Research Journal of Chemical Sciences ISSN 2231-606X
Vol. **4(4),** 78-88, April **(2014)** *Res. J. Chem. Sci.*

Review Paper

Diverse Pharmacological aspects of Benzimidazole Derivatives: A Review

Sreenivasulu Enumula, Anees Pangal†, Muiz Gazge†, Javed A. Shaikh and Khursheed Ahmed*
Dept. of Chemistry & Post Graduate Research Centre, Abeda Inamdar Sr. College of Arts, Science & Commerce, Camp, Pune – 411001, INDIA

Available online at: www.isca.in, www.isca.me
Received 6th February 2014, revised 1st March 2014, accepted 15th March 2014

Abstract

Benzimidazole is the heterocyclic compound formed by the fusion of benzene and imidazole ring. Benzimidazole analogs are of great significant because of their various clinical applications and biological activity. Benzimidazoles are considered as an optimistic class of bioactive heterocyclic compounds that possesses a range of biological activities. The work in this article relates to benzimidazole as it is a versatile heterocycle possessing a wide spectrum of biological activities like antimicrobial, antiviral, antidiabetic, anticancer activity, numerous antioxidant, antiparasitic, antihelmintics, antiproliferative, antiHIV, anticonvulsant, anti-inflammatory, antihypertensive, antineoplastic, proton pump inhibitor and antitrichinellosis. Benzimidazoles possess significant biological activities likepotential antitumor agents, smooth muscle cell proliferation inhibitors and in various areas of chemistry.

Keywords: Diverse, pharmacological, benzimidazole, heterocyclic, fusion, imidazole ring.

Introduction

Benzimidazole is a well known famous structure in medicinal chemistry with various biological activities. It is a benzannulated ring system in which benzene ring is fused with a five member ring system having hetero atom at 1 and 3 positions. The properties of benzimidazole and its analogs have been studied since over hundred years. However a special interest of researchers towards benzimidazole derivatives was originated by the fact that 5, 6-dimethyl-1-(α-Dribofuranosyl) benzimidazole is an basic part of the structure of vitamine B_{12}[1]. Moreover benzimidazole is a structural unit of naturally occurring nucleotide, due to which it easily interacts with the biopolymers of living system. This character is responsible for its numerous biological aspects like antihelminthic[2], antifungal[3], anti-allergic, antimicrobial[4-6], antiviral[7] and antineoplastic[8] activities. Since proteases have been linked with several disease states, including thrombosis, inflammation, bronchoconstiction and tumor growth and invasion[9]. The incorporation of the nucleus is an important synthetic strategy in studies of antimicrobial drug discovery.

In the past few decades, benzimidazole and its derivatives have grasped much attention due to their chemotherapeutic values[10]. Furthermore, the pharmacological properties as well as therapeutic applications of benzimidazole depend upon the pattern of substitution and recently they are reported to possess many pharmacological activities. This review highlights the importance of Benzimidazole in medicinal world along with a few examples of clinically used drugs. Additionally review of some of the work concerning benzimidazole reported in the recent literature has also been provided.

Antibacterial Activity

He et al. reported synthesis of a series of benzimidazole with general molecular structure **(1)** which exhibits potent broad spectrum antibacterial activity and started a research program to discover novel antibiotics against Gram positive bacteria by targeting rRNA[11].

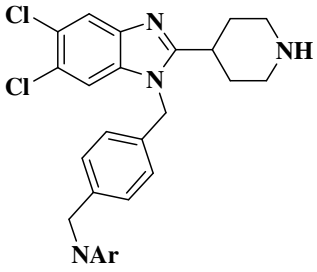


Figure-1
General structure for benzimidazole derivatives (1)

Kumar *et al.* synthesized some novel 2-(6-fluorochroman-2-yl)-1-alkyl/acyl/aroyl-1H-benzimidazoles and found that they exhibited good antibacterial activity against *Salmonella typhimurium*. They also reported synthesis of a series of functionalized novel benzimidazole derivatives and evaluated for their potential antibacterial[12].

Synthesis of benzimidazole as 1-(substituted-methyl)-2-(substituted-phenyl) benzimidazole **(2)** was reported by Leonardo *et al*. Compounds **2a, 2b and 2c** were screened for their antibacterial activity against *S. aureus, B. pumillus* and *P. Aeurugenosa.* Compound 3a showed MIC (6.25) at 100μM/mL and exhibited good antibacterial activity[13].

Synthesis of 2,3,4,-trisubstituted-1,2-dihydropyrimido[1,2-*a*]benzimidazole derivatives **(3)** were reported by Deshmukh *et al*. The compounds were tested for their fungicidal activities against *Aspergillus niger* MTCC-2255 and *Penicillium chrysogenum*-NCIM-723 using Greiseofulvin as control[14].

The efficient synthesis of novel 3-chloro-1-5-(2-methyl-1*H*-bezimidazol-2-yl)-4-(substituted) phenylazetidin-2-one **(4)** was reported by Ansari *et al*. Compounds were screened for antibacterial activity against *B. substilis* and *E. coli* and compound **4a, 4b and 4c** shown MIC at 100µg/mL, 100µg/mL and 200µg/mL doses[15].

The two series of benzimidazole derivatives were synthesized by Kazimierczuk et al., the first one was based on 2-thioalkyland thioaryl substituted benzimidazole **(5)**, the second one was based on 5,6-dinitrobenzimidazole **(6)** and the antibacterial activity of the compound against *Stenotrophomonas malthophilia* was examined[16].

Ansari and Lal evaluated novel azetidine-2-one for antibacterial and antifungal activity against *B. subtilis, E.coli, C. albicans, A. niger* and *A. flavus*. All these tested compounds were less effective against Gram negative bacteria[17-18]. Some benzimidazole 2-substituted-1-[{(5-substituted-alkyl/aryl)-1,3,4-oxadziazolyl-2-yl}] derivatives were assessed for antimicrobial activities against Gram +ve and Gram –ve bacteria by Ansari and Lal and they are moderately active against tested organism[17-18].

Gupta and co-workers prepared 2-thiohalogenonitrophenyl benzimidazole **(7)** and screened them for their antifungal activity against *H. sativum, A. niger* and *F. oxysporum*. The percentage inhibition of the fungal spores was recorded at 10ppm[19].

Ghoneim et al. prepared 2-[(4-aminophenyl)sulphonyl] derivative **(8)** of benzimidazole and tested the antimicrobial activity of compounds against *E. coli* using agar diffusion method. All 4-amino and 2,4-diaminophenylsulphonyl derivatives showed antimicrobial activity[20].

