Arabian Journal of Chemistry (2017) **10**, S157–S173

King Saud University

**Arabian Journal of Chemistry**

www.ksu.edu.sa
www.sciencedirect.com

**REVIEW**

# Benzimidazoles: A biologically active compounds

**Salahuddin** [a,*], **Mohammad Shaharyar** [b], **Avijit Mazumder** [a]

[a] *Department of Pharmaceutical Technology, Noida Institute of Engineering and Technology (NIET), Knowledge Park-II, Greater Noida 201306, India*
[b] *Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Jamia Hamdard, New Delhi 110062, India*

Received 1 February 2012; accepted 23 July 2012
Available online 3 August 2012

**KEYWORDS**

Benzimidazole;
Pharmacological activity;
Antimicrobial activity

**Abstract** Synthesis of commercially available benzimidazole involves condensation of o-phenylenediamine with formic acid. The most prominent benzimidazole compound in nature is N-riosyldimethylbenzimidazole, which serves as a axial ligand for cobalt in vitamin B12. The benzimidazole and its derivatives play a very important role as a therapeutic agent e.g. antiulcer and anthelmintic drugs. Apart from this the benzimidazole derivatives exhibit pharmacological activities such as antimicrobial, antiviral, anticancer, anti-inflammatory, analgesic, etc. The substituted benzimidazoles are summarized in this review to know about the chemistry as well as pharmacological activities.


**Contents**



## 1. Introduction

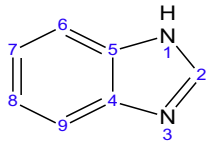
Imidazole is the accepted name for the parent compound in the series, the numbering of which follows the accepted pattern for heterocyclic compound. Imidazole or iminazoline is an azapyrrole, the nitrogen atom is separated by one carbon atom. This compound was earlier also called as glyoxalin as it was first prepared in 1958 from glyoxal and ammonia.

* Corresponding author. Tel.: +91 9891872142.
E-mail address: sallu_05@yahoo.co.in ( Salahuddin).
Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.arabjc.2012.07.017

The benzo derivative of imidazole is referred to as benzimidazole (Bansal, 2002). Although benzimidazole is the commonest name of the parent compound of the series, other names such as benzimidazole and 1,3-benzodiazole (**1**) are often used.




1*H*-benzimidazole

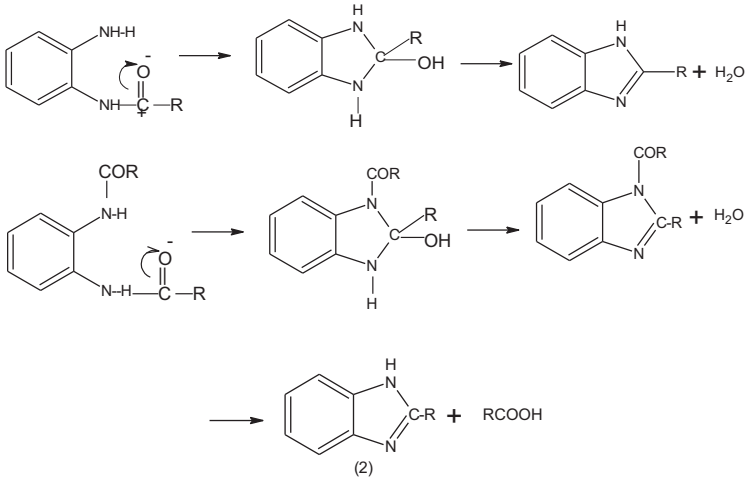
(2)

Mono acyl derivative of o-phenylenediamine is readily converted into the corresponding benzimidazole by the action of heat alone. These conversions are generally carried out at a temperature somewhat above the melting point of the starting compounds. This is a convenient method for preparing benzimidazoles when monoacyl derivatives are easily obtainable. The procedure may be improved by heating the monoacyl derivative of diamine in an atmosphere of nitrogen to prevent oxidation (Kelly, 1945).The diacyl derivatives of o-phenylenediamines are also converted into benzimidazoles but higher temperatures are required (Bistrzycki, 1890).

mono basic acid in 4 N hydrochloric acid. The benzimidazole is then precipitated by neutralizing the solution with ammonium hydroxide. Benzoic acid gives only traces of 2-phenylbenzimidazole. Apparently this method is not applicable to the aromatic monobasic acid.

Benzimidazole derivative are associated with various types of pharmacokinetic and pharmacodynamic properties. Benzimidazole nucleus is one of the bioactive heterocyclic compounds that exhibit a range of biological activities. Specifically, this nucleus is a constituent of vitamin $B_{12}$ (O'Neil et al., 2001).The pharmacological activities of the benzimidazole containing moiety have been well documented (Amari et al., 2002). Albendazole, Mebendazole and Thiabendazole are widely used as anthelmintic drugs (Kohler, 2001).

Literature survey reveals that the various derivatives of benzimidazole have been synthesized for their pharmacological activities. Some of the already synthesized compounds from the above mentioned field have found very strong application in medicine praxis (Mavrova et al., 2006). The activity against bacteria, fungi and helminthes resulted their mode of action, which resulted in the blockage of microtubule in various nematode, trematode and cystode. (Campbell and Denham, 1983).



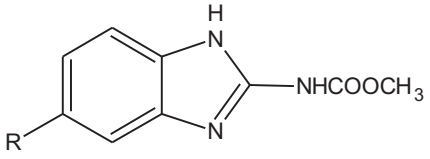

(3)

Benzimidazole is also synthesized from o-phenylenediamine and mono or di-basic acid**.** In this method, the diamine is simply heated with excess acid (Fischer, 1905).This procedure has been recommended as a means of identifying fatty acid α-hydroxy acid as well as phenylacetic acid and diphenylacetic acid are converted into the corresponding benzimidazoles when heated with o-phenylenediamine.

Phillips modification of the above procedure consists in refluxing with the (Philips, 1928) o-phenylenediamine and

## 2. Antimicrobial

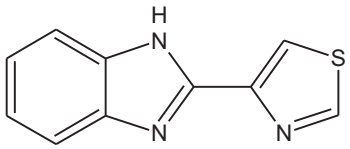
The two series of benzimidazole derivatives were synthesized, the first one was based on 2-thioalkyland thioaryl substituted benzimidazole (**6**), the second one was based on 5,6-dinitrobenzimidazole (**7**) and the antibacterial activity of the compound against nosocomial strains of *Stenotrophomonas malthophilia* was examined (Kazimierczuk et al., 2002).



