Chemistry & Biology Interface, 2021, 11, 6, 197-216

REVIEW PAPER ISSN: 2249 –4820

CHEMISTRY & BIOLOGY INTERFACE

An official Journal of ISCB, Journal homepage; www.cbijournal.com

Biological significance of benzimidazole derivatives: A Review

Sonu Kumar[1]*, Ashish Bhatt[2], Ravi Kant[1]

[1]Faculty of Chemical Sciences, Institute of Natural Sciences and Humanities,ShriRamswaroop Memorial University,Lucknow-Deva Road, Barabanki, Lucknow -225003, U.P., INDIA
[2]Department of Chemistry, MewarUniversity, Chittorgarh, (Rajasthan),312901, India.
**Corresponding AuthorEmail-sonusmile_verma@yahoo.co.in*
Received; 24 August 2021, Accepted; 11 November 2021

Abstract: Benzimidazole is the heterocyclic compound which contains a phenyl ring fused to an imidazolering. The properties of benzimidazole and its derivatives have been studied over more than one hundred years. Benzimidazole derivatives are useful intermediates/subunits for the development of molecules of pharmaceutical or biological interest. Benzimidazoleanalogues are of crucial importance because of their different clinicalapplications and biological activity. Benzimidazoles are known as an optimistic class of bioactiveheterocyclic compounds possessing a wide variety of biological activities such asantimicrobial, antibacterial, antiviral, anticancer, antioxidant, anti-diabetic, anti-proliferative, antitumor, anti-HIV, anti-ulcerative, anti-leishmanial, antiprotozoal, analgesic, anti-inflammatory, antihypertensive, androgen receptor antagonist, anti-parasitic activity, anti-fungal activity and vasorelaxant etc.

This review will further helpful for the researcher on the basis of substitution pattern around the nucleuswith an aim to help medicinal chemists for developing an SAR on benzimidazoledrugs/compounds.

Keywords: Benzimidazole, Pharmacological activity,Chemistry,Biological activity, Review.

Introduction

The benzimidazole scaffold is very useful for the development of molecules of pharmaceutical or biological interest. Benzimidazole is a benzo derivative of imidazole in which benzene ring is fused with afive member ring system having hetero atom at 1 and 3positions. The properties of benzimidazole and its analogs havebeen studied since over hundred years. However a specialinterest of researchers towards benzimidazole derivatives wasoriginated by the fact that 5, 6-dimethyl-1-(α-Dribofuranosyl) benzimidazole is an basic part of the structure of vitaminB12[1].Moreover benzimidazole is a structural unit of naturallyoccurring nucleotide, due to which it easily interacts with thebiopolymers of living system. They exhibit significant activitylike antihelminthic[2], antifungal[3],anti-allergic, antimicrobial[4-6], antiviral[7] and antineoplastic[8]activities. Since proteases have been linked with

several diseasestates, including thrombosis, inflammation, bronchoconstriction and tumour growth and invasion[9]. The incorporation of thenucleus is an important synthetic strategy in studies ofantimicrobial drug discovery.In the past few decades, benzimidazole and its derivatives havegrasped much attention due to their chemotherapeutic values[10].

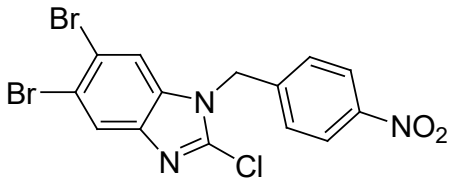
Furthermore, the pharmacological properties andtherapeutic applications of benzimidazole depend upon thepattern of substitution and recently they are reported to possessmany pharmacologicalactivities.Somepharmaceutical drugs which contain a benzimidazole group include etonitazene, pantoprazole, mavatrep, albendazole, rabeprazole, lansoprazole, omeprazole etc. The drugs like pimozide, droperidol and benperidolantiprotozoal agents which contains benzimidazole nucleus. The antiprotozoal drugs such as metronidazole, benznidazole containing imidazole nucleus.

This review highlights theimportance of Benzimidazolederivatives in medicinal world by representing numerous derivatives with their biological activities.

Biological Activities

Antimicrobial activity:

Synthesis of a new set of heterocyclic sulfonamide-bound molecules (1)were synthesized and tested for antibacterial activity by Naaz F et al[11] [Figure1]. During antibacterial screening with the broathdilution method, it has been found that molecules are found to be highly active against different human pathogens, namely *B. cerus, S. aureus, E. coli* and *P. aeruginosa*, and most effective against *E. coli*.antibacterial lead using the combination approach.

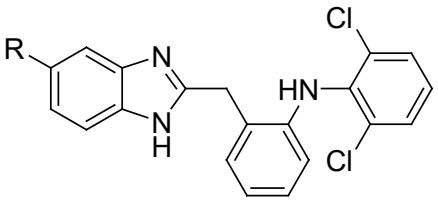


(1)

Figure 1: Sulphonamide derivative of benzimidazole

Analgesicactivity:

Sravanthi et al[12]reported syntheses of 2-substituted benzimidazoles (2a-c) . All the synthesized compounds[Figure 2] were tested for analgesic activity by tail flick method at 25 mg/kg doses orally and compared with indomethacin. The compounds (2a), (2b) and (2c) showed analgesic activity (86%, 85% and 74%).



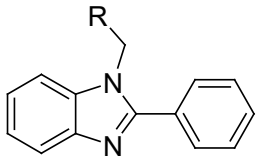
R = NO_2**(2a)**, Br **(2b)**, Cl**(2c)**

Figure 2.2-substituted benzimidazoles

Antibacterial activity:

Synthesis of a series of 1, 2-disubstituted-1Hbenzimidazole-Nalkylated-5-carboxamidine derivatives was reported by Goker et al[13]and evaluated antibacterial activities against *S. aureus*and methicillin resistant *S. aureus*. The study revealed thebest activity, with MIC values of 0.78 - 0.39µg/mL against these species[14]. Mohamed et al. synthesizedbenzimidazoles as 1-(substituted-methyl)-2(substituted-phenyl) benzimidazoles (3) and compounds (3a), (3b) and (3c)were screened for their antibacterial activity against *S. aureus, B. pumillus*and *P. aeurugenosa*[Figure 3]. Compound 3ashowed

MIC (6.25) at 100 μm/ML and exhibited good antibacterial activity. Various Chloro and dichlorosubstituted benzimidazole also possess antibacterial activities.

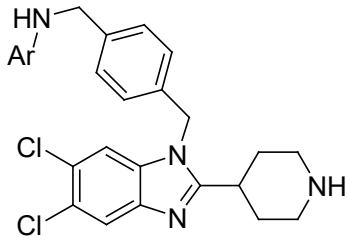


R= amine**(3a),**Dimethylamine**(3b),**Morphilono(3c)

(3)

Figure 3.

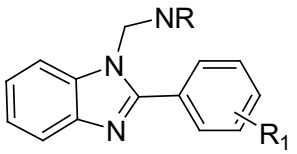
Synthesis of a series of benzimidazole withgeneral molecular structure (4)were reported by He et al[15]which exhibits potent broadspectrum antibacterial activity and started a research program to discover novel antibiotics against Gram positive bacteria bytargeting rRNA [Figure 4].



(4)

Figure 4. General structure for benzimidazole derivatives

Leonardo et al[16]reported synthesis of benzimidazole as 1-(substituted-methyl)-2-(substituted-phenyl) benzimidazole(5). Compounds 5a, 5b and 5cwere screened fortheir antibacterial activity against *S. aureus, B. pumillus*and *P.Aeurugenosa*[Figure 5].Compound 5a showed MIC (6.25) at 100μM/mLand exhibited good antibacterial activity.

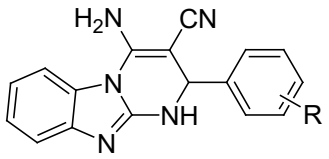


R = piperizine**(5a)**, dimethylamine**(5b)**, diethylamine**(5c)**, R_1 = Cl

(5)

Figure 5.

Deshmukhet al[17] reported synthesis of 2,3,4,-trisubstituted-1,2-dihydropyrimido[1,2-*a*]benzimidazole derivatives (6)[Figure 6]. The compounds were tested for their fungicidal activities against *Aspergillusniger*MTCC-2255 and *Penicilliumchrysogenum*-NCIM-723 using Greiseofulvin as control.

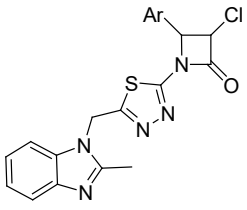


R = -OCH3, -OH

(6)

Figure 6.