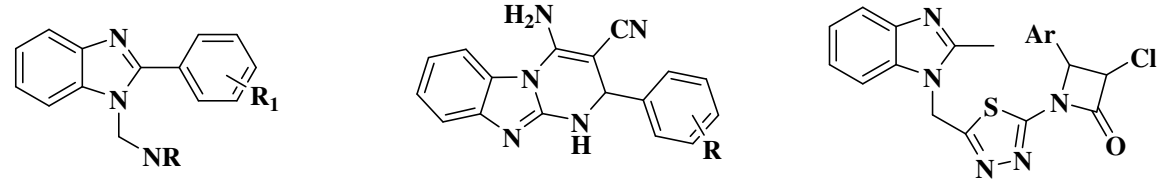


Figure-2
General Structures for benzimidazole derivatives (2), (3) and (4)

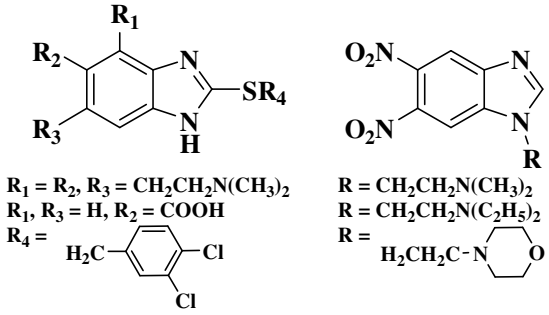


Figure-3
2-thioalkyland thioaryl substituted benzimidazole (5) & 5, 6-dinitrobenzimidazole (6)

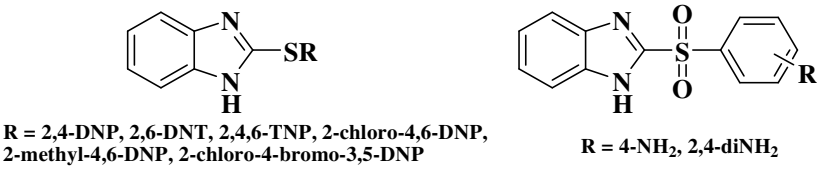


Figure-4
2-mercaptobenzimidazole (7) & 2-[(4-aminophenyl)sulphonyl] derivative (8)

Various benzimidazoles were also prepared and evaluated by Mane et al. towards *A. brassicicola, F. oxysporum , S. aureus* and *Escherichia. coli* at 500 ppm concentration. The compounds with nitro and chloro substituent possess good antimicrobial activity against[21].

Mavrova and co-workers synthesized the 1H-benzimidazole-2-yl thioacetylpiperazine derivatives **(9, 10, 11)** and screened them for *in-vitro* activity in contrast to *T. spiralis* and *in-vivo* anti-nematode activity against *S. obvelata.* Most of the synthesized compounds exhibit higher activity towards *T. spiralis* than albendazole and comparable to that of ivermectin. Few compounds exhibited 96.0%, 98.2% and 100% activities at a dose of 200µg/ml after 48h. Some of the compounds were most active with 76%, 73% and 77% towards *S. obvelata*[22].

Yadav *et al.* synthesized a series of 4-[1-(substituted aryl/alkyl carbonyl)-benzoimidazol-2-yl]-benzene sulphonic acids and tested them for antifungal activity and found two compounds 4-[1-(4-Nitrobenzoyl)-1H-benzoimid-azol-2-yl] benzenesulfonic acid and 4-(1-octadec-9-enoyl-1H-benzoimidazol-2-yl)-benzenesulfonic acid were most effective[23].

Antiviral Activity

A new series of 2-arylbenzimidazoles **(12)** was reported by Vitale *et al*. They assessed them for antiviral activity and antiproliferative. Compounds were screened against *Flaviviridae* family, i.e. *Flaviviruses* and *Pestiviruses, Retroviridae, Picornaviridae, Paramyxoviridae, Rhabdo-viridae and Reoviridae, Herpesviridae and Poxviridae*. Compounds **12a, 12b and 12c** showed moderate activity against Yellow Fever Virus[24].

A new series of benzimidazole and substituted benzimidazole β-L- and β-D-2'-deoxyribonucleosides derivatives was reported by Budow et al and screened for antiviral activity against selected RNA and DNA viruses[25].

Synthesis of 2-(benzylthio)-5, 6-dichloro-1-(*β-D*-ribofuranosyl)benzimidazoles **(13)** was reported by Devivar *et al* 10. Compounds 6a, 6b and 6c performed anti-viral activity towards HSV-1 and HCMV and compound 6c shown maximum activity at 90% inhibitory concentration (µM)[26].

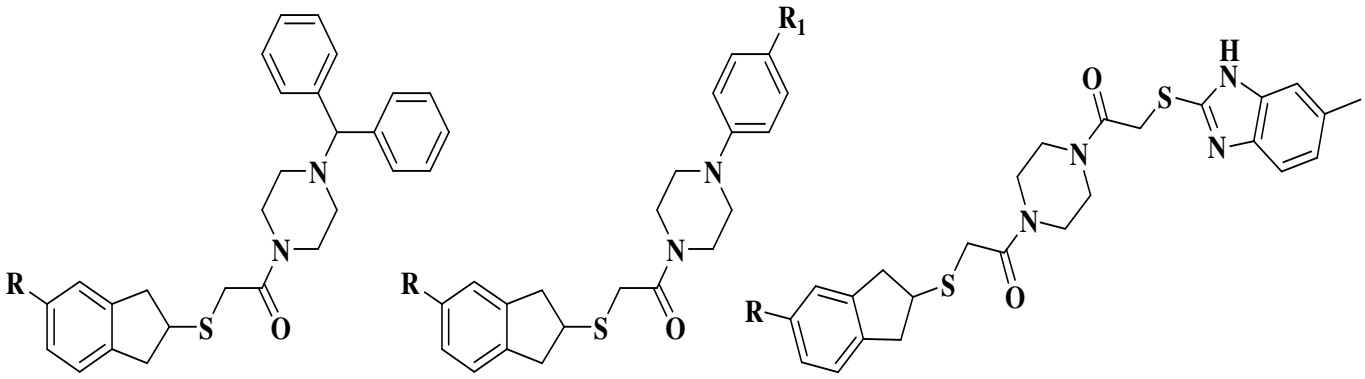


Figure-5
The 1H-benzimidazole-2-yl thioacetylpiperazine derivatives (9, 10, 11)

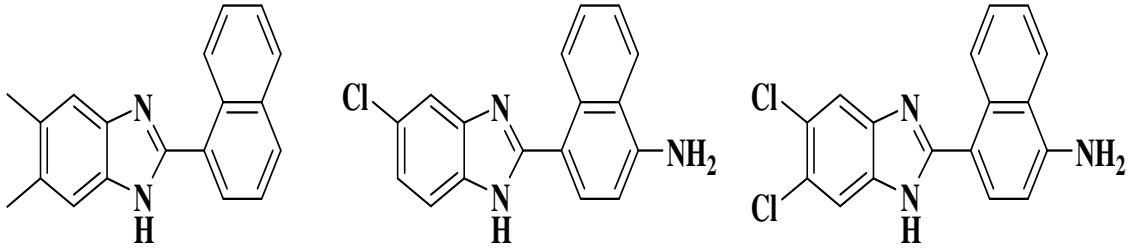
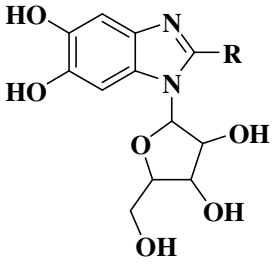


Figure-6
2-arylbenzimidazoles derivatives (12)



R = SCH_3, SO_2CH_3, SO_2Ph

Figure-7
2-(benzylthio)-5, 6-dichloro-1-(β-D-ribofuranosyl)benzimidazoles (13)