(4)

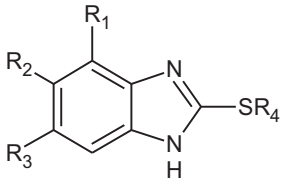
Albendazole R= -$SCH_2CH_2CH_3$

Mebendazole R= -$COC_6H_5$



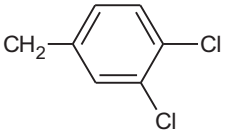
(5)

Thiabendazole

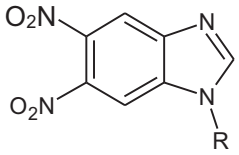


$R_1$=$R_2$, $R_3$=H, $R_4$=$CH_2CH_2N(CH3)_2$

$R_1$, $R_3$= H, $R_2$= COOH

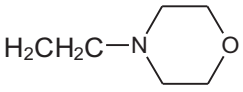


(6)



R= $CH_2CH_2N(CH_3)_2$

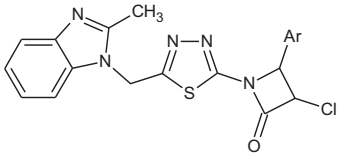
R= $CH_2CH_2N(C_2H_5)_2$



(7)

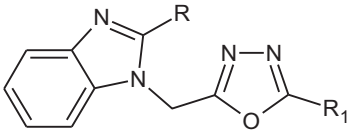
Novel azetidine-2-one (**8**) has been synthesized and evaluated for their antibacterial activity against *Bacillus subtilis, Escherichia coli, Candida albicans, Aspergillus niger* and *Aspergillus flavus*. The tested compounds are more effective against gram positive bacteria. The strong lipophilic character of molecule plays an essential role in producing antimicrobial effects (Ansari and Lal, 2009a,b).

Some derivatives of benzimidazole were synthesized by nucleophilic substitution of substituted benzimidazole 2-substituted-1-[{(5-substituted-alkyl/aryl)-1,3,4-oxadziazolyl-2-yl}] (**9**) and were evaluated for antimicrobial activities toward Gram + ve and Gram –ve bacteria. Some of the synthesized compounds showed moderate activity against tested fungi (Ansari and Lal, 2009a,b).



(8)

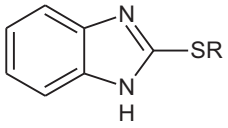
R= $C_6H_5$, 4-$BrC_6H_5$, 2-$ClC_6H_4$, 4-$C_6H_4$, 2-$OCH_3C_6H_4$, 4-$OCH_3C_6H_4$, 2-$OHC_6H_4$, 4-$OHC_6H_4$



(9)

R= H or $CH_3$

$R_1$= $CH_3$, $C_2H_5$, $CH_2Cl$, $C_6H_5$, 2-$ClC_6H_4$, 4-$ClC_6H_4$, 2-$OHC_6H_4$, 4-$OHC_6H_4$, 2-$OCH_3C_6H_4$, 4-$OCH_3C_6H_4$

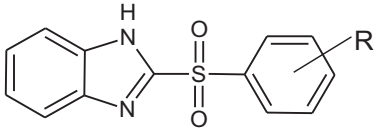


(10)

R= 2,4-DNP, 2,6-DNP, 2,4,6-TNP, 2-chloro 4,6-DNP, 2-methyl- 4,6-DNP, 2-chloro-4-bromo-3,5-DNP(DNP= dinitrophenyl, TNP= trinitrophenyl)

Gupta and Rani (1977) synthesized 2-thiohalogenonitrophenyl benzimidazole by the condensation of halogenonitrobenzenes and sodium salt of 2-mercaptobenzimidazole (**10**) and tested for their antifungal activity against *Helmithosporium sativum, A. niger and Fusarium oxysporum* by spore germination method. The percentage inhibition of the spores at 10 ppm has been recorded.

Ghoneim et al. (1998) synthesized 2-[(4-aminophenyl)sulphonyl] derivative (**11**) of benzimidazole and tested the antimicrobial activity of compounds against *E. coli* using agar diffusion method.

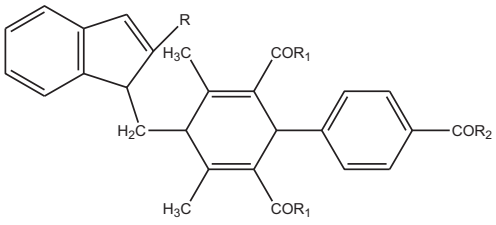


(11)

R= 4-$NH_2$ and 2,4-di$NH_2$

All 4-amino and 2,4-diaminophenylsulphonyl derivatives showed antimicrobial activity.

Various benzimidazoles (**12**) were prepared and evaluated by Mane et al. against *Alternaria brassicicola, Fusarium, Staphylococcus* (Gram + ve) *and E. coli* (Gram –ve) using filter paper disc method at 500 ppm concentration using 5 mm size filter paper. It was found that the compound having $NO_2$ and chloro substituent showed good activity against fungi as well as bacteria (Mane et al., 1995).



(12)

R= H, $CH_3$, $C_2H_5$, $C_6H_5$

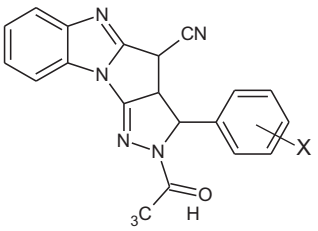
R1= $CH_3$, $OCH_3$, $OC_2H_5$

R2= H, 4-$CH_3$, 4-$OCH_3$, 3-Cl, 3-$NO_2$, 4-$NO_2$, 4'-OH

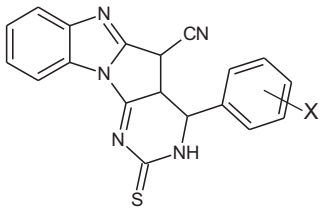
A series of fused and spiropyrazolones (**13**), isoxazolines (**14**), pyrimidines (**15**), β-lactam (**16**) and thiazolidinones (**17**) incorporating 2-cyanomethyl benzimidazole were synthesized by Khalafallh et al. (1995).

The synthesized compounds have been tested against some bacterial and fungal strains using the filter paper disc method and 3-cyano-2,3dihydropyrolo[1,2-a]benzimidazole-1(H)-one is more potent against bacteria and fungi than pyrazolines and pyrimidines.