The efficient synthesis of novel 3-chloro-1-5-(2-methyl-1*H*bezimidazol-2-yl)-4-(substituted) phenylazetidin-2-one (7)wasreported by Ansari et al[18]. Compounds were screened forantibacterial activity against *B. substilis*and *E. coli* andcompound 7a,and7b[Figure 7]shown MIC at 100μg/mL, 100μg/Ml and 200μg/mL doses.

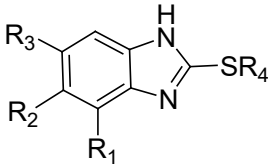


(7)

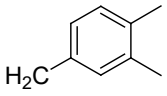
Ar = 2-PhCl **(7a)**, 2-PhOH **(7b)**

Figure 7.

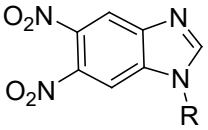
Kazimierczuk et al[19]reported two series of benzimidazole derivatives, the first one was based on 2-thioalkyland thioaryl substituted benzimidazole**(**8a**)**, the secondone was based on 5,6-dinitrobenzimidazole (8b)[Figure 8] and the antibacterial activity of the compound against *Stenotrophomonasmalthophilia* was examined.



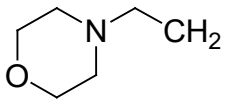
R1 = R2, R3 = CH2CH2N(CH3)2
R1, R3 = H, R2 = COOH

R4 = 

(8a)

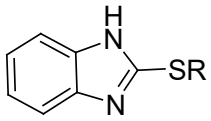


R = CH2CH2N(CH3)2
R = CH2CH2N(C2H5)2

R = 

(8b)
Figure 8.

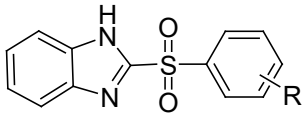
The compound 2-thiohalogenonitrophenylbenzimidazole(9) [Figure 9] was synthesized by Gupta and co-workers[20] and screened for their antifungal activity against *H. sativum, A. niger*and *F. oxysporum*. The percentage inhibition of the fungal spores was recorded at10ppm.



R = 2,4-DNP/ 2,6-DNT/ 2,4,6-TNP/2-chloro 4,6-DNP/2-methyl-4,6-DNP/ 2-chloro-4-bromo-3,5-DNP

(9)
Figure 9.

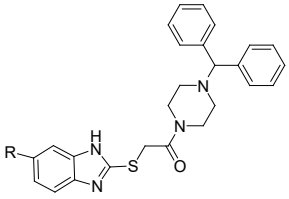
Ghoneim et al[21]reported the synthesis of 2-[(4-aminophenyl)sulphonyl]derivative (10)[Figure 10] of benzimidazole and these derivatives were tested for antimicrobial activity against *E. coli* using agar diffusion method. All 4-amino and 2,4-diaminophenylsulphonyl derivatives showed antimicrobial activity.



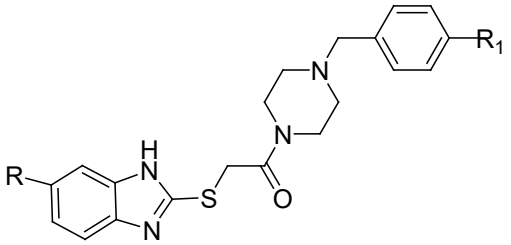
R = 4-NH_2/ 2,4-diNH_2

(10)
Figure 10.

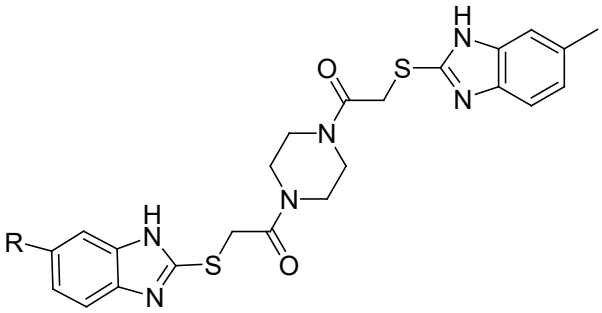
Mavrovaandco-workers[22]reportedthesynthesis of 1H-benzimidazole-2-yl thioacetylpiperazine derivatives (11a-c) [Figure 11]and screened them for *in-vitro* activity in contrast to *T. spiralis* and *in-vivo* antinematode activity against *S. obvelata.* Most of the synthesized compounds exhibit higher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



(11a) R=H,CH_3



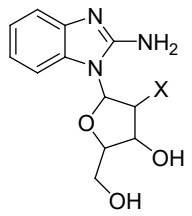
(11b) R=H,CH_3,NO_2,Cl
R_1=CH_3,Cl



(11c) R=H,CH_3
Figure 11.

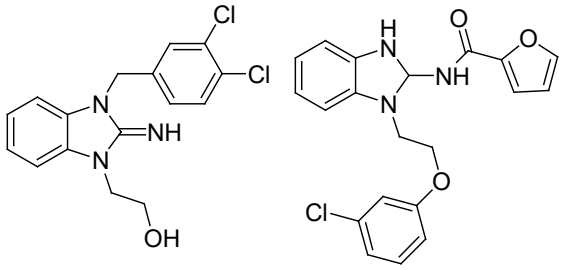
Antiviral activity:

Kharitonova MI et al[23], reported that β-D-ribo- and 2′-deoxyribofuranosides of 2-amino-5,6-difluorobenzimidazole nucleosides **(12)**[Figure 12] were synthesized using the enzymatictransglycosylation reaction. 2-Amino-5,6-difluoro-benzimidazole riboside exhibited selective antiviral activity against a wild strain of the herpes simplex virus, and against cidofovir, acyclovir and foscarnet resistant virus strains. It has been hypothesized that this compound can be used totreat herpes infections in such cases, when acyclovir is ineffective.



X= -H(2-deoxyriboside)
X= -OH(riboside)active against -HSV-1
(12)
Figure 12.2-amino-5,6-difluorobenzimidazole nucleosides

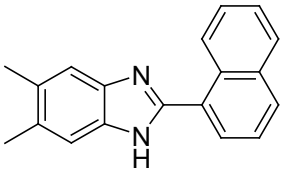
Zarubaev VV et al[24] reported the synthesis of a series of 1,3-disubstituted-2-iminobenzimidazolines (13a and 13 b)[Figure 13] and a number of their tautomeranalogues. Synthesized compounds were tested for toxicity toMDCK cells and for inhibiting activity against influenza virus A/California/07/09 (H1N1) pdm09. It has been found that some of synthesized benzimidazole derivatives have a potent virusinhibitingactivity against pandemic influenza virus with fairly modest cytotoxicity.



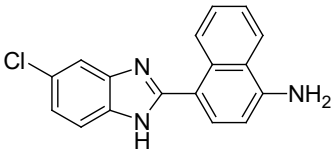
(13a) **(13b)**
Figure 13.1,3-disubstituted 2-iminobenzimidazolines

Vitale et al[25]reported a new series of 2-arylbenzimidazoles (14)[Figure 14]. They assessed them for antiviral activity and antiproliferative activity. Compounds were screened against *Flaviviridae* family, i.e. *Flaviviruses*and *Pestiviruses,Retroviridae, Picornaviridae, Paramyxoviridae, Rhabdo-viridaeand Reoviridae, Herpesviridae and*

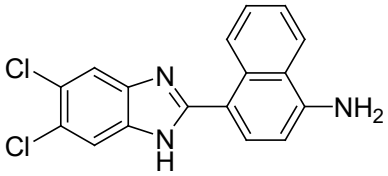
Poxviridae. Compounds14a, 14b and 14c showed moderate activity against Yellow Fever Virus.



(14a)



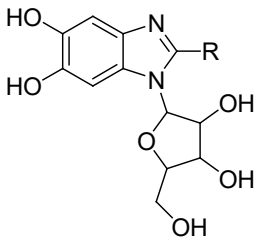
(14b)



(14c)

Figure14. 2-arylbenzimidazoles derivatives (14)

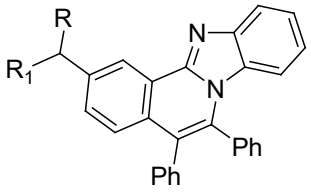
Synthesis of 2-(benzylthio)-5, 6-dichloro-1-(β-*D*-ribofuranosyl)benzimidazoles(15) [Figure 15]was reported by Devivaretal[26]. Compounds 15a, 15b and 15c performed anti-viral activitytowards HSV-1 and HCMV and compound 18c shown maximum activity at 90% inhibitory concentration (μM).