Some 7-(arylamidoalkyl)-3,4-diphenyl-isoquinolinyl-[1,5-c]-benzimidazoles **(14)** have been synthesized by Pandey and Shukla and were evaluated for their in vivo against influenza virus (IV) by inoculating it in 10 day old embryonated hen's egg at the concentration of 0.5 mg per embryo. After 48 h it was found that the isoquinonyl benzimidazole derivative with nicotinamido group showed the maximum activity[27,21]

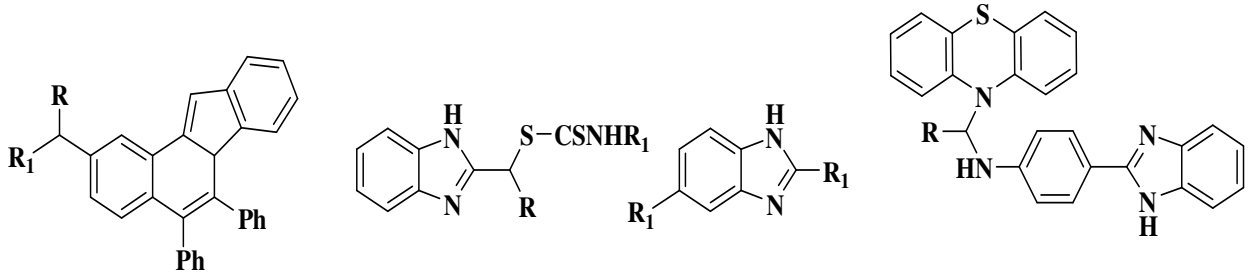
Various benzimidazol-2-ylalkyl N-aryldithiocarbamates **(15)**, 2-arlimino-4-methyl/H-2H, 4H[1,3,4]dithiazino[4,5-a]benzimidazole (37), 1-aryl-4-methyl/H-1, 2-dihydro-4H-[1,3,4]thiadiazino[4,5-a]benzimidazole-2-thiones (38) 1-aryl-4-methyl/H-1, 2-dihydro-4H-[1,3,4]thiadiazino[4,5-a]benzimidazole-2-ones (39) were synthesized and tested for their antiviral activity by Yadav and Pal[28].

Kristina et al. prepared a set of 2-substituted-5-amidino-benzimidazole **(16)** derivatives bearing amidino substistuent at C-5 of benzimidazole ring by substituting various heterocyclic nuclei at C-2 and were evaluated for their antiviral activity towards *coxsackie* viruses and *echo* viruses. The most selective activity towards *coxsackie* viruses and *echo* viruses was observed with the compound having pyridine ring at C-2[29].

Some new 10-(a-p-benzimidazolyl-1-aminobenzyl) phenothiazines **(17)** have been synthesized and their antiviral activity was performed against JEV and HSV-1 by Bishnoi et al[30].

Anti-Inflammatory Activity

Synthesis and anti-inflammatory activity of phenyl benzimidazole **(18)** was reported by Leonardo *et al*. Compounds 1a, 1b, 1c and 1d were screened for anti-inflammatory activity and they showed percent inhibition (22.1%, 52.2%, 54.6% and 49.6%) at 50 mg/kg each doses. By these values the compound 1c showed maximum (54.6%) inhibition of edema at doses of 50mg/kg[31].

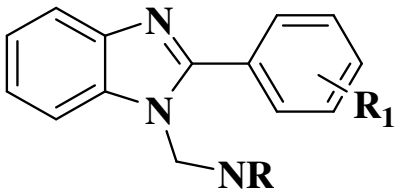


R = H, R_1 = salicylamido

R_1 = Heterocyclic substituent
R_2 = Amidino substituent

R = Substituted phenyl

Figure-8
Benzimidazole derivatives (14-17)



R = morphine, diphenylamine, dimethylamine, imidazole
R_1 = Cl

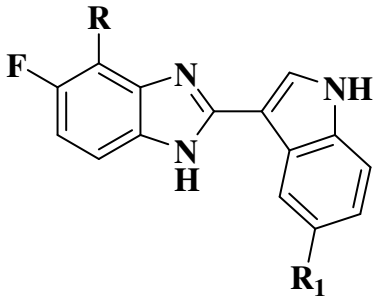
Figure-9
Phenyl benzimidazole derivatives (18)

Khan and Nandan synthesized some 2-substituted benzimidazoles and assessed them for analgesic and anti-inflammatory activities. The compounds exhibited good anti-inflammatory activity at 50mg/kg dose[32].

Evans et al reported a new synthesis 1H-benzimidazole and screened their anti-inflammatory activity by assessing on rat and indomethacin is used as standard. The result shwed 30% or greater reduction in non-injected paw volume against the result for indomethacin compared when compared to control[33].

Antioxidant Activity

Synthesis of some 6-flouro-5-substituted benzimidazole **(19)** reported by Alagoz *et al.* and tested for antioxidant activity and compound **(19e)** showed strong anti-oxidant effect on superoxide anion at 0.001M concentration[34].



R = 4-$CH_3C_5H_{10}$, 4-$CH_3C_5H_{10}N$, 4-$C_6H_5C_4H_9N_2$ 4-$C_6H_5C_4H_9N_2$, 4-$C_6H_5C_4H_9N_2$, R_1 = H, Br, OCH_3

Figure-10
6-flouro-5-substituted benzimidazole derivatives (19)

Antiulcerative Activity

Pantoptazole, Omeprazole, lansoprazole, Rabeprazole are some commercially available benzimidazole-based drugs. These drugs are used in combination with antibiotics to treat the gastric infection with *H. pylori* and reduce the gastric acid output by inhibiting the H+/K+-ATPase proton pumps[35].

Although H2 antagonist are also prescribed but proton pump inhibitors (PPIs) show faster pain relief, more rapid ulcer healing and far greater efficacy in oesophageal reflux diseases. PPIs are weak bases which are absorbed from the small intestine and delivered to the parietal cell via blood where they accumulate in the acidic, tubulovesicular system. In actively secreting parietal cells where tubulovesicular space is very highly acidic, they converted to a cyclic sulfonamide. These reactive sulfhydryl reagents binds to the active site of the enzyme by covalent interaction with the thiol groups of cysteine residue located at position of 813 and 822 between transmembrane domain 5 and 6 of the alpha subunit of the H^+/K^+-ATPase. The interaction of rearranged inhibitory sulfonamides derived from PPIs with the active site of the enzyme prevents proton pumping and production of hydrochloric acid. Hence helps in treating ulcers[36-40].

Series of novel pyrimidyl-thio-methyl- benzimidazole **20(a)** pyrimidyl-sulfinylmethylbenzimidazole **20(b)** synthesized and reported by Bariwal *et al*[8]. Compounds evaluated for the antiulcer activity. Compound **20a** and **20b** at 10 and 30 mg/kg doses reduced the ulcer formation significantly comparable to standard (Omeprazole) and **20b** (sulfinyl derivative) compound was more effective than **20a** (thio derivative)[41].