Kumar et al. (2006) synthesized some novel 2-(6-flurochroman-2-yl)-1-alkyl/acy/aroyl-1-H-benzimidazoles (**18**) with different types of electrophiles. Some of the compounds show

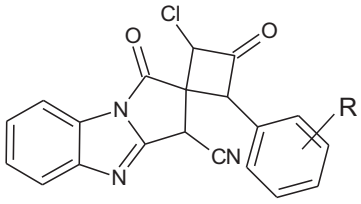


(13, 14)

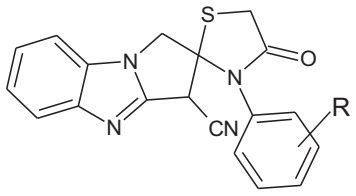


(15)

X= H, *P*-$NO_2$, P-$(NCH_3)_2$

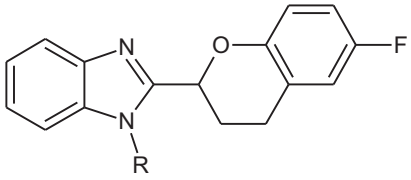


(16)



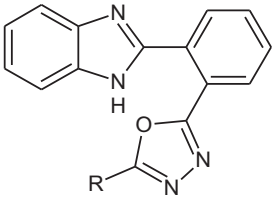
(17)

R= OH, 4-N-$(CH_3)_2$, 2-OH, 4-benzosubstituted, 5,6- benzosubstituted

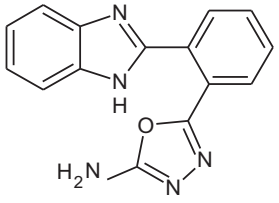


(18)

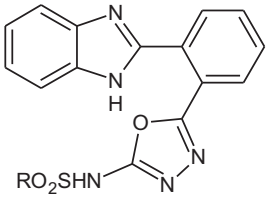
R= $CH_3$, $C_2H_5$, -CO-Phenyl, -$So_2$-phenyl, Benzyl, *p*-fluorophenyl



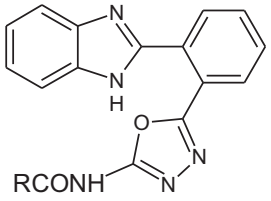
(19)



(20)



(21)



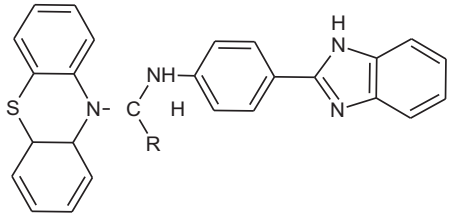
(22)

R= aryl

good antibacterial activity against *Salmonella typhimurium* and poor activity against *Staphylococcus aureus*.

Kaghtara et al. (1999) reported when 2-(benzimidazol-2-yl) benzoyl hydrazide condensed with any aromatic acid and $POCl_3$ gives 2-aryl-5-[(2′-benzimidazol-2″-yl)phenyl]-1,3,4-oxadiazoles (**19**). The acid hydrazide on cyclization with CNBr yields 2-amino-5-[2′-(benzimidazol-2″-yl-phenyl)-1,3,4-oxadiazole (**20**) which on reaction with any sulphonyl chloride and substituted benzoyl chloride gives the corresponding sulphonamides (**21**) and amides (**22**) respectively. All the synthesized products have been evaluated *in vitro* for their antimicrobial activity against several microbes.

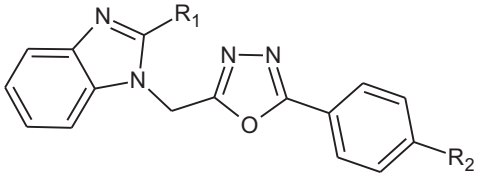
Bishnoi et al. (2002) reported various 10-(α-*p*-benzimidazol-yl-aminobenzyl)phenothiazines (**23**). All the compounds were evaluated for their antifungal activity against *Fusarium solani*.



(23)

R= phenyl and substituted phenyl

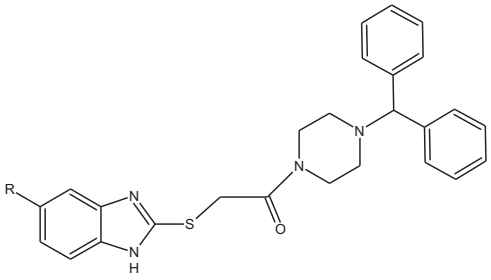
A new series of 2-substituted-1-[(5-substituted-phenyl-1,3,4-oxadiazole-2-yl)methyl-1*H*-benzimidazole (**24**) have been synthesized. The newly synthesized compounds were evaluated for their antibacterial activity (MIC in μg/mL) by the serial dilution method *in vitro* against Gram positive bacteria namely *E. coli, S. aureus* and Gram negative bacteria namely *Pseudomonas aeruginosa* (Gowda et al., 2010).



(24)

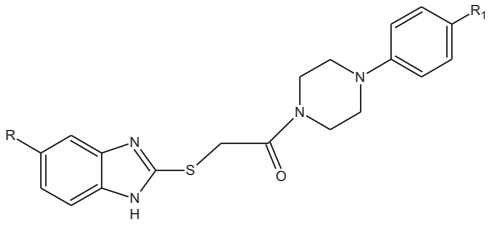
R1= Propyl, Benzyl R2= H, Cl, Br, Me, OMe,

The 1H-benzimidazole-2-yl thioacetylpiperazine derivatives (25, 26, 27) were synthesized and evaluated for their *in vitro* activity against *T. spiralis* as well as their *in vivo* antinematode activity against *S. obvelata* (Mavrova et al., 2006). The *in vitro* activity showed that most of the tested compounds exhibit higher activity than albendazole against *T. spiralis* and comparable to that of ivermectin. Some of the compounds demonstrated 96.0%, 98.2% and 100% activities at a dose of 200 μg/mL after 48 h. Some of the compounds were found most active with 76%, 73% and 77% against *S. obvelata*.