R = SCH_3 **(15a)**, SO_2CH_3 **(15b),** SO_2Ph **(15c)**

Figure 15.2-(benzylthio)-5, 6-dichloro-1-(β-Dribofuranosyl)benzimidazoles (15)

Some 7-(arylamidoalkyl)-3,4-diphenyl-isoquinolinyl-[1,5-c]-benzimidazoles (16) [Figure 16] have been synthesized by Pandey and Shukla etal[27] 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 hours it was found that the isoquinonylbenzimidazole derivative with nicotinamido group showed the maximum activity.

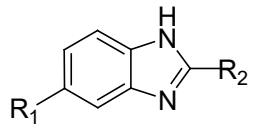


R1 = salicylamido, R = H

(16)

Figure 16.

Kristina et al[28], reported the synthesis of a set of 2-substituted-5-amidinobenzimidazole(17) [Figure 17]derivatives bearing amidinosubstistuent 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.



R_1 = Heterocyclic substituent

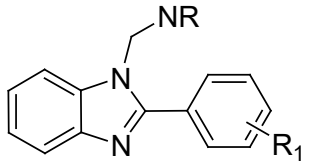
R_2 = Amidino substituent

(17)

Figure 17.

Anti-Inflammatory Activity:

Leonardo et al[29], reported synthesis and anti-inflammatory activity of phenylbenzimidazole(18a-d). Compounds 18a, 18b, 18c and 18d[Figure 18] 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 compound21c showed maximum (54.6%) inhibition of edema at doses of 50mg/kg.

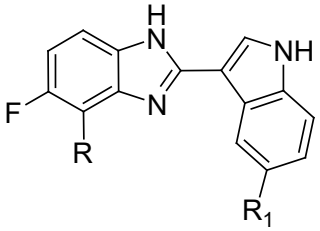


R = morphine (18a), diphenylamine (18b), dimethylamine (18c), imidazole (18d), R_1 = Cl

Figure18. Phenyl benzimidazole derivatives.

Antioxidant Activity:

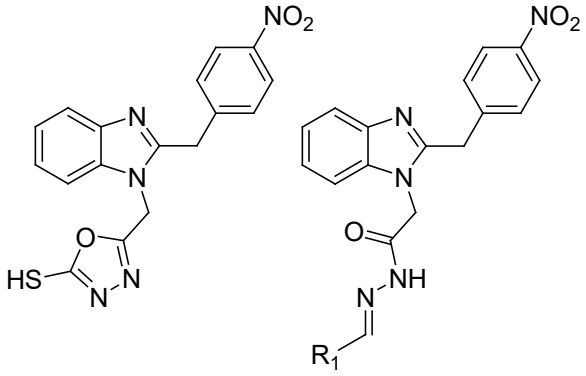
Alagoz et al[30] synthesized some 6-flouro-5-substituted benzimidazoles (19a-e)[Figure 19] and tested for antioxidant activity and compound (19e) showed strong anti-oxidant effect onsuperoxide anion at 0.001M concentration.



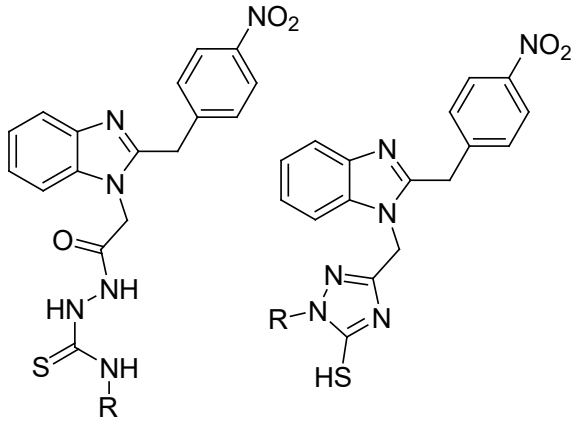
R = 4-$CH_3C_5H_{10}$ (19a), 4-$CH_3C_5H_{10}N$ (19b), 4-$C_6H_5C_4H_9N_2$ (19c), 4-$C_6H_5C_4H_9N_2$ (19d), 4-$C_6H_5C_4H_9N_2$ (19e), R1 = H, Br, OCH_3

Figure 19.6-flouro-5-substituted benzimidazole derivatives.

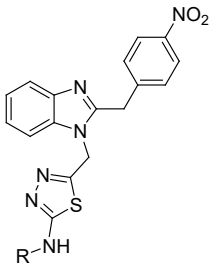
Karaali N et al[31], synthesized a number of new 2-(4-nitrobenzyl)-1*H*-benzimidazolederivatives with thiosemicarbazide, triazole, oxadiazole and thiadiazole units (20a-e)[Figure 20]present in the 1st position of benzimidazole ring and tested for its antioxidant activity. The inhibitor activities of the synthesized compounds were determined with CUPric Reducing Antioxidant Capacity (CUPRAC), ABTS (2,2-azinobis(3-ethylbenzothiazoline-6 sulfonicacid)/persulfate and DPPH (1,1-diphenyl-2-picrylhydrazyl) assays. Most of the compounds show significant antioxidant activity.



(20a) **(20b)**



(20c) **(20d)**



(20e)

R -CH_3 -C_2H_5 -C_6H_5.

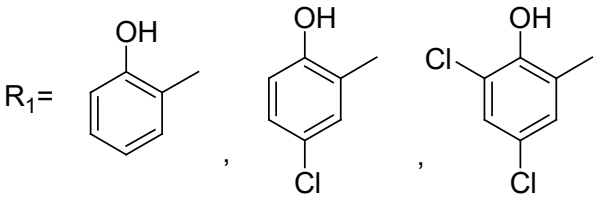
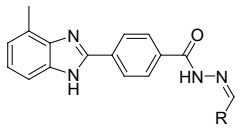


Figure 20: 2-(4-nitrobenzyl)-1*H*-benzimidazole derivatives bearing thiosemicarbazide,triazole, oxadiazole and thiadiazole moieties

Taha M et al[32], synthesized some novel 4-Methylbenzimidazole derivatives (21)[Figure 21] and evaluated for their antioxidant activity. All synthesized compounds were evaluated for DPPH activity. Some of the compounds showed excellent activities, ranging 12-29µM, better than the standard drug n-Propylgallate (IC50 ¼ 30.30 ± 0.40 µM). For superoxide anion scavenging activity, many of the compounds showed better activity than standard n-Propylgallate(IC50 ¼ 106.34 ± 1.6 µM) and ranged from 82-104 µM.



(21)

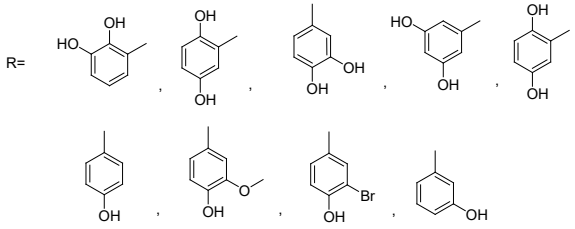
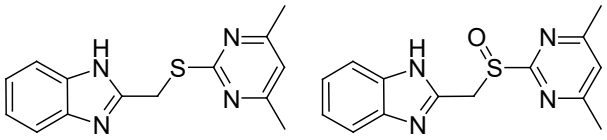


Figure 21: 4-Methylbenzimidazole derivatives

Anti-ulcerative Activity:

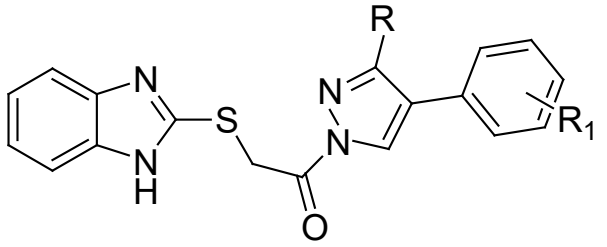
Bariwal et al[33]synthesized and reported a series of novel pyrimidyl-thio-methyl- benzimidazole(22a) ndpyrimidylsulfinylmethylbenzimidazole(22b) [Figure 22]. Compounds evaluated for theantiulcer activity. Compound 22a and 22b at 10 and 30 mg/kgdoses reduced the ulcer formation significantly comparable tostandard (Omeprazole) and 22b (sulfinyl derivative) compoundwas more effective than 22a (thio derivative).



(22a) **(22b)**

Figure 22. Pyrimidyl-thio-methyl-benzimidazole 22(a) and pyrimidyl-sulfinylmethylbenzimidazole 22 (b)

Nadeem H et al[34], synthesized and reported a series of six new benzimidazole-pyrazole hybrid molecule (23a-f)[Figure 23]. In vivo anti ulcerogenic activity wasevaluated for all compounds synthesized. All six compounds synthesized showed higher anti-ulcer activity as compared against standard omeprazole. The results clearly show that these new benzimidazole-pyrazole hybrids may constitute a new category of potential anti-ulcer compounds and may be considered as new anti-ulcer drugs upon further investigation.

