole-2-yl) benzamide derivatives **(28)**. These compounds were screened for anti-inflammatory, analgesic kinase (CDK-1, CDK-5 & GSK-3) inhibition activities.[32]

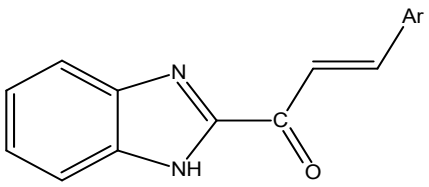


	R1	R2	R3	X
3a	Cl	H	H	NH
3b	NO2	H	H	NH
3c	NO2	H	OCH3	NH
3d	CH3	CH3	H	NH
3e	H	H	H	O
3f	H	H	OCH3	O

(28)

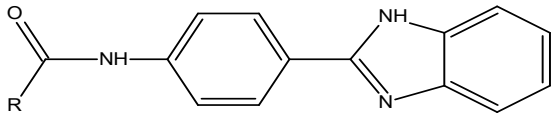
2.9. Anti-Helminthic Activity

Ouattara*et al.,* (2011) synthesized a series of 1-(1*H*-benzimidazol-2-yl)-3-aryl-2-propen-1-one compounds **(29)**. All the compounds were screened for nematocidal activity against *Haemonchuscontortus.* Anti-helminthic activities of synthesized compound are compared with Fenbendazole and Ivermectin.[33]



(29)

Shahare*et al.,* (2012) synthesized 2-substituted benzimidazole derivatives **(30)** and it was screened for anti-helminthic activity. The anti-helminthic activity of 2-substituted benzimidazole (2a-2d) compounds was evaluated for mean paralysis and mean death time.[34]



R: -CH3, -CH2Cl

(30)

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