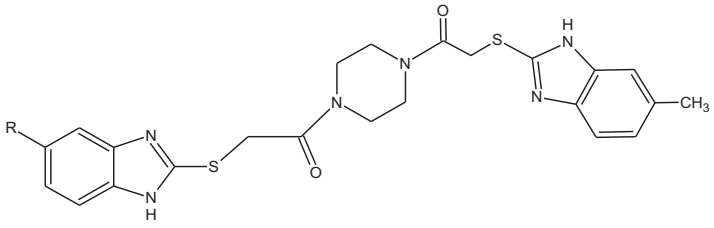
(25)

R= H, $CH_3$



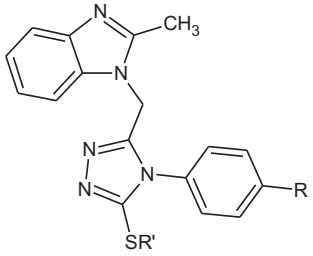
(26)

R= H, $CH_3$, $NO_2$, Cl R1= $CH_3$, Cl



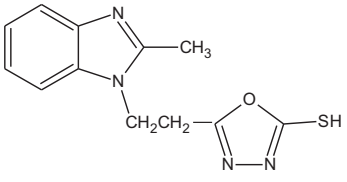
(27)

R= H, $CH_3$

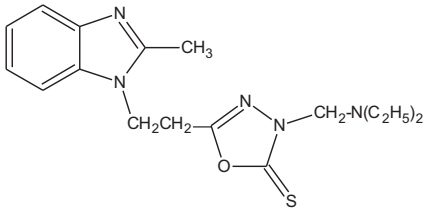


(28)

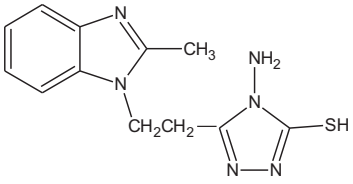
R= $CH_3$, $C_2H_5$, $CH(CH_3)C_2H_5$, $(CH_2)_3CH_3$, $CH_2Ph$, $CH_2COOC_2H_5$, $CH(CH_3$



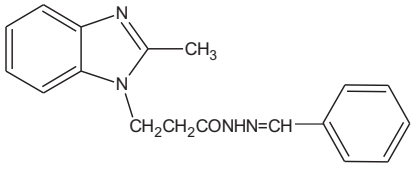
(29)



(30)



(31)

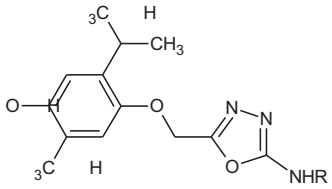


(32)

A series of 1-[(4-(4′-substituted)phenyl-3-alkyl/aralkyl-thio-4*H*-1,2,4-triazoles (**28**) have been prepared and screened for their antimicrobial activity against pathogenic organisms *S. citrus, B. subtilis* and *E. coli* and antifungal against *A. fumigatus, C. albicans and F. heterosporum* by single disc method at different concentration method (50 and 100 μg/mL) using ampicillin and miconazole as standard drugs for antibacterial and antifungal activities respectively (Shetgiri and Kokitkar 2001)

5-[2-(2-Methylbenzimidazol-1-yl)ethyl][1,3,4]oxadiazole-2(3H)-thione (**29**), 5-[2-methylbenzimidazol-1-yl)ethyl]-3-diethylaminoethyl (**30**), 5-[2-(2-methylbenzimidazol-1-yl)ethyl]-4-amino[1,2,4]triazole-3-thiol (**31**), 3-(2-methylbenzimidazol-1-yl)propionic acid hydrazide Schiff's base (**32**) have been synthesized and were tested for their antimicrobial activity against Gram +ve bacteria (*Bacillus cereus*), and Gram –ve bacteria (*E. coli*) (AfafH El-masry et al., 2000).

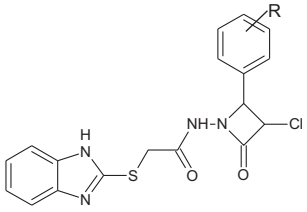
2-Arylamino-5-(*p*-nitrosothymoxymethyl)-1,3,4-oxadiazoles (**33**) were prepared along with their derivatives by chemoselective heterocyclization with $NaOH/I_2$ of thiosemicarbazide. The compounds were screened for their antimicrobial activity against Gram +ve bacteria *S. citrus* and *B. mega* and against Gram –ve bacteria *E. coli* and *S. typhosa* and for antifungal activity against *A. niger* by the cup plate method at a concentration of 50 μg/mL using DMF as a solvent. The activity was compared with the known standard drug viz. ampicillin, chloramphenicol, norfloxacin and griseofulvin at same concentration (Vashi et al., 1996).



(33)

R= Aryl

The efficient and rapid synthesis of novel azetidin-2-ones (**34**) has been established. Thus, both microwave and conventional condensation of 2-{(1H-benzimidazol)-ylthio}-N0-2-(substituted phenyl) hydrazide with chloroacetylchloride were



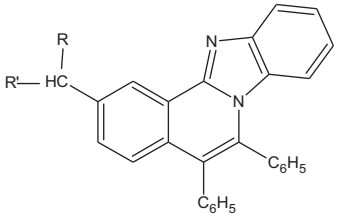
(34)

R= 4-$NO_2$, 3,4,5-$(OCH_3)_3$, 3-OH,4-OH, 5-OH, 2-$OCH_3$, 4-$OCH_3$, 2-Cl, 3-Cl, 4-Cl

carried out in DMF-benzene solvent in the presence of $Et_3N$ catalyst. The resulting compounds have been evaluated for their antibacterial activity against *B. subtilis, S. aureus* and *E. coli.*

### 3. Antiviral

Some 7-(arylamidoalkyl)-3,4-diphenyl-isoquinolinyl-[1,5-c]-benzimidazoles (**35**) have been synthesized 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 in allantoic cavity. After 48 h it was found that the isoquinonyl benzimidazole derivative with nicotinamido group showed the maximum activity (Pandey and Shukla 1999).

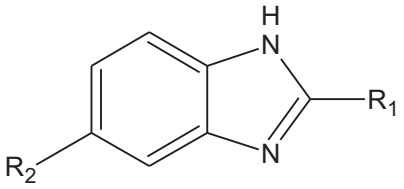


(35)

R= H, R'= Salicylamido

Various benzimidazol-2-ylalkyl N-aryldithiocarbamates (**36**), 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 (Yadav and Pal, 1996).