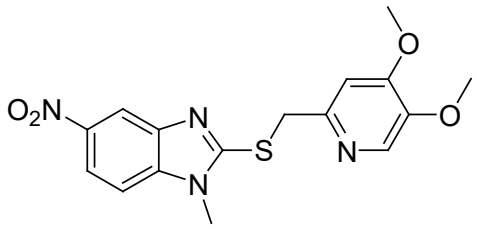


	23a	23b	23c
R	$-C_6H_5$	$-2\text{-}OHC_6H_5$	$-2\text{-}OHC_6H_5$
R_1	-2-OH	-2-OH	-3-OH, $-4\text{-}OCH_3$

	23d	23e	23f
R	-4-OHC$_6$H$_5$NH	-C$_6$H$_5$	-3-OH, -4-OCH$_3$
R$_1$	-2-OH	-H	-H

Figure 23.Benzimidazole–pyrazole hybrid molecule

Madala SR et al[35], reported that 1-methyl-2{[(3,4- di methoxy pyridine2-yl) methyl] sulfanyl}-5-nitro-1*H*-benzimidazole (24) was synthesized by coupling 1-methyl-2-mercapto-5-nitro-1Hbenzimidazole with pyridine derivative in presence of a base at room temperature. The synthesized compound [Figure 24] was tested for antiulcer activity by using the technique of cold and restraint ulcer. The results showed that the compound showed significant activity.

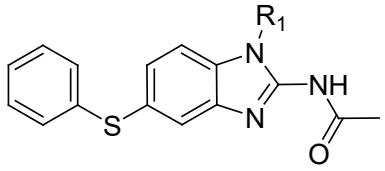


(24)

Figure 24: 1-methyl-2{[(3,4- di methoxy pyridine2-yl) methyl] sulfanyl}-5-nitro-1*H*benzimidazole

Anti-leishmanial Activity:

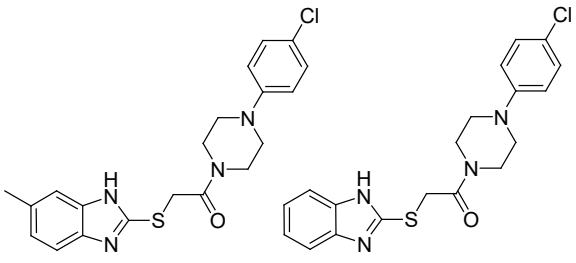
Solominova et al[36]reported the synthesis of 2-benzimidazole carbamic acid methyl ester derivatives . Compounds 25a and 25b[Figure 25] shown anthelmintic activity against Nippostrongilus, Ankilostoma and Haemonhus larvae that exceeded 65% upon per oral administration in animals (rats, sheep, dogs) at 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.



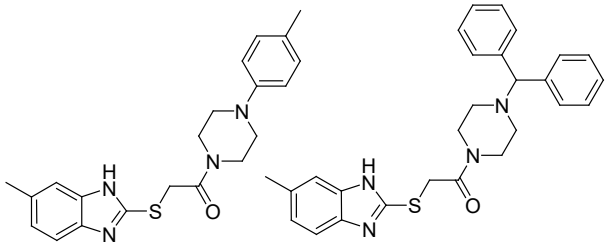
R_1= $COOCH_2CH_2OCH_3$ (25a), $CONHCH_2CH_2COOCH_3$ (25b)

Figure 25. 2-benzimidazole carbamic acid methyl ester derivatives

Mavrova et al[37] synthesized 5(6)-(un)substituted-1Hbenzimidazol-2-yl thioacetylpiperazine 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 (26a) was the most active. They also synthesized some new piperazine derivatives of (1H-benzimidazol-2-ylthio) acetic acid (26b-d) [Figure 26] 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(2H)-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.



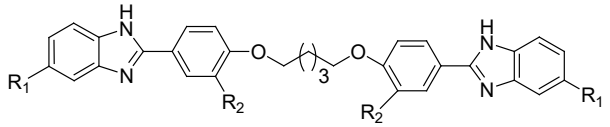
(26a) **(26b)**



(26c) (26d)

Figure 26.Piperazine Derivatives of (1H-Benzimidazol-2-ylthio)Acetic Acid (26 a-d)

Torres et al[38] had synthesized 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 (27). The results obtained were much in agreement because many of the compounds exhibited activity comparable withstandard drugs meteronidazole and pentamidine. Only compound with -CF_3 at 5th position ringexhibited moderate anti-malarial activity with IC_{50} of 6.53µM.



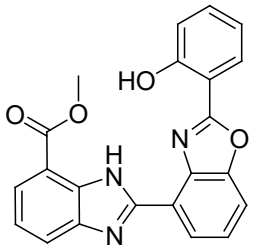
R1 = H, OCH_3, CH_3, NO_2, CF_3
R2 = H, OCH_3

(27)

Figure 27. 5-Substituted Benzimidazole Derivatives

Anticancer Activity:

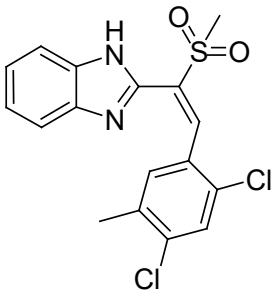
Cancer characterized by rapid or slow uncontrolled growth of cells. On the basis of the type, a number of anticancer drugs are now a days in medicinal practice. Carbomethoxy-substituted benzimidazolederivatives of UK-1 [a bis(benzoxazole) natural product] were obtained from Streptomyces strains by Kumar etal[39] and assessed its cytotoxicity against 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 (28)[Figure 28] possesses activity towards the tested cell lines against a concentration ranging from 7.0 to 100µM.



(28)

Figure 28.methyl 2-[2-(2-hydroxyphenyl)-1,3-benzooxazol-4-yl]-1H-benzimidazole-4-carboxylate

Vedula and co-workers[40] screened new styrylsulfones 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 (29)[Figure 29]showed 51% inhibition of tumour growth in mice with HT-29 at 400mg/kg orally.

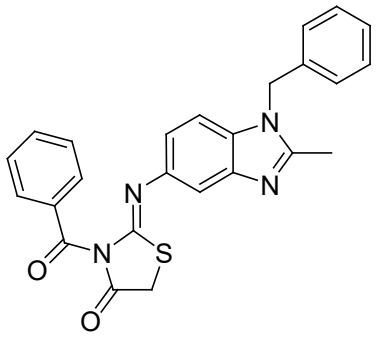


(29)

Figure 29. 6-chloro-1H-(benzo[d]imidazol-2-yl) methyl[(E)-2-(4-chloro-3-methylphenyl)-1-ethenyl] sulphone.

Ramla et al[41]synthesized derivatives of 2-(1-benzyl-2-methyl-1Hbenzimidazol-5-

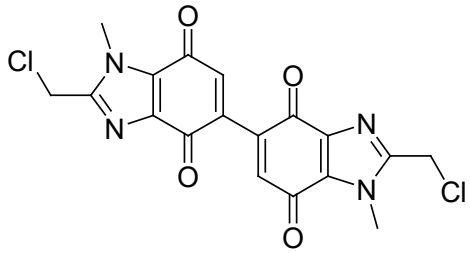
ylimino)-3-(substituted)-thiazolidines-4-ones and 3-(2-methyl-1H-benzimidazol-5-yl)-2 substitutedthiazolidines-4-ones. They significantly assessed them for antitumor activity against the EBV-EA activation by introducing 12-O-tetradecanoyl phorbol-13-acetate. 3-benzoyl-2-(1-benzyl-2-methyl-1H-benzimidazol-5-yl-imino)thiazolidin-4-one (30)[Figure 30].



(30)

Figure 30. 3-benzoyl-2-(1-benzyl-2-methyl-1H-benzimidazol-5-yl-imino) thiazolidin-4-one

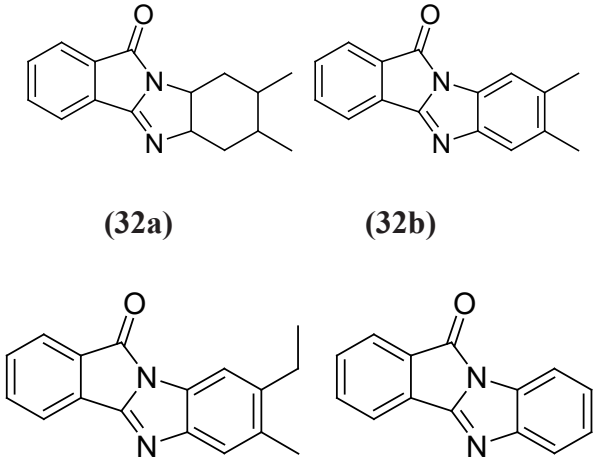
Benzimidazole-4,7-diones substituted at position-2 were designed by Gellis et al[42]. Their anti-cancer activity was studied on lung cancer, colon cancer and breast cancer cell lines. Out of these, 2,20-bis(chloromethyl)-1,10-dimethyl-5,50-bi(1Hbenzimidazole)-4,40,7,70-tetraone (31) [Figure 31]possesses significant cytotoxicity against mitomycinC.