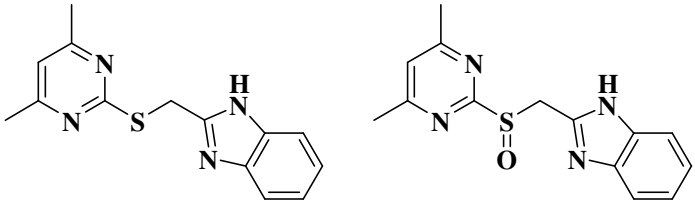
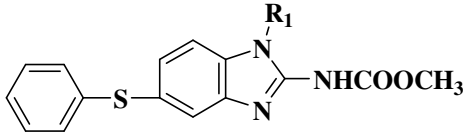


Figure-11
Novel pyrimidyl-thio-methyl-benzimidazole 20(a) and pyrimidyl-sulfinylmethylbenzimidazole 20(b)

Antileishmanial Activity

Solominova *et al* synthesized 2-benzimidazole carbamic acid methyl ester derivatives **(21)**. Compounds 20a and 20b shown anthelmintic activity against *Nippostrongilus*, *Ankilostoma* and *Haemonhus* larvae that exceeded 65% upon per oral administration in animals (rats, sheep, dogs) at a dose of 2.5-50mg/kg. In another group of animal inhibition action is below 40% upon per oral administration in a dose of 50-100mg/kg[42].



R_1 = $COOCH_2CH_2OCH_3$, $CONHCH_2CH_2COOCH_3$

Figure-12
2-benzimidazole carbamic acid methyl ester derivatives (21)

Mavrova et al. synthesized 5(6)-(un)substituted-1H-benzimidazol-2-yl thioacetyl piperazine derivatives and assessed for anthelmintic activity against *T. spirilis*. Compound 2-(2-{2-[4-(4-chlorophenyl)piperazin-1-yl]-2-oxoethyl}thio)-5(6)-methyl-1H-benzimidazole **(22)** was the most active[43].

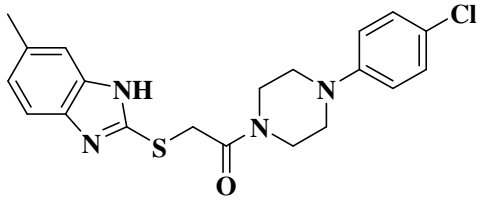


Figure-13
2-(2-{2-[4-(4-chlorophenyl)piperazin-1-yl]-2-oxoethyl}thio)-5(6)-methyl-1H-benzimidazole (22)

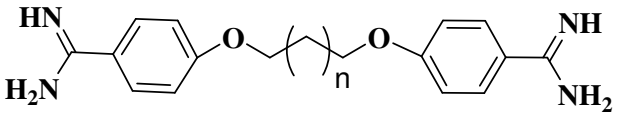
Vallezo et al. successfully studied COMFA on 1H-benzimidazole derivatives and determine the tautomeric form which fits a target receptor in *E. histolytica*. The results showed

that the anti-amoebic activity is favored with electron deficient group at 2nd position and steric size at position 5 of benzimidazole ring[44].

Pentamidine, an aromatic diamidine is a well known drug used to treat leishmaniasis[45]. Despite its efficiency, it is non-functional by problems including poor bioavailability and other unpleasant side effects[46]. So as to overcome these limitations many structural modifications have been done and which deal with linking both benzamidine groups. The resultant compounds like Furamidine **(23)**[47] and 4-4'-piperazine-1,4-diyl)bisbenzamidine **(24)**[48] were recently come out as encouraging drug molecules for the treatment of *Trypanosomiasis* and *P. carinii pneumonia*, respectively.

Mayence *et. al.* masked the amidine groups by encapsulating into unsaturated cyclic system specially benzimidazole system[49]. The resultant compounds were much more active against *Leishmania donovanii* .Torres *et al*. had also made some hybrid compounds by using benzimidazole and pentamidine with central pentyldioxyphenyl piece at the end and the terminal amidine groups were substituted by 5-substituted benzimidazole frame[50]. The results obtained were much in agreement because many of the compounds exhibited activity in comparable withstandard drugs meteronidazole and pentamidine. Only compound with -CF_3 at 5th position ring exhibited moderate anti-malarial activity with IC_{50} of 6.53µM.

Marrova et al. synthesized some new piperazine derivatives of (1*H*-benzimidazol-2-ylthio)acetic acid **(25-28)** and investigated them for antihelmintic efficacy in order to compare them with albendazole and ivermectin. The same group of scientist have also synthesized 2-substituted-[1,3]thiazolo[3,2-a]benzimidazol-3(2*H*)-ones. SAR of these compounds was also comparable to the known drugs, albendazole and ivermectin. These results proved the hypothesis of introduction of a condensed ring in the benzimidazole system, favored to the interaction of these compounds with the biological targets[51].



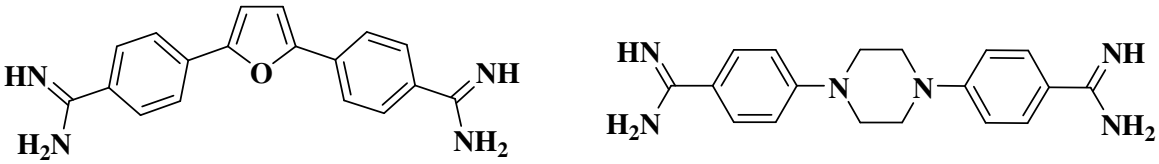
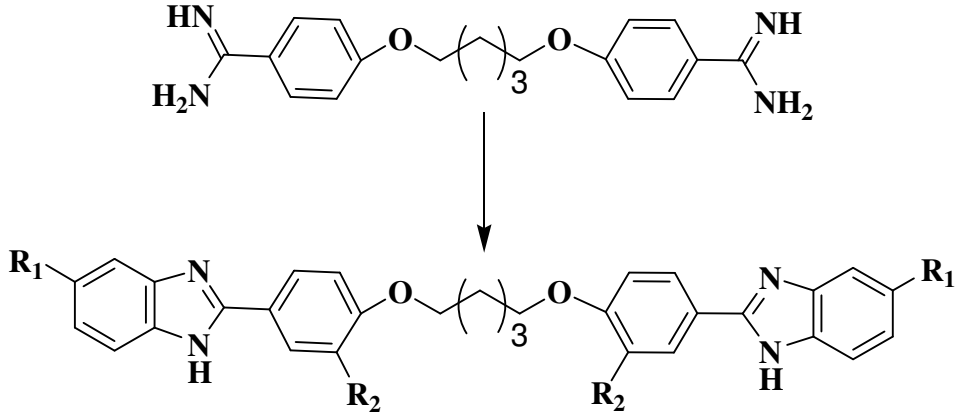


Figure-14
Furamidine (23) & 4-4'-piperazine-1,4-diyl)bisbenzamidine (24)



R_1 = H, OCH_3, CH_3, NO_2, CF_3
R_2 = H, OCH_3

Figure-15
5-Substituted Benzimidazole Derivatives

Anticancer Activity

Cancer characterized by rapid or slow uncontrolled growth of cells.On the basis of the type, a number of anticancer drugs are now a days in medicinal practice. Carbomethoxy-substituted benzimidazole derivatives of UK-1 [a bis (benzoxazole) natural product] were obtained from *Streptomyces strains* by Kumar et al. and assessed its cytotoxicity gainst four cell lines such as PC-3, HT-29, MCF-7 and HL-60. Only one compound methyl-2-[2-(2-hydroxyphenyl)-1,3-benzooxazol-4-yl]-1H-benzimidazole-4-carboxylate **(29)** possesses activity towards the tested cell lines aginst a concentration ranging from 7.0 to 100µM[52].