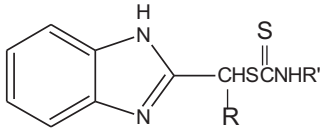
A set of 2-substituted-5-amidino-benzimidazole (**40**) derivatives bearing amidino substistuent at C-5 of benzimidazole ring were synthesized by introducing various heterocyclic nuclei at C-2 and were evaluated for their antiviral activity towards c *oxsackie viruses* and *echo viruses*. The most selective activity towards coxsackie viruses and echo viruses was observed with the compound having pyridine ring at C-2 (Kristina et al., 2007).



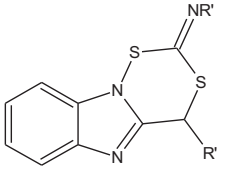
(40)

$R_{1=}$ Heterocyclic substituent

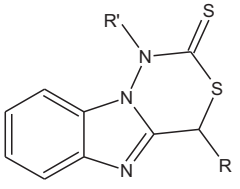
$R_2$ = Amidino substituent



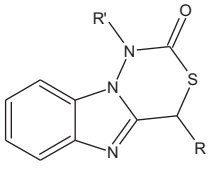
(36)



(37)

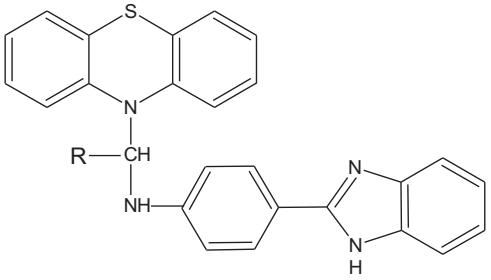


(38)



(39)

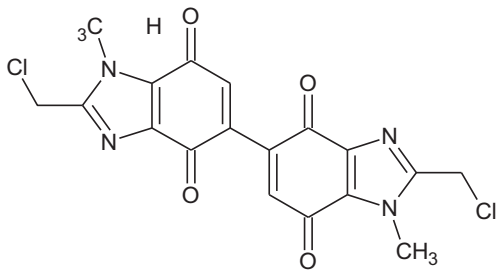
Some new 10-(α-*p*-benzimidazolyl-1-aminobenzyl) phenothiazines (**41**) have been synthesized and their antiviral activity was performed against *JEV* and *HSV-1* (Bishnoi et al., 2002).



(41)

R= Substituted phenyl

cancer activity has been evaluated on colon, breast and lung cancer cell lines. Among this 2,2′-bis(chloromethyl)-1,1′-dimethyl-5,5′-bi(1H-benzimidazole)-4,4′,7,7′-tetraone (**43**) was shown to possess excellent cytotoxicity comparable to that of mitomycin C (Gellis et al., 2008).



(43)

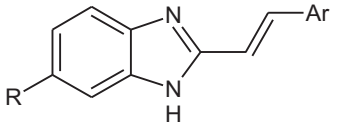
## 4. Anticancer

A novel series of benzimidazole substituted Schiff bases (**42**) were synthesized by the reaction of aromatic aldehydes with corresponding 2-aminobenzimidazoles. The synthesized Schiff bases were tested on their antiproliferative activity *in vitro* and exerted non-specific antiproliferative activity on the tested cell lines at the highest tested concentration (Hranjec et al., 2011).

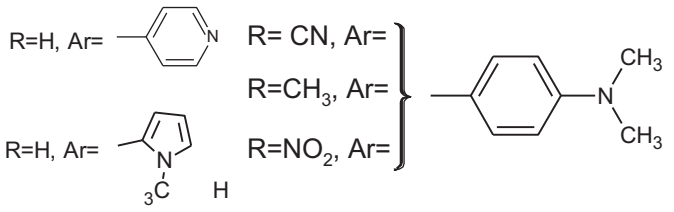
Benzimidazole-4,7-diones substituted at position-2 were synthesized via a microwave-assisted reaction using 2-chloromethyl-1,5,6-trimethyl-1H-benzimidazole-4,7-dione. Their anti

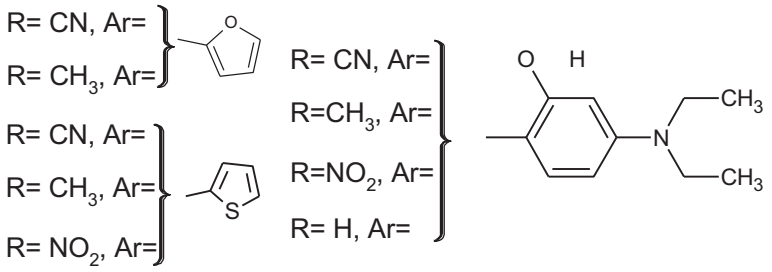
Various heterocyclic benzimidazole derivatives (**44**–**47**) have been synthesized by the condensation of succinic acid, homophthalic acid and 2,3-pyrazinedicarboxlic acid with various substituted diamines under microwave irradiation. All these compounds evaluated for anticancer activity at 50 mg/kg po exhibit good anticancer activity against ovary (IGR-OV-1), breast (MCF-7) and CNS (SF-295) human cancer cell lines (Sondhi et al., 2010).

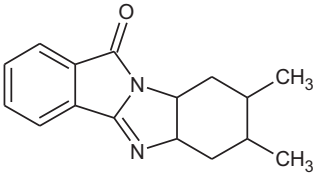
Some 1-methylene-2,3-diaryl-1,2-dihydropyrazino[1,2-a]benzimidazoles (**48**) and some 1-(2-arylvinyl)-3-arylpyrazino[1,2-a]benzimidazole derivatives (**49**) have been synthesized and their anticancer activity was reported. It can be seen that



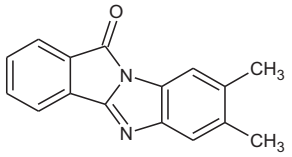
(42)



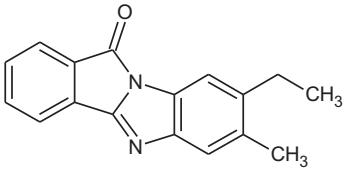




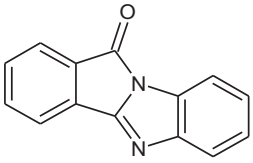
(44)



(45)