(31)

Figure 31. 2,20-bis(chloromethyl)-1,10-dimethyl-5,50-bi(1H-benzimidazole)-4,40,7,70-tetraone

Various heterocyclic benzimidazole derivatives (32a-d) [Figure 32] were prepared from succinic acid, homophthalic acid and 2,3-pyrazinedicarboxlic acid and various substituted diamines by Sondhi et al[43]. 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.

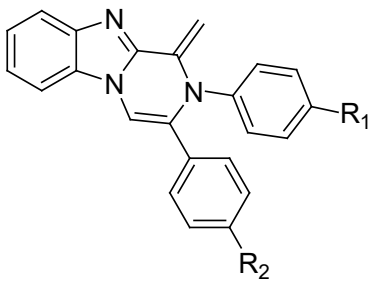


(32a) **(32b)**

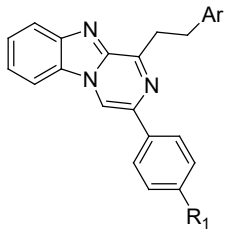
(32c) **(32d)**

Figure 32.Various heterocyclic benzimidazole derivatives.

1-methylene-2, 3-diaryl-1, 2-dihydropyrazino [1,2-a]benzimidazoles(33a)and some 1-(2-arylvinyl)-3-arylpyrazino[1,2-a] benzimidazole derivatives (33b)[Figure 33] have been synthesized and their anticancer activity was reported by Demirayak et al[44]. $\log_{10}$GI50 values are less than –4 against standard drug.



(33a)



(33b)

R_1= H, CH_3, OCH_3, CI

R2 = H, CH_3, OCH_3, CI, NO_2

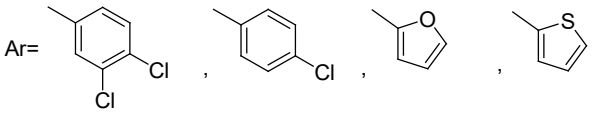
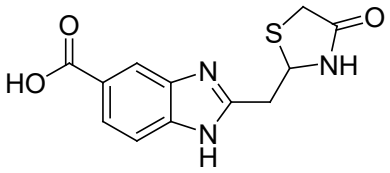
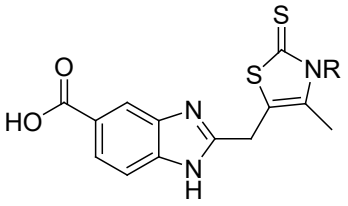


Figure 33. 1-methylene-2,3-diaryl-1,2-dihydropyrazino[1,2-a]benzimidazoles (33a) and 1-(2-arylvinyl)-3-aryl pyrazino[1,2-a] benzimidazole derivatives (33b).

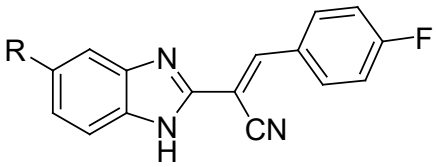
The synthesis of series of benzimidazole like: 2-[(4-oxothiazolidin-2-ylidene)-methyl (34a)and (4-amino-2-thioxothiazol-5-yl) benzimidazoles(34b), 2-[(4-fluorobenzylidene (34c)and cycloalkylidene)-cyanomethyl] benzimidazoles was carried out by Refaat et al[45]. All the prepared compound [Figure 34] were assessed against three cell line , HEPG2 and MCF7.



(34a)



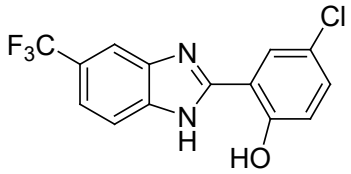
(34b) R = -Ph, -CH_2Ph



(34c) R = -Cl, -COOH

Figure 34. Benzimidazole Derivatives

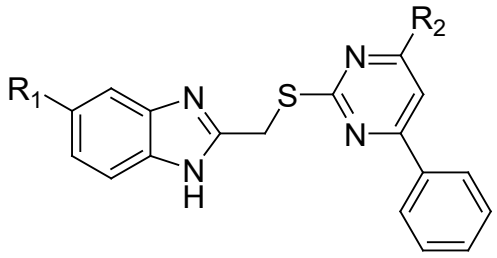
MookJr RA et al[46], developed a new class of benzimidazole inhibitors of Wnt/β-catenin signaling based on SAR studies of the Niclosamidesalicylanilidechemo type. These studies identified 4-chloro-2-(5-(trifluoromethyl)-1*H*-benzo[d]imidazol-2-yl) phenol [Figure 35] andconcerned derivatives with higher Wnt/β-catenin signaling inhibition vs. differential effects on cellular ATP homeostasis. These compounds may be useful in elucidating the mechanism ofNiclosamide's inhibition of Wntsignaling, and may aid in the discovery of inhibitors having improved pharmacologic properties in the treatment of cancer and diseases in which Niclosamidehas vital biological activity.



(35)

Figure 35: 4-chloro-2-(5-(trifluoro methyl)-1*H*-benzo[d]imidazol-2-yl) phenol derivative

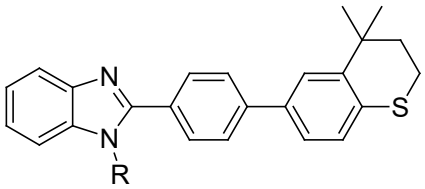
Shao KP et al[47], synthesized a series of pyrimidine–benzimidazol hybrids (36) [Figure 36] and investigated anticancer activity in four human cancer cell lines including MCF-7, MGC-803, EC-9706 and SMMC-7721. Some of the synthesized compounds showed moderate to strong activity against MGC-803 and MCF-7.



R_1= -H, R_2= -4-CH_3O-C_6H_5-NH
R_1=-Cl, R_2= -4-CH_3O-C_6H_5-NH
Figure 36: Pyrimidine-benzimidazole derivatives (36)

Anti-Diabetic Activity:

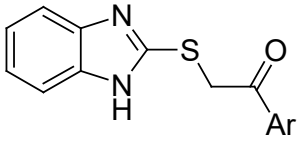
A synthesis of a series of novel and substituted benzimidazole derivatives (37)[Figure 37]was reported by Kumar et al[48] Compounds shown anti-diabetic activity against DPP-IV and PTP-IB. Compound 37aand 37bshown inhibitory activity against PTPIB (1.64%, 2.42%) at 30μM doses.



(37)
R = H **(37a)**, $CH_2CH_2CH_2CH_3$ **(37b)**
Figure 37.Benzimidazole derivatives.

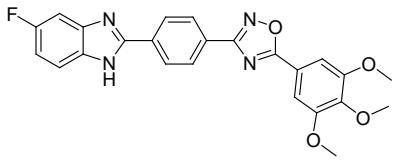
Anti-proliferative activity:

Abdel-Aziz HA et al[49], reported that a series of 2-((benzimidazol-2-yl)thio)-1-arylethan-1-ones (38)[Figure 38] were synthesized. All compounds were evaluated against anti-proliferative activity against the neoplastic colon HT-29 cell line. In addition, their inhibitory activity against cellsurface expression of CD133, a potent marker for cancer stem cells (CSCs) in the same cells, was assessed by flow cytometry at 10 μM.

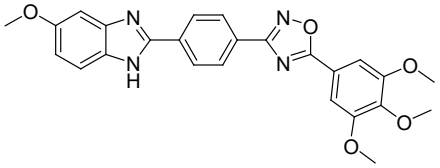


Ar = -2,3,4-$(OCH_3)_3$-C_5H_2 (38)
Figure 38: 2-((Benzimidazol-2-yl)thio)-1-arylethan-1-one derivatives.

Kamal A et al[50], synthesized a new series of 2-aryl-1,2,4-oxadiazolo-benzimidazole conjugates (39a and 39b)[Figure 39] and investigated their anti-proliferative activity in the group of sixty cancer cell lines. The compounds (39a) and (39b) showed remarkable cytotoxic activity against most of the cancer cell lines in the one dose assay and were administered at five dose levels (0.01, 0.1, 1, 10 and 100 μM) with GI50 values in the range of 0.79–28.2 μM. The flow cytometric results of these compounds showed increased cells in the G2/M phase, indicating a G2/M cell cycle arrest. Furthermore, these compounds showed inhibition of tubulin polymerization and disruption of microtubule formation.