Vedula and co-workers screened new styryl sulfones for anticancer activity against different cell lines. Out of the various molecules prepared only one compound 6-chloro-1H-(benzo[d]imidazol-2-yl) methyl[(E)-2-(4-chloro-3-methylphenyl)-1-ethenyl] sulphone **(30)** showed 51% inhibition of tumour growth in mice with HT-29 at 400mg/kg orally[53].

Ramla et al. derivatised 2-(1-benzyl-2-methyl-1H-benzimidazol-5-ylimino)-3-(substituted)-thiazolidines-4-ones and 3-(2-methyl-1H-benzimidazol-5-yl)-2-substituted-thiazolidines-4-ones. They significantly assessed them for antitumor activity against the EBV-EA activation by introducing 12-O-tetradecanoyl phorbol-13-acetate. 3-benzoyl-2-(1-benzyl-2-methyl-1H-benzimidazol-5-yl-imino)thiazolidin-4-one **(31).**[54].

Hranjec et al prepared a novel series of substituted benzimidazole Schiff bases. The prepared hydrazones were screened for antiproliferative activity *in-vitro* and showed antiproliferative activity on the tested cell lines at higher concentrations[55].

Benzimidazole-4,7-diones substituted at position-2 were designed by Gellis et al. Their anti-cancer activity was studied on lung cancer, colon cancer and breast cancer cell lines. Out of thess, 2,20-bis(chloromethyl)-1,10-dimethyl-5,50-bi(1H-benzimidazole)-4,40,7,70-tetraone **(32)** possessessignificant cytotoxicity against mitomycin C[56].

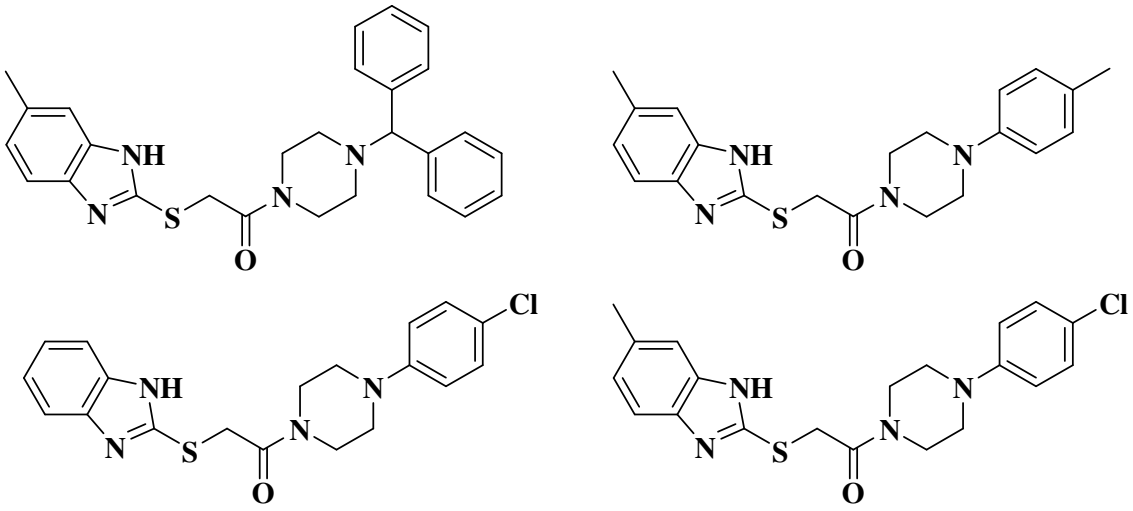


Figure-16
Piperazine Derivatives Of (1H-Benzimidazol-2-Ylthio) Acetic Acid (25-28)

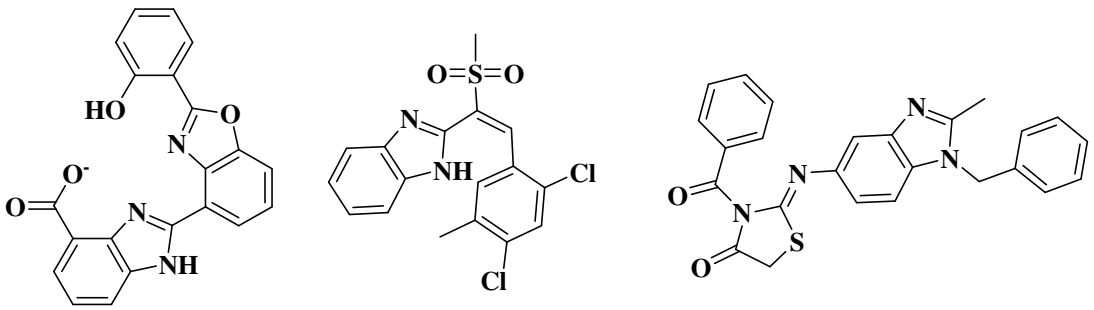


Figure-17
29 = methyl 2-[2-(2-hydroxyphenyl)-1,3-benzooxazol-4-yl]-1H-benzimidazole-4-carboxylate, 30= 6-chloro-1H-(benzo[d]imidazol-2-yl) methyl[(E)-2-(4-chloro-3-methylphenyl)-1-ethenyl] sulphone, 31= 3-benzoyl-2-(1-benzyl-2-methyl-1H-benzimidazol-5-yl-imino)thiazolidin-4-one

Various heterocyclic benzimidazole derivatives **(33-36)** were preparedfrom succinic acid, homophthalic acid and 2,3-pyrazinedicarboxlic acid and various substituted diamines by Sondhi et al. All these compounds screened for their antitumor assay at 50mg/kg showed good anticancer activity against IGROV-1, MCF-7 and SF-295 human cancer cell lines[57].

1-methylene-2, 3-diaryl-1, 2-dihydropyrazino [1,2-a] benzimidazoles **(37)** and some 1-(2-arylvinyl)-3-arylpyrazino[1,2-a]benzimidazole derivatives **(38)** have been synthesized and their anticancer activity was reported by Demirayak et al. $\log_{10}$GI50 values are less than –4 gainst standard drug[58].

The synthesis of series some of benzimidazole like: 2-[(4-oxothiazolidin-2-ylidene)-methyl **(39)** and (4-amino-2-thioxothiazol-5-yl) benzimidazoles **(40)**, 2-[(4-fluorobenzylidene **(41)** and cycloalkylidene)-cyanomethyl] benzimidazoles was carried out by Refaat et al. All the prepared compound were assessed against three cell line , HEPG2 and MCF7[59].