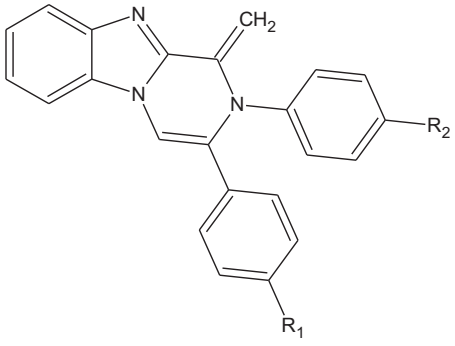
(46)



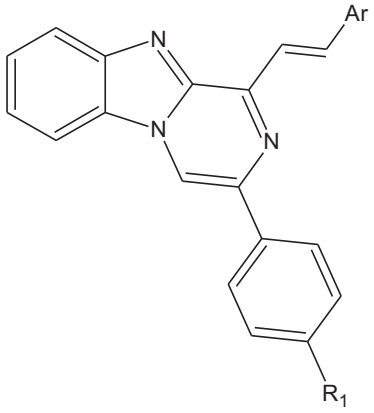
(47)

for all the compounds, $\log_{10}G_{I50}$ values are smaller than –4. Melphalan *cis*-diaminodichloroplatinum, one of the chemotherapeutic agents, was used as standard compound (Demirayak et al., 2002).

Shaharyar et al. (2010) synthesized 2-{5-[(substituted)phenyl]-4,5-dihydro-1H-3-pyrazolyl}-1H-benzoimidazole (**54**) and 2-{5-[(substituted)phenyl]-1-phenyl-4,5-dihydro-1H-3-pyrazolyl}-1H-benzimidazole (**55**) and screened at the

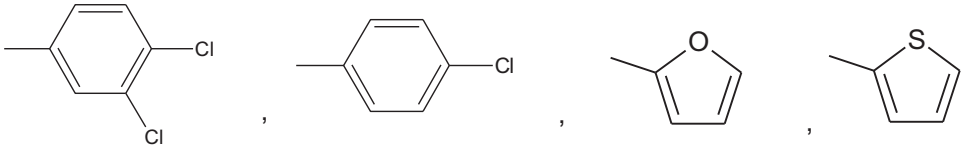


(48)



(49)

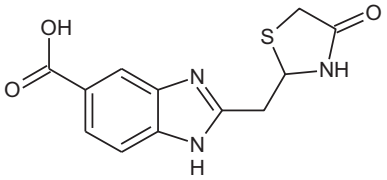
$R_1$= H, $CH_3$, $OCH_3$, Cl, $R_2$= H, $CH_3$, $OCH_3$, Cl, $NO_2$

Ar = 

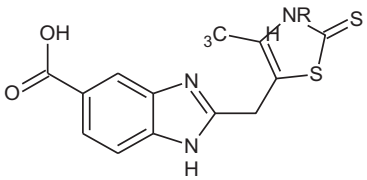
The synthesis of some series of benzimidazole like: 2-[(4-oxothiazolidin-2-ylidene)-methyl (**50**) and (4-amino-2-thioxothiazol-5-yl) benzimidazoles (**51**), 2-[(4-fluorobenzylidene (**52**) and cycloalkylidene)-cyanomethyl] benzimidazoles was carried out (**53**). All the synthesized compound were evaluated against three cell lines representing three common forms of human cancer i.e. human hepatocellular carcinoma cell line (HEPG2), human breast adenocarcinoma cell line (MCF7) and colon carcinoma cell line (HCT 116) (Refaat, 2010).

National Cancer Institute (NCI), USA for anticancer activity at a single high dose (10 μM) in full NCI 60 cell panel. Among the selected compounds, 2-[5-(3,4-dimethoxyphenyl)-1-phenyl-4,5-dihydro-1H-3-pyrazolyl]-1H-benzimidazole was found to be the most active candidate of the series and selected for further evaluation at five dose level screening.

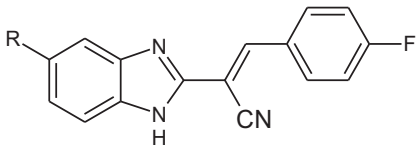
A novel series of trisubstituted benzimidazole and its precursors were synthesized. The title compounds were evaluated for inhibition against MDA-MB-231 breast cancer cell



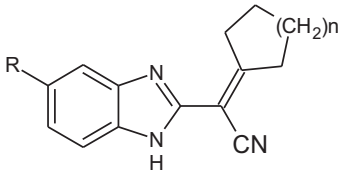
(50)



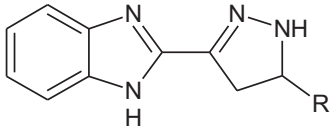
(51) R=$C_6H_5$, $CH_2C_6H_5$



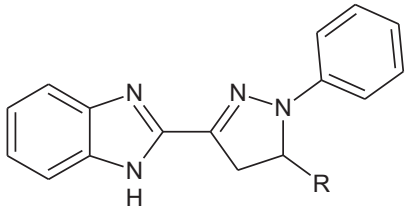
(52) R= Cl, COOH



(53) R= Cl, COOH n= 1 and 2



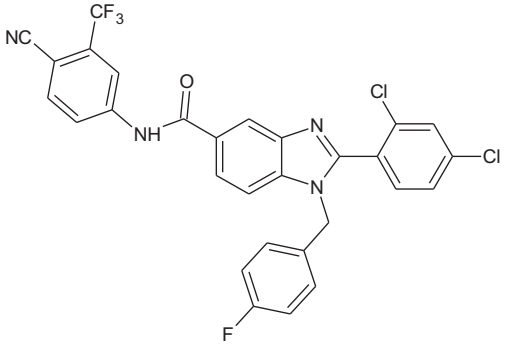
(54)



(55)

R= Phenyl, 4-Methoxyphenyl; 4-Chlorophenyl; 4-Bromophenyl; 4-Fluorophenyl; 3,4-Dimethoxy phenyl; 2,6-Dichloro phenyl

proliferation. The results revealed that the compound N-(4-cyano-3-(trifluoromethyl) phenyl)-4-fluoro-3-nitrobenzamide (**56**) was the potent inhibitor (Thimmegowda et al., 2008).