(39a)

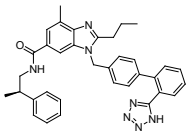


(39b)
Figure 39: 2-aryl-1,2,4-oxadiazolo-benzimidazole conjugates.

Antihypertensive activity:

Han XF et al[51], reported that novel angiotensin

II receptor type 1 (AT1) blockers bearing 6-substituted carbamoylbenzimidazoles with a chiral centre were developed and synthesized as the first step in the development of new antihypertensive agents. The newly synthesized compounds were tested for their potential ability to displace [^{125}I] Sar^{1} Ile^{8}-Ang II, which was specifically bound to human AT_1 receptor. The candidate (40) [Figure 40]was identified on the basis of plasma analyses, toxicology studies, and chronic oral tests for its excellent efficacy in anti-hypertensionand relatively low toxicity.

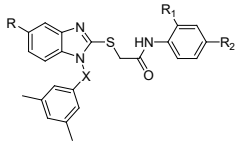


(40)

Figure 40: 6-substituted aminocarbonylbenzimidazole derivative

HIV Inhibitors:

MariaMonforte A et al[52] reported the synthesis of some N_1-aryl-2-arylthioacetamido-benzimidazoles (41)[Figure 41]as a novel class of Non-nucleoside reverse transcriptase inhibitors (NNRTIs). Most of the new compounds well tried to be very much effective in inhibiting every RT enzyme protein at Nano molar concentrations and HIV-1 replication in MT4 cells with low toxicity.



(41)

X = -CH_2, -SO_2

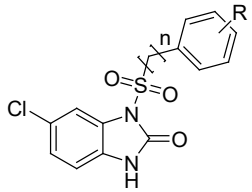
R = -H, -Cl

R_1 = -Br, -Cl, -NO_2;

R_2= -H, -CH_3, -$COOCH_3$, -SO_2CH_3, -SO_2NH_2

Figure 41: N1-aryl-2-arylthioacetamido-benzimidazole derivatives.

Ferro SF et al[53], reported that non-nucleoside reverse transcriptase inhibitors (NNRTIs) are an integral part of the currently available combination antiretroviral therapy (cART) which helps to reduce the AIDS-mortality and turned the disease from fatal to chronic. In this context, they recently reported a series of 6-chloro-1-(3-methylphenylsulfonyl)-1,3-dihydro-2H-benzimidazol-2- ones (42)[Figure 42] as potent non-nucleoside HIV-1 reverse transcriptase inhibitors (Figure 17). All the newly obtained compounds were evaluated as RT inhibitors and were tested against RTs containing single amino acid mutations. Finally, molecular docking studies were conducted to rationalize theidentified activity of the most promising compound.



(42)

R = -H, -2-Cl, -3-Cl, -4-Cl, -2-CH_3, -3-CH_3, -4-CH_3

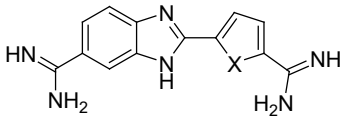
n = 1 or 2

Figure 42: 6-chloro-1-(substituted-phenylsulfonyl)-1,3-dihydro-2*H*-benzimidazol-2-one

Antiprotozoal activity:

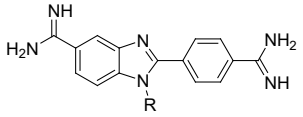
Farahat AA et al[54], prepared a series of novel benzimidazolediamidines[Figure 43] from the corresponding dicyano analogues either by using Pinner method or by preparing amidoximes intermediates which were reduced to the corresponding amidines. The new amidines (43a) and (43b) were evaluated against the protozoan parasite *Trypanosomabruceirhodesiense* by *in vitro* method. The thiophene analogue and the *N*-methyl compound showed superior antitrypanosomal activity compared to that of

the parent I.



X=-O,-S

(43a)

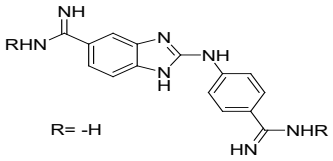


R= -CH_3, -C_2H_5, -C_3H_7, -Cyclohexyl

(43b)

Figure 43: Benzimidazolediamidine analogues

Karaaslan C et al[55], synthesized a number of mono and dicationic new 2-anilinobenzimidazolecarboxamidines (44)[Figure 44]starting from 4-amino-3-nitrobenzonitrile and corresponding o-phenylenediamines. Their antiparasitic activity against *Plasmodium falciparum* and *Trypanosomabruceirhodesiense*was investigated *in vitro*. Some of the dicationic compounds showed equal or very close activity against *T.b. rhodesiense*with melarsoprol and co-exhibited a promising activity against *P. falciparum* compared to chloroquine.

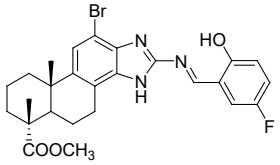


(44)

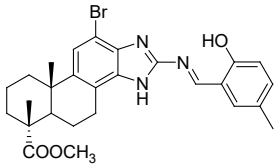
Figure 44: mono and dicationic-2-anilinobenzimidazole carboxamidines

Antitumor activity:

Gu W et al[56], designed and synthesized a series of new 1*H*-benzo[*d*]imidazole derivatives of dehydroabietic acid (45a and 45b) [Figure 45]as potent antitumor agents. In the *in vitro* method, most of the compounds showed significant cytotoxic activity against two carcinoma cells (SMMC-7721 and HepG2) and reduced toxicity to noncancerous human hepatocyte (LO2).



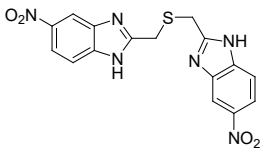
(45a)



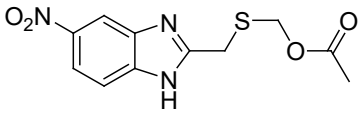
(45b)

Figure 45: 1*H*-benzo[*d*]imidazole derivatives of dehydroabietic acid.

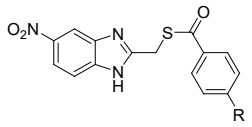
El-Gohary NS et al[57], prepared and tested new benzimidazoleanalogues (46a-c)[Figure 46]for anti-tumouractivity. In vitro antitumor screening of the new benzimidazoles toward HepG2, HCT-116 and MCF-7 cancer cell lines showed that these compounds are the most potent analogues to all cell lines tested. The three potent in vitro antitumor analogues were further examined for the in vivo method of antitumor activity on EAC in mice, and in vitro cytotoxicity against the normal W138 cell line.



(46a)

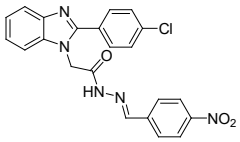


(46b)



(46c)
R= -Cl; –Br
Figure 46: Some new benzimidazoleanalogs.

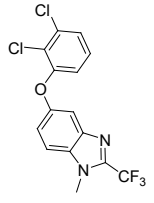
BalramSoni et al[58],reported the synthesis of a series of benzimidazole derivatives and screened for their in vitro cytotoxic activity. From the cytotoxic activity study, it was observed that compound with the presence of a 2-chloro on aromatic ring and 2-NO_2 on benzylidene amino group (47) [Figure 47]in most cases gives better cytotoxic activity against human K-562 cell line.



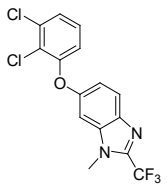
(47)
Figure 47.Benzimidazole derivatives

Antiparasitic Activity:

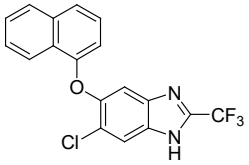
Dinesh K. Agarwal and co-authors[59] reported biological profile of various Benzimidazole derivatives. Hernandez-Luis and co authors[60] synthesized a series of benzimidazole derivatives and studied their in vitro antiparasitic activity against various protozoan parasites viz. L. Mexicana, G. intestinalis, E. histolytica and T. vaginalis considering Albendazole, mebendazole and pentamidine as standard drugs. Compounds 48a, 48b and 48c exhibited good antiparasitic activity [Figure. 48].



(48a)



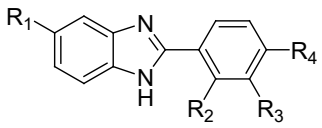
(48b)



(48c)
Figure 48.