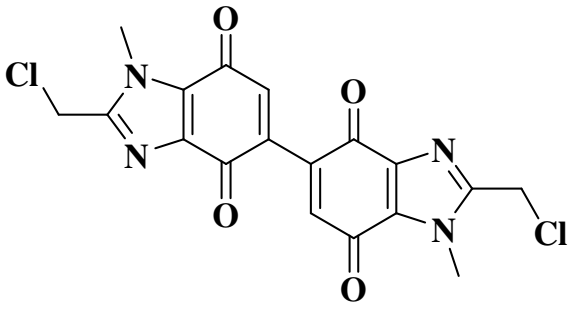


Figure-18
2,20-bis(chloromethyl)-1,10-dimethyl-5,50-bi(1H-benzimidazole)-4,40,7,70-tetraone (32)

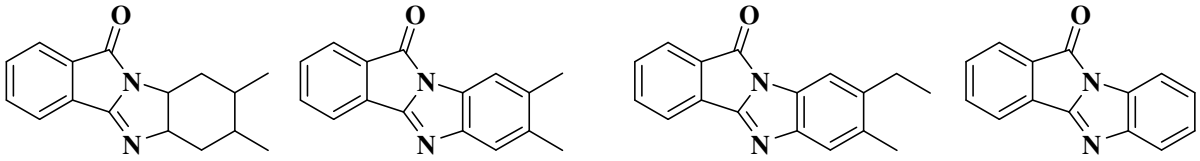
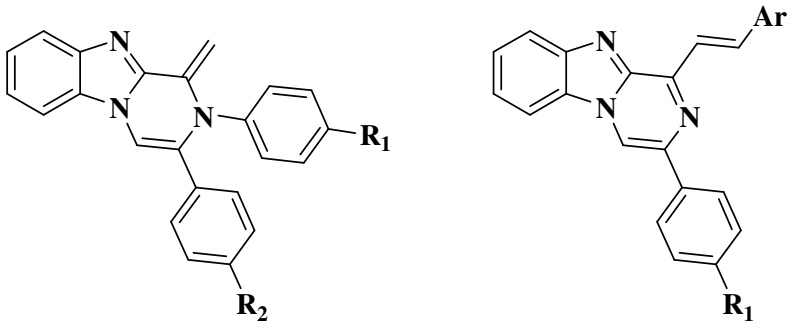


Figure-19
Various heterocyclic benzimidazole derivatives (33-36)



R_1= H, CH_3, OCH_3, CI
R_2 = H, CH_3, OCH_3, CI, NO_2
Ar =

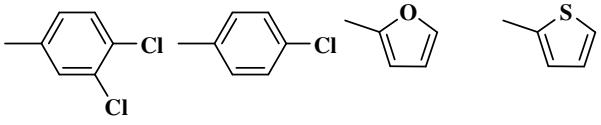


Figure-20
37 = 1-methylene-2,3-diaryl-1,2-dihydropyrazino[1,2-a]benzimidazoles, 38 = 1-(2-arylvinyl)-3-arylpyrazino[1,2-a]benzimidazole derivatives

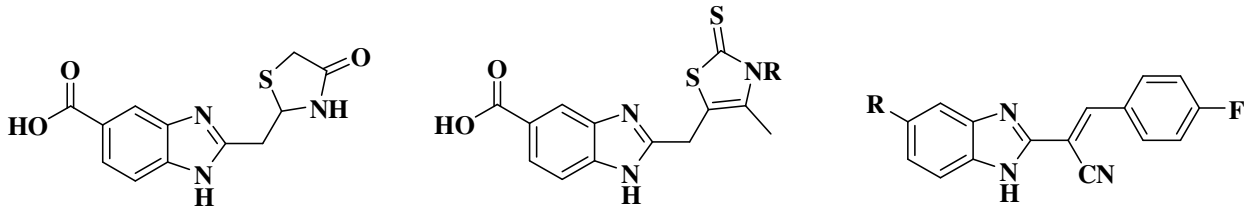


Figure-21
Benzimidazole Deriviatives (39-41)

Anti-Diabetic Activity

A synthesis of a series of novel and substituted benzimidazole derivatives **(42)** was reported by Kumar *et al*. Compounds shown anti-diabetic activity against DPP-IV and PTP-IB. Compound **42a** and **42b** shown inhibitory activity against PTP-IB (1.64%, 2.42%) at 30µM doses and 14c shown inhibitory activity against DPP-IV (3%) at 0.3µM doses[60].

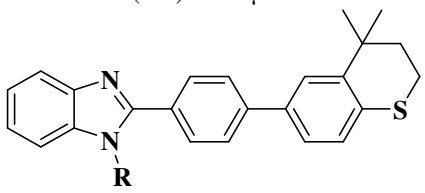


Figure-22
Benzimidazole derivatives (42a & 42b)

Conclusion

The present studies reflect that benzimidazole is a nucleous that can be used potentially in drug discovery area and medicines as it has versatile biological activities. Moreover existing literature reveal that benzimidazole derivatives can act as alternate medicine to overcome problem like resistance associated with currently available drugs. Therefore this substrate has a great scope for the discovery of new, better, safer and more potent chemotherapeutic agents.

References

1. Spasov A.A. and Yozhitsa I.N., Benzimidazole derivatives: spectrum of pharmacological activity and toxicological properties, *J. Pharm. Chem*., **33**, 232-243 **(1999)**

2. Mavrova A.T.S., Anichina K.K. and Vuchev D.I., Synthesis and antitrichinellosis activity of some 2-substituted-[1,3]thiazolo[3,2-a]benzimidazol-3(2H)-ones, *Bioorg. Med. Chem*., **13(9),** 5550-5559 **(2005)**

3. Goker H., Kus C. and Boykin D.W., Synthesis of some new 2-substituted-phenyl-1H-benzimidazole-5-carbonitriles and their potent activity against Candida species, *Bioorg. Med. Chem***., 10**, 2589-96 **(2002)**

4. Goker H., Kus C., Boykin D.W., Synthesis and Potent Antibacterial Activity against MRSA of Some Novel 1,2-Disubstituted-1*H*-Benzimidazole-*N*-alkylated-5-carboxamidines, *Eur. J. Med. Chem*., **40**, 1062 **(2005)**

5. Andrzejewska M. and Yepez M.L. Synthesis, antiprotozoal and anticancer activity of substituted 2-trifluoromethyl- and 2-pentafluoroethylbenzimidazoles*, Eur. J. Med. Chem*., **37**, 973 **(2002)**

6. Ozden S., Atabey D. and Goker H., Synthesis and potent antimicrobial activity of some novel methyl or ethyl 1H-benzimidazole-5-carboxylates derivatives carrying amide or amidine groups, *Bioorg. Med. Chem*., **13**, 1587-97 **(2005)**

7. Ramla M.M. and Omar M.A., Discovery and optimization of pyrrolo[1,2-*a*] pyrazinones leads to novel and selective inhibitors of PIM kinases, *Bioorg. Med. Chem*., **14**, 7372 **(2006)**

8. Boiani M. and Gonzalez M., Imidazole and benzimidazole derivatives as chemotherapeutic agents, *Mini Rev. Med. Chem*., **5**, 409-424 **(2005)**

9. János Béahdy, Recent Developments of Antibiotic Research and Classification of Antibiotics According to Chemical Structure, *Advances in Applied Microbiology*, **18**, 309–406**(1974)**

10. Devender Pathak, Nadeem Siddiqui, Bhanupriya Bhrigu, Waquar Ahsan, M. Shamsher Alam, Benzimidazoles: A New Profile of Biological Activities, *Der Pharmacia Lettre*, **2(2)**, 27-34**(2010)**

11. Y. He, B. Wu, J. Yang, D. Robinson, L. Risen, L.B. Ranken, S. Sheng & E. Swayze., *Bioorg. Med.Chem. Lett.,* **13(19)**, 3253-6 **(2003)**