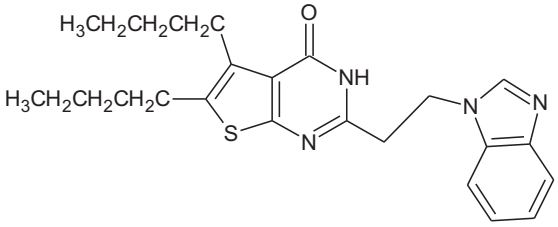
(56)

## 5. Antiprotozoal

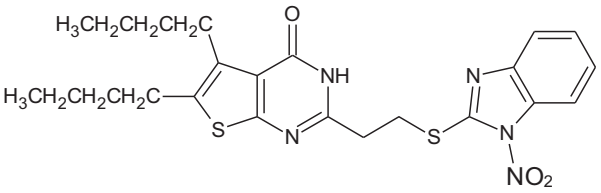
Some thieno[2,3-d]pyrimidin-4(3H)-ones containing benzimidazol-2-yl-thioethyl- and benzimidazol-2-yl-methanethioethyl moiety in the second position of the pyrimidine ring were synthesized in order to determine their antitrichinellosis and antiprotozoal effects. The benzimidazole derivatives of thieno[2,3-d]pyrimidin-4-(3H)-ones (**57**) exhibited higher activity against *Trichinella spiralis in vitro* in comparison to albendazole. The most active compound, 2-[2-(5-nitro-1H-benzimidazol-1-yl)ethyl]-5,6,7,8-tetrahydro[1]benzothieno[2,3-d] pyrimidin-4(3H)-one (**58**) revealed 95% activity at a dosage of 5 mg/kg. The compound 2-{2-[(5(6)-nitro-1H-benzimidazol-2-yl)thio]ethyl}-5,6,7,8-tetrahydro[1]-benzothieno[2,3-d]pyrimidin-4(3H)-one exhibited 90% efficacy (Mavrova et al., 2010).

Novel series of some hybrids from benzimidazole and pentamidine (**59**) were prepared and each compound was tested *in vitro* against the protozoa *Trichomonas vaginalis, Giardia lamblia*, *Entamoeba histolytica, Leishmania mexicana*, and *Plasmodium berghei*. The tested compounds were compared with pentamidine and metronidazole (Gomez et al., 2008).

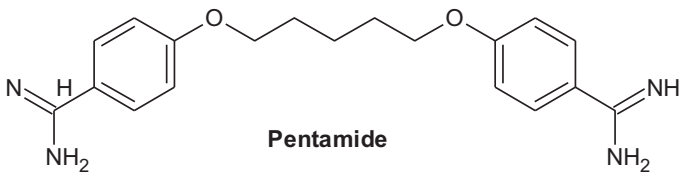
Biphenyl benzimidazolesdiamidines (**60**) were synthesized from their respective diamidoximes, through the bis-*o*-acetoxyamidoxime followed by hydrogenation. The target compounds contain hydroxy and/or methoxy substituted 1,3-phenyl groups as the central space between the two amidino bearing aryl groups. All the compounds have performed



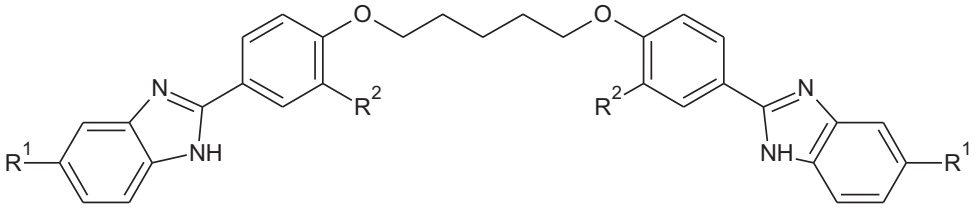
(57)



(58)




Hybridisation with benzimidazole

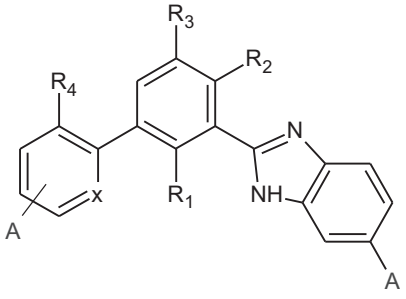


(59)

$R^1$= H, $OCH_3$, $CH_3$, $CF_3$, $NO_2$ $R^2$= H, $OCH_3$

DNA binding studies [ΔTm values for poly(dA.dT)$_2$] and *in vitro* evaluation against *Trypanosoma b. rhodesiense (T.b.r.)* and *P. falciparum* for the diamidino biphenyl benzimidazoles (Ismail et al., 2004).

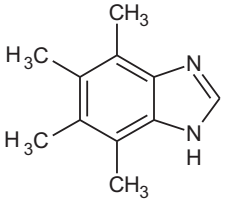
Various chloro-, bromo and methyl-analogues of 1*H*-benzimidazole (**61**–**64**), 1*H*-benzotriazole and their N-alkyl derivatives (**65**–**68**) have been synthesized and evaluated *in vitro* against the protozoa *Acanthamoe bacastellanii*. It



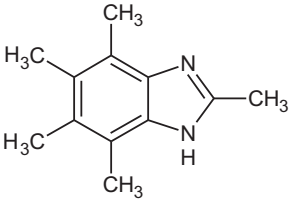
(60)

X= N, CH $R_1$= H, OH $R_2$= H, OH, OMe $R_3$= H, OMe $R_4$= H, Me

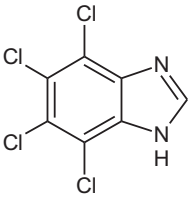
A= *p*-(C=NH)$NH_2$



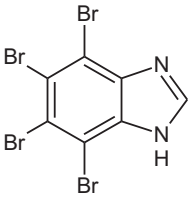
(61)



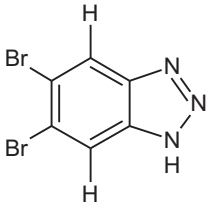
(62)



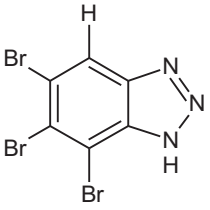
(63)



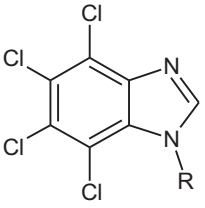
(64)



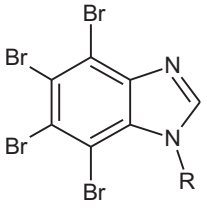
(65)



(66)



(67)



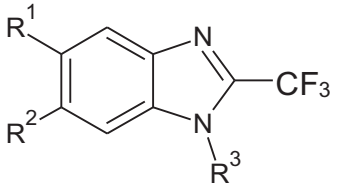
(68)

R= methyl, ethyl, propyl

was found that 5,6-dimethyl-1Hbenzotriazole (**11**) and 5,6-dibromo-1H-benzotriazole (**14**) have higher efficacy than the antiprotozoal agent chlorohexidine (Kopanska et al., 2004).