Vasorelaxant activity:

Navarrete-Vazquez G et al[61], reported that a series of 1*H*-benzo[d]imidazole analogues (49)[Figure 49]of Pimobendan, substituted at position 5 with either –CF3 or –NO2, were synthesized using a short synthetic route. All the nitro derivatives were potent, and showed a partial endothelium dependent vasorelaxant effects, with EC50s <5 μM. 2-Methoxy-4-[5-nitro-1H-benzo[d]imidazol-2-yl]phenol was the most potent derivative in the series, showed an EC50 value of 1.81 μM and Emaxof 91.7% for ex vivo relaxant response in intact aortic rings, resulting in a 2.5-fold higher activity compared to Pimobendan. The closely related 5-CF_3 analogue was 19 times less potent than –NO_2substituted compound.

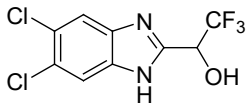


(49)
R1= -CF3, -NO2
R2= -H, -OMe, -OEt, -NO2, -OiPr,
R3= -H, -OMe, -O-CH2-O,
R4= -H, -OH, -OPr, -N(Me)2, -OMe
Figure 49: Pimobendan analogues of 1*H*-benzo[d]imidazole.

Androgen receptor antagonist:

Ng RA et al[62], reported the synthesis and in vivoSAR of 5,6-dichloro-benzimidazolederivatives (50)[Figure 50] as new selective androgen receptor antagonists. During the screening of 2-alkyl benzimidazoles,

it has been found that a trifluoromethyl group greatly improves antagonist activity in the prostate. This Benzimidazole derivative is a potent AR antagonist in the rat prostate (ID50 = 0.15 mg/day).

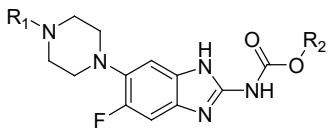


(50)

Figure 50: 5,6-dichloro-benzimidazole derivative

Antifungal Activity:

Thuraya Al–Harthy et al[63], reported the synthesis and bio-activity of seventeen Benzimidazole-based carbamate derivatives (51a–f) as fungicides. The synthesized compounds exhibited an acceptable activity against soil-borne pathogens. The growth of Pythium was significantly affected by 51a-3, 51a-2, 51b-2, 51a-1 and 51b-1 [Figure 51]. The benzimidazoles with benzyl derivatives (51a-1 and 51b-1) showed very high and promising results and were the most efficacious fungicide formulations in terms of reducing the growth of Pythium resulting in a 96% growth inhibition in Pythium at 100 mg·L−1.



51a-1: R1:Me, R2:Bn	51a-2: R1:Me, R2:t-But
51a-3: R1:Me, R2:Me	51b-1: R1:Et, R2:Bn
51b-2: R1:Et, R2:t-But	51b-3: R1:Et, R2:Me
51c-1: R1:But, R2:Bn	51c-2: R1:But, R2:Me
51d-1: R1:Ph, R2:Bn	51d-2: R1:Ph, R2:t-But
51d-3: R1:Ph, R2:Me	51e-1: R1:4-F-Ph, R2:Bn
51e-2: R1:4-F-Ph,R2:t-But	51e-3: R1:4-F-Ph, R2:Me
51f-1: R1:2-F-Ph, R2:Bn	51f-2: R1:2-F-Ph,R2:t-But
51f-3: R1:2-F-Ph, R2:Me	

(Me-Methyl, Et-Ethyl, Bn-Benzyl, t- But-Tertiary Butyl, F-Ph - Fluoro Phenyl and Ph-Phenyl)

(51 a-f)

Figure 51: Benzimidazole-based carbamate derivatives

Conclusion

The present literature reveals that the benzimidazole nucleus, which can potentially be used in thefield of drug discovery area and medicines, has versatile biological activities. This substrate has a great scope for the discovery of new, better, safer and more potent chemotherapeutic agents also. In future, therefore, there is a great scope for developing a new class of substituted benzimidazoles to show better efficacy.

Conflict of interest:

There is no conflict of interest.

Acknowledgement:

The authors are thankful to Faculty of Chemical Sciences, Institute of Natural Sciences and Humanities, ShriRamswaroop Memorial University, Lucknow for providing necessary facilities.

References

1. Spasov A.A. and Yozhitsa I.N., Benzimidazole derivatives: spectrum of pharmacological activity and toxicological properties, J. Pharm. Chem.,1999, 33, 232-243.
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., 2005, 13(9), 5550-5559.
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., 2002, 10, 2589-96.
4. Goker H., Kus C., Boykin D.W., Synthesis and Potent Antibacterial Activity against MRSA of Some Novel 1,2-Disubstituted-1H-Benzimidazole-N-alkylated-5-carboxamidines, Eur. J. Med. Chem., 2005, 40, 1062.
5. Andrzejewska M. and Yepez M.L. Synthesis, antiprotozoal and anticancer activity of substituted 2-trifluoromethyl- and 2-pentafluoroethylbenzimidazoles, Eur. J. Med. Chem.,2002, 37,973.
6. Ozden S., Atabey D. and Goker H., Synthesis and potent antimicrobial activity of some novel methyl or ethyl 1Hbenzimidazole-5-carboxylates derivatives carrying

amide or amidine groups, Bioorg. Med. Chem.,2005, 13, 1587-97.
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.,2006, 14, 7372.
8. Boiani M. and Gonzalez M., Imidazole and benzimidazole derivatives as chemotherapeutic agents, Mini Rev. Med. Chem., 2005, 5, 409-424.
9. Janos Beahdy, Recent Developments of Antibiotic Research and Classification of Antibiotics According to Chemical Structure, Advances in Applied Microbiology, 1974, 18, 309-406.
10. DevenderPathak, NadeemSiddiqui, BhanupriyaBhrigu,WaquarAhsan, M. ShamsherAlam, Benzimidazoles: A New Profile of Biological Activities, Der Pharmacia Letter, 2010, 2(2), 27-34.
11. Naaz F, Srivastava R, Singh A, Singh N, Verma R, Singh VK, Singh R K.Molecularmodeling, synthesis, antibacterial and cytotoxicity evaluation of sulfonamide derivatives of benzimidazole, indazole, benzothiazole and thiazole. Bioorganic and Medicinal Chemistry, 2018, 26 (12), 3414-3428.
12. JB Bariwal; AK Shah; MK Kathiravan; RS Somani; JR Jagtap; KS Jain, Ind. J. Pharm. Edu. Res., 2008,42, 225-231.
13. W Ramanpreet; Hedaitullah; NS Farha; I Khalid; HS Lamba, 2011, 1(3), 565-570.
14. GE Mohamed; N Ibrahmin, Int. J. Chem. Tech. Res., 2010, 2(4), 2097-2100.
15. Y. He, B. Wu, J. Yang, D. Robinson, L. Risen, L.B.Ranken, S. Sheng & E. Swayze., Bioorg. Med.Chem. Lett., 2003, 13(19), 3253-3256.
16. JT Leonard; L Jeyaseeli; M Kumar; R Sivakumar. Synthesis, anti-inflammatory and antibacterial activities of 4-substituted phenyl benzimidazoles, Asian J. Chem, 2006, 1104-1106.
17. 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., 2009, 86B, 302-305.
18. KF Ansari; C Lal. 'Synthesis and evaluation of some new benzimidazole derivatives as potential antimicrobial agents, Eur. J. Med. Chem., 2009, 44, 2294-2299.
19. 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, ActaBiochim. Pol., 2002, 49(1), 185- 195.
20. Gupta S.P. and Rani S., Synthesis and fungitoxicity of some 5-substituted- 3-polynitrophenyl rhodanines, J. Ind. Chem. Soc., 1997, 478.
21. 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., 1998, 37B, 904.
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., 2006,41, 1412-20.
23. Kharitonova MI, Denisova AO, Andronova VL, Kayushin AL, Konstantinova ID, Kotovskaya SK et al. New modified 2-aminobenzimidazole nucleosides: Synthesis and evaluation of their activity against herpes simplex virus type 1. Bioorganic and Medicinal Chemistry Letters, 2017, 27 (11), 2484-2487.
24. Zarubaev VV, Morkovnik AS, Divaeva LN, Karpinskaya LA, Borodkin GS. Tautomeric and non-tautomeric N-substituted 2-iminobenzimidazolines as new lead compounds for the design of anti-influenza drugs: An in vitro study. Bioorganic and Medicinal Chemistry. 2016, 24 (22), 5796-5803.
25. 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.,2008, 4, 605-615.
26. R. V. Devivar, E. kawashima, Benzimidazoleribonucleosides: design, synthesis, and antiviral activity of certain 2-(alkylthio)-and 2-(benzylthio)-5,6-dichlro-1-(dribofuranosyl)benzimidazoles. J. Med. Chem., 1994, 37, 2942-2949.
27. Pandey, V.K., Shukla, A., Synthesis and biological activity of isoquinolinylbenzimidazoles. Ind. J. Chem., 1999, 38B, 1381.
28. 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. 2007,15, 4419-4422.
29. JT Leonard, L Jeyaseeli, M Kumar, R Sivakumar, Synthesis, anti-inflammatory and antibacterial activities of 4-substituted phenyl benzimidazoles. Asian J. Chem., 2006,18, 1104-1106.
30. ZA Alagoz; C Kus T Coban., Synthesis and antioxidant properties of novel benzimidazoles containing substituted indoles. J. Enz. Inhib. Med. Chem., 2004. 20(3), 325-331.
31. Karaa1i N, Baltas N, Menteşe E. Synthesis and antioxidant, antiurease and anti-xanthine oxidase activities of some new benzimidazoles bearing triazole, oxadiazole, thiadiazole and imin function. Indian. Journal of Chemistry, 2018, 57 (B), 374-384.
32. Taha M, Ismail NH, Jamil W, Rashwan H, Kashif SM, Sain AA et al. Synthesis of novel derivatives of 4-methylbenzimidazole and evaluation of their biological activities. European. Journal of Medinalc Chemistry, 2014, 84, 731-738.
33. JB Bariwal; AK Shah; MK Kathiravan; RS