12. Kumar, B. V. S., Vaidya, S. D., Kumar, R.V., Bhirud, S.B., Mane, R.B.. Synthesis and anti-bacterial activity of some novel 2-(6-fluorochroman-2-yl)-1-alkyl/acyl/aroyl-1H-benzimidazoles, *Eur. J. Med. Chem.,* **41**, 599**–**604 **(2006)** DOI PMid:16527375

13. JT Leonard; L Jeyaseeli; M Kumar; R Sivakumar. Synthesis, anti-inflammatory and antibacterial activities of 4-substituted phenyl benzimidazoles, *Asian J. Chem*, ***18***, 1104-1106 **(2006)**

14. Deshmukh M.B., Suryavanshi A.W., Deshmukh S.A., Jagtap S.A., Microwave assisted synthesis of 2,3,4-

trisubstituted 1,2- dihydropyrimido-[1,2-*a*]benzimidazole, *Ind. J. Chem*., **86B**, 302-305 **(2009)**

15. KF Ansari; C Lal. 'Synthesis and evaluation of some new benzimidazole derivatives as potential antimicrobial agents', *Eur. J. Med. Chem*., **44**, 2294-2299 **(2009)**

16. Kazimierczuk Z., Upcroft, J.A., Upcroft, P., Gorska, A., Starosciak, B., Laudy, A., Synthesis, antiprotozoal and antibacterial activity of nitro- and halogeno-substituted benzimidazole derivatives, *Acta Biochim. Pol.*, **49(1)**, 185-95, **(2002)**

17. Ansari K.F. and Lal C., Synthesis and evaluation of some new benzimidazole derivatives as potential antimicrobial agents, *Eur. J.Med. Chem*., **44**, 2294-99 **(2009)**

18. Ansari K.F. and Lal C., ynthesis, physicochemical properties and antimicrobial activity of some new benzimidazole derivatives, *Eur. J. Med. Chem*., **44(11)**, 4028-33 **(2009)**

19. Gupta S.P. and Rani S., Synthesis and fungitoxicity of some 5-substituted- 3-polynitrophenyl rhodanines, *J. Ind. Chem. Soc.*, **LIV**, 478 **(1997)**

20. Ghoneim K.M., Essawi M.Y.H., Mohamed M.S., Kamal A.M., Synthesis of 2-[(4-amino or 2,4-diaminophenyl)sulfonyl] derivatives of benzimidazole, benzothiazole and 6-methyluracil as potential antimicrobial agents, *Ind. J. Chem*., **37B**, 904 **(1998)**

21. Mane D.V., Shinde D.B., Thore S.N. and Shingare M.S., Synthesis and biological activity of some new 2-alkyl-1-(l-dihydroxypyridyl-methyl)benzimidazoles, *Ind. J. Chem*., **34B**, 917 **(1995)**

22. Mavrova A.T., Anichina K.K., Vuchev D.I., Tsenov J.A., Denkova P.S., Magdalena S.K., Micheva M.K., Antihelminthic activity of some newly synthesized 5(6)-(un)substituted-1H-benzimidazol-2-ylthioacetylpiperazine derivatives, *Eur. J. Med. Chem*., **41**, 1412-20 **(2006)**

23. Yadav S., Kumar P., Clercq E.D., Balzarini J., Pannecouque C., Dewan S.K., Narasimhan B., 4-[1-(Substituted aryl/alkyl carbonyl)-benzoimidazol-2-yl]-benzenesulfonic acids: Synthesis, anti-microbial activity, QSAR studies, and anti-viral evaluation, *Eur. J. Med. Chem*., **45**, 5985-5997 **(2010)** DOI PMid:20971531

24. Vitale G., Carta A., Loriga M., Paglietti G., Colla P., Busonera B., Collu D., Loddo R., 2-Arylbenzimidazoles as Anti-viral and Anti-proliferative Agents-Part 1, *Med. Chem*., **4**, 605-615 **(2008)** DOI PMid:18991746

25. Budow S., Kozlowska M., Gorska A., Kazimierczuk Z., Eickmeier H., Colla, P.L.,Gosselin, G., Seela, F. Substituted benzimidazoles: anti-viral activity and synthesis of nucleosides. ARKIVOC **iii**: 225- 250**(2009)**

26. R. V. Devivar, E. kawashima, Benzimidazole ribonucleosides: design,synthesis, and antiviral activity of certain 2-(alkylthio)-and 2-(benzylthio)-5,6-dichlro-1-(d-ribofuranosyl)benzimidazoles, *J. Med. Chem*., ***37***, 2942-2949**(1994)**

27. Pandey, V.K., Shukla, A., Synthesis and biological activity of isoquinolinyl benzimidazoles, *Ind. J. Chem.*, **38B**, 1381**(1999)**

28. Yadav, L. D. S., Pal, D.R., Synthesis and antiviral activity of new 1,3,4-dithi(thiadi)azino(4,5-a) benzimidazole derivatives involving oxidative N-S and N-N bond formations, *Ind. J. Chem*. **35B**, 111**(1996)**

29. Kristina S., Marijeta M., Katja E., Ivan S., Magdalena G., Kresimir P., Grace, K. Z., Synthesis, antiviral and antitumor activity of 2-substituted-5-amidino-benzimidazoles, *Bioorg. Med. Chem*. **15**, 4419-4422**(2007)**

30. Bishnoi A., Pandey V. K., Saxena R., Synthesis and characterization of benzimida-zolylphenothiazine derivatives and a studyof their antiviral and antifungal activities, *Ind. J. Chem.,* **41B**, 1978**(1978)**

31. JT Leonard, L Jeyaseeli, M Kumar, R Sivakumar, Synthesis, anti-inflammatory and antibacterial activities of 4-substituted phenyl benzimidazoles, *Asian J. Chem*., **18**, 1104-1106 **(2006)**

32. Khan S. A., Nandan S. A., 2-Substituted benzimidazoles as anti-inflammatory and analgesic agents, *Indian J. Heterocycl. Chem.,* **7(1)**, 55-58 **(1997)**

33. Evans D., Hicks T. A., Williamson W. R. N., Meacock S. C. R., Kitchen E. A., Synthesis of a group of 1H–benzimidazoles and their screening for antiinflammatory activity, *Eur. J. Med. Chem.*, **31**, 635 **(1996)**

34. ZA Alagoz; C Kus T Coban., Synthesis and antioxidant properties of novel benzimidazoles containing substituted indoles, *J. Enz. Inhib. Med. Chem*., **20(3)**, 325-331 **(2004)**

35. R.A. Michael, K.E.Dennis, A. K. Bhattacharjee., Efficacy of Proton Pump Inhibitor Drugs against *Plasmodium falciparum* In Vitro and Their Probable Pharmacophores, *Antimicrob. Agent Chemother.*, **46(8)**, 2627-32 **(2002)**

36. G. Sachs, E. Carison & P. Lindberg., Gastric H,K-ATPASE as Therapeutic Target, *Annual Review of Pharmacology and Toxicology*, **28***,* 269-284 **(1988)**