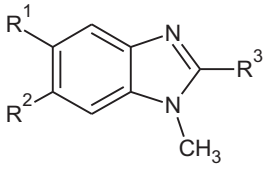
Padilla et al. (2009) reported the synthesis and antiprotozoal activity *in vitro* of 1-methylbenzimidazolederivatives (**69**) substituted with chlorine atoms at the benzenoid ring and aminocarbonyl, N-methylaminocarbonyl, N,N-dimethylaminocarbonyl,ethoxycarbonyl, 1-hydroxyethyl and acetyl at position-2. Some of the compounds are more active than metronidazole, the drug of choice against *Giardia intestinalis* and most of them against *T. vaginalis*. The most active group of compounds for both parasites in this series is substituted with 2-ethoxycarbonyl.

The derivatives of 2-(tri-fluoromethyl)benzimidazole (**70**) against *T. spiralis*. These compounds were also tested for their effect on tubulin polymerization and none inhibited tubulin polymerization (Vazquez et al., 2001).



(70)

$R^1 = R^2 =$ H, Cl $\qquad R^3 = CH_3$



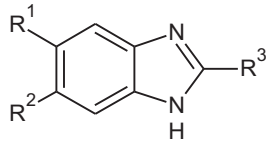
(69)

$R^1 = R^2 =$ H, Cl

$R^3 = CONH_2, CONHCH_3, CON(CH_3)_2, CO_2CH_2CH_3, CH(OH)CH_3, COCH_3$

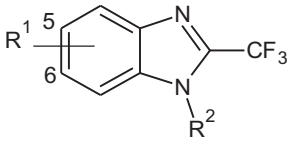
substituted at the 1-, 5-, and 6-positions have been synthesized and tested *in vitro* against the protozoa *G. lamblia, E. histolytica*, and the helminth *T. spiralis*. The tested compounds are more active as antiprotozoal agents than albendazole and metronidazole. One compound (**20**) was as active as albendazole

Various 1-*H*-benzimidazoles (**71**) have been synthesized and tested *in vitro* against the protozoa *G. lamblia, E. histolytica* and the helminth *T. spiralis*. The compounds were also tested for the inhibition of rat brain tubulin polymerization and compared with standard drug. Most of the compounds tested were



(71)

$R^1$= $R^2$= H, Cl $R^3$= H, $CH_3$, $NH_2$, $NHCO_2CH_3$, SH, $SCH_3$



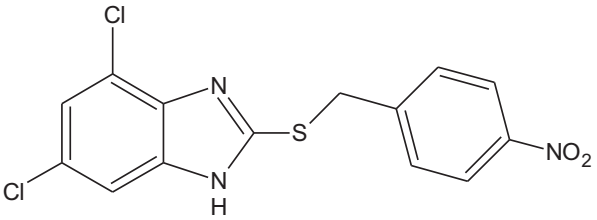
(72)

$R_1$= 5(6)-H, 5(6)-Cl, 5(6)-F, 5(6)-$CF_3$, 5(6)-CN, 5-$CF_3$, 6-$CF_3$ $R_2$= H, $CH_3$

more active as antiprotozoal agents than metronidazole and albendazole. None of the compounds was as active as albendazole against *T. spiralis* (Valdez et al., 2002).

2-(Trifluoromethyl)-1H-benzimidazole derivatives (**72**) with various bioisosteric substitutents (-Cl, -F, -$CF_3$, -CN) were prepared and tested *in vitro* against *G.* intestinalis and *T.* vaginalis in comparison with albendazole and metronidazole. Some analogues had $IC_{50}$ values $<1$ μM against both species, which make them more potent than either standard (Vazquez et al., 2006).

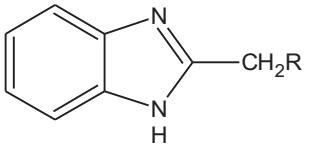
Some thio-alkylated and thio-arylated derivatives of c-substituted benzimidazole (**73**) have been synthesized and evaluated as antiprotozoal activity against nosocomial strains of *S. malthophilia* using metronidazole as standard. One of the tested compounds, 4,6,-dichloro-2-(4-nitrobenzylthio)-benzimidazole showed the most distinct antiprotozoal activity (Kazimierczuk et al., 2002).



(73)

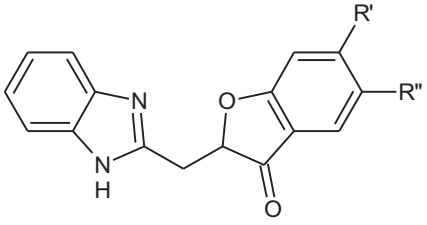
## 6. Anti-inflammatory and analgesic activities

Some 2-substituted benzimidazoles (**74**, **75**) have been synthesized by the condensation of o-phenylenediamine with 2-coumaranonyl acetic acid derivatives and indole 3-acid and evaluated their anti-inflammatory and analgesic activities. The compounds were found to have significant anti-inflammatory activity at 50 mg/kg dose (Khan and Nandan, 1997).



(74)

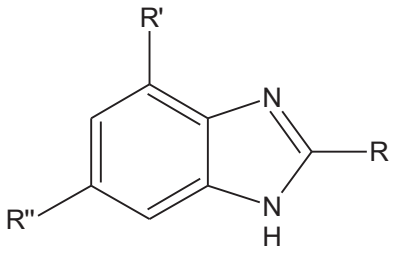
R= indolyl, 3-skatolyl, 1-[2-(3-indolyl)-ethyl]



(75)

R′= R″= H R′= R″ = PhenylR′= H, R″ = $CH_3$

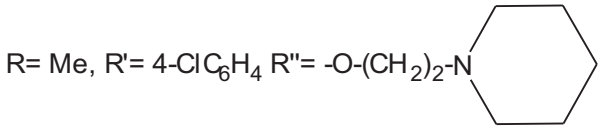
A new synthesis and their anti-inflammatory activity of a group of 1*H*-benzimidazole (**76**) were reported. The compounds were assessed on rat adjuvant arthritis screen and indomethacin as standard compound. The