Somani; JR Jagtap; KS Jai 'Synthesis and antiulcer activity of novel pyrimidylthiomethyl and Pyrimidylsulfinylmethylbenzimidazoles as potential reversible proton pump inhibitors. Ind. J. Pharm. Ed. Res., 2008, 42, 225-231.

34. Nadeem H, Noor A, Qazi NG, Khan A, Paracha RZ, Ali F, Saeed A. Synthesis, characterization, anti-ulcer action and molecular docking evaluation of novel benzimidazole-pyrazole hybrids. Chemistry Central Journal, 2017, 11 (85), 1-13.
35. Madala SR, Anusha D. Synthesis, characterization and evaluation of anti-ulcer activity of benzimidazole derivative. World Journal of Pharmacy and Pharmaceutical Sciences. 2017, 6 (8), 1258-1262.
36. PS Solominova; VS Pilyugin; AA Pyurin. 'Targated search for new anthelmentic among 5 (6-Aminophenylthio (oxy)-2-amino benzimidazole derivatives. Part- 1 quantative structure activity relationship', J. Pharm. Chem., 2004, 38, 425-430.
37. 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-ylthioacetyl piperazine derivatives, Eur. J Med Chem, 2006, 41,1412–1420.
38. 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., 2008, 18(110), 3147-51.
39. Kumar D, Jacob MR, Reynolds MB, Kerwin SM Synthesis and evaluation of anticancer benzoxazoles and benzimidazoles related to UK-1, Bioorg Med Chem, 2002, 10(12), 3997–4004.
40. 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 styrylsulfones as anticancer agents, Eur J Med Chem, 2003, 38(9), 811–824.
41. 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, 2007, 15(19), 6489–6496.
42. 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., 2008, 43(9), 1858-1864.
43. 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., 2002, 37(10), 835–843.
44. 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., 2002, 37(3), 255-260.
45. Refaat, H.M., Synthesis and anticancer activity of some novel 2-substituted benzimidazole derivatives, Eur. J. Med. Chem., 2010, 45(7), 2949-60.
46. MookJr RA, Ren XR, Wang J, Piao H, Barak LS, Lyerly HK, Chen W. Benzimidazole inhibitors from the Niclosamidechemotype inhibit Wnt/β-catenin signaling with selectivity over effects on ATP homeostasis. Bioorganic and Medicinal Chemistry, 2017, 25 (6), 1804-1816.
47. Shao KP, Zhang XY, Chen PJ, Xue DQ, He P, Ma LY et al. Synthesis and biological evaluation of novel pyrimidine–benzimidazol hybrids as potential anticancer agents. Bioorganic and Medicinal Chemistry Letters, 2014, 24 (16), 3877-3881.
48. BB Kumar, PV Rao, Synthesis and structural studies on transition metal complexes derived from 1-(2-thienyl)-1-ethanole-1H-benzimidazole, Asian J. Chem., 2006, 18, 3060- 3064.
49. Abdel-Aziz HA, Ghabbour HA, Eldehna WM, Al-Rashood STA, Al-Rashood KA, Kun Fun H et al. 2-((Benzimidazol-2-yl)thio)-1- arylethan-1-ones: Synthesis, crystal study and cancer stem cells CD133 targeting potential. European Journal of Medinal Chemistry, 2015, 104, 1-10.
50. Kamal A, Reddy TS, Vishnuvardhan MVPS, Nimbarte VD, SubbaRao AV, Srinivasulu V, Shankaraiah N. Synthesis of 2-aryl-1,2,4-oxadiazolo-benzimidazoles: Tubulin polymerization inhibitors and apoptosis inducing agents. Bioorganic and Medicinal Chemistry, 2015, 23 (15), 4608-4623.
51. Han XF, He X, Wang M, Xu D, Ping Hao L, Hua Liang A et al. Discovery of novel, potent and low-toxicity angiotensin II receptor type 1 (AT1) blockers: Design, synthesis and biological evaluation of 6-substituted amino carbonyl benzimidazoles with a chiral center. European Journal of Medicinal Chemistry, 2015, 103, 473-487.
52. Maria Monforte A, Luca LD, RosaBuemi M, Agharbaoui FE, Pannecouque C, Ferro S. Structural optimization of N1-aryl-benzimidazoles for the discovery of new non-nucleoside reverse transcriptase inhibitors active against wild-type and mutant HIV-1 strains. Bioorganic and Medicinal Chemistry, 2018, 26 (3), 661-674.
53. Ferro SF, RosaBuemi M, DeLuca L, Agharbaoui FE, Pannecouque C, MariaMonforte A. Searching for novel N1-substituted benzimidazol-2-ones as non-nucleoside HIV-1 RT inhibitors. Bioorganic and Medicinal Chemistry, 2017, 25 (14), 3861-3870.
54. Farahat AA, Vaughn CB, Mineva EM, Kumar A, Wenzler T, Brun R. Synthesis, DNA binding and antitrypanosomal activity of benzimidazole analogues of DAPI. Bioorganic and Medicinal Chemistry Letters, 2016, 26 (24), 5907-5910.

55. Karaaslan C, Kaiser M, Brun R, Goker H. Synthesis and potent antiprotozoal activity of mono/di amidino 2-anilinobenzimidazoles versus Plasmodium falciparum and Trypanosomabruceirhodesiense. Bioorganic and Medicinal Chemistry, 2016, 24 (18), 4038-4044.
56. Gu W, Miao TT, Hua DW, Jin XY, Tao XB, Huang CB, Wang SB. Synthesis and in vitro cytotoxic evaluation of new 1H-benzo[d]imidazole derivatives of dehydroabietic acid. Bioorganic and Medicinal Chemistry Letters, 2017, 27 (5),1296-1300.
57. El-Gohary NS, Shaaban MI. Synthesis, antimicrobial, antiquorum-sensing and antitumor activities of new benzimidazoleanalogs. European. Journal of Medicinal Chemistry, 2017, 137, 439-449.
58. S Balram; SR Mahendra; B Anil; S Ramba, Internationa J. Drug Res. Tech, 2012, 2 (7), 479-485.
59. Dinesh K. Agarwal and PradeepK.Goyal, Synthetic and Biological Aspects of Benzimidazole Derivatives, Chemistry & Biology Interface, 2021, 11, 1, 6-12.
60. F Hernandez-Luis, A Hernandez-Campos, R Castillo, G Navarrete-Vazquez, O Soria-Arteche, M Hernandez-Hernandez, L Yepez-Mulia, Eur J Med Chem, 45, 2010, 3135.
61. Navarrete-Vazquez G, Hidalgo-Figueroa S, Torres-Piedra M, Vergara-Galicia J, Rivera- Leyva JC, Estrada-Soto S et al. Synthesis, vasorelaxant activity and antihypertensive effect of benzo[d]imidazole derivatives. Bioorganic and Medicinal Chemistry. 2010, 18, 3985–3991.
62. Ng RA, Guan J, Alford Jr VC, Lanter JC, Allan GF, Sbriscia T et al. Synthesis and SAR of potent and selective androgen receptor antagonists: 5,6-Dichloro-benzimidazole derivatives. Bioorganic and Medicinal Chemistry Letters, 2007, 17 (3), 784-788.
63. Al–Harthy, T.; Al-Sadi, A.M.; Zoghaib, W.; Moghadam, E.S.; Stoll, R.; Abdel-Jalil, R. Design, Synthesis and Bioactivity of Benzimidazole–2–Carbamates as Soil–Borne Anti–Fungal Agents. Chem. Proc. 2021, 3, 64.