37. B. Wallmark & O. Lorentzon, *J. Gastroenterol*, The mechanism of action of omeprazole--a survey of its inhibitory actions in vitro, *Scand J Gastroenterol Suppl.*, **20(108)**, 37-51**(1985)**

38. H. Larsson & E. Carlson, Inhibition of gastric acid secretion by omeprazole in the dog and rat, *J. Gastroenterol*., **85(4)**, 900-907 **(1983)**

39. V. Figala, K. Klemm & B. Kohl., Acid activation of (H+–K+)-ATPase inhibiting 2-(2-pyridylmethyl-sulphinyl)benzimidazoles: isolation and characterization of the thiophilic 'active principle' and its reactions, *J. Chem. Soc., Chem. Commun*., **2**, 125-127 **(1986)**

40. Lindberg P, Nordberg P, Alminger T, Brändström A, Wallmark B., The mechanism of action of the gastric acid secretion inhibitor omeprazole, **29(80)**, 13271329 **(1986)**

41. JB Bariwal; AK Shah; MK Kathiravan; RS Somani; JR Jagtap; KS Jai 'Synthesis and antiulcer activity of novel pyrimidylthiomethyl and Pyrimidylsulfinylmethyl benzimidazoles as potential reversible proton pump inhibitors', *Ind. J. Pharm. Ed. Res*., **42**, 225-231 **(2008)**

42. JS Shukla; S Saxena; R Rastogi, Synthesis of some newer, 1-heterocyclic amino/iminomethyl-2-substituted benzimidazoles as a potent CNS, anticonvulsant and monoamine oxidase inhibitory agents, *Curr. Sci*., **51(17)**, 820-822 **(1982)**

43. Mavrova AT, Anichina KK, Vuchev DI, Issenov JA, Denkova PS, Kondeva MS, Micheva MK ,Antihelminthic activity of some newly synthesized 5(6)-(un)substituted-1H-benzimidazol- 2-ylthioacetylpiperazine derivatives, *Eur J Med Chem*, **41**,1412–1420 **(2006)**

44. Lopez-Vallezo F, Medina-Franco JS, Hernandez-Campos A, Rodriguez- Morales S, Yepez L, Cedillo R, Castillo R Molecular modeling of some 1H-benzimidazole derivatives with biological activity against Entamoeba histolytica: a comparative molecular field analysis study, *Bioorg Med Chem*, **15**,1117–1126**(2007)**

45. Croft S. L., Yardley V., Chemotherapy of leishmaniasis, *Curr. Pharm. Des*., **8(4)**, 319-342 **(2002)**

46. R.R. Tidwell, S.K. Jones, N.A. Naiman, L.C. Berger, W.B. Brake, C.C. Dykstra, J.E. Hall, Activity of cationically substituted bis-benzimidazoles against experimental Pneumocystis *carinii pneumonia*, *Antimicrobial Agents and Chemotherapy*, **37(8)**, 1713-1716 **(1993)**

47. D. W. Boykin, A. Kumar, J. Spychala, M. Zhou, R. Lombardy, W. D. Wilson, C. C. Dykstra, S. K. Jones, J. E. Hall, R. Tidwell, C. Laughton, C. M. Nunn & S. Neidle, Dicationic diarylfurans as anti-Pneumocystis carinii agents, *J. Med. Chem*., **38(6)**, 912-916 **(1995)**

48. Cushion M. T.; Walzer P. D.; Ashbaugh A.; Rebholz S.; Brubaker R.; Vanden E. J. J.;Mayence A.; Huang T. L., In vitro selection and in vivo efficacy of piperazine- and alkanediamide-linked bisbenzamidines against Pneumocystis pneumonia in mice, *Antimicrob Agents Chemother*, **50(7)**, 2337-43 **(2006)**

49. A. Mayence, E.J. Vanden, L. LeCour, L.A. Walker, B.L. Tekwani & T.L. Huang, Piperazine-linked bisbenzamidines: a novel class of antileishmanial agents, *Eur. J. Med. Chem.*, **39(6)**, 547-553 **(2004)**

50. T.G. Hector, E.H. Nunez, I.L. Rivera & J.G Alvarez., Design, synthesis and in vitro antiprotozoal activity of benzimidazole-pentamidine hybrids, *Bioorg. Med. Chem. Lett*., **18(110)**, 3147-51 **(2008)**

51. A.T. Mavrova, K. K. Anichina, D. I. Vuchev, J.A. Tsenov, P.S. Denkova, S. Kondeva Magdalena & M.K. Micheva, Antihelminthic activity of some newly synthesized 5(6)-(un)substituted-1H-benzimidazol-2-ylthioacetylpiperazine derivatives, *Eur. J. Med. Chem.*, **41(12)**, 1412-20 **(2006)**

52. Kumar D, Jacob MR, Reynolds MB, Kerwin SM Synthesis and evaluation of anticancer benzoxazoles and benzimidazoles related to UK-1, *Bioorg Med Chem*, **10(12)**, 3997–4004 **(2002)**

53. Vedula MS, Pulipaka AB, Venna C, Chintakunta VC, Jinnapally S, Kattuboina VA, Vallakati RK, Basetti V, Akella V, Rajgopal S, Reka AK, Teepireddy SK, Mamnoor PK, Rajagopalan R, Bulusu G, Khandelwal A, Upreti VV, Mamidi SR New styryl sulfones as anticancer agents, *Eur J Med Chem*, **38(9)**, 811–824 **(2003)**

54. Ramla MM, Omar MA, Tokuda H, El-Diwani HI Synthesis and inhibitory activity of new benzimidazole derivatives against Burkitt's lymphoma promotion, *Bioorg Med Chem,* **15(19)**, 6489–6496 **(2007)**

55. Hranjec, M., Starcevic, K., Pavelic, S.K., Lucin, P., Pavelic, K., Zamola, G.K., Synthesis, spectroscopic characterization and antiproliferative evaluation in vitro of novel Schiff bases related to benzimidazoles, *Eur. J. Med. Chem*., **46(6)**, 22742-279 **(2011)**

56. Gellis A., Kovacic H., Boufatah N., Vanelle P., Synthesis and cytotoxicity evaluation of some benzimidazole-4,7-diones as bioreductive anticancer agents, *Eur. J. Med. Chem*., **43(9)**, 1858-1864**(2008)**

57. Sondhi SM, Rajavanshi S, Johar M, Bharti N, Azam A, Singh K Anti-inflammatory, analgesic and antiamoebic activity evaluation of pyrimido[1,6-a]benzimidazole derivatives synthesized by the reaction of ketoisothiocyanates with mono and diamines, *Eur J Med Chem*., **37(10)**, 835–843**(2002)**

58. Demirayak, S., Mohsen, U.A., Karaburun, A.C. Synthesis and anticancer and anti-HIV testing of some pyrazino[1,2-a]benzimidazole derivatives, *Eur. J. Med. Chem*., **37(3)**, 255-260**(2002)**

59. Refaat, H.M., Synthesis and anticancer activity of some novel 2-substituted benzimidazole derivatives, *Eur. J. Med. Chem*., **45(7)**, 2949-60 **(2010)**

60. BB Kumar, PV Rao, Synthesis and structural studies on transition metal complexes derived from 1-(2-thienyl)-1-ethanole-1*H*-benzimidazole, *Asian J. Chem*., ***18***, 3060-3064**(2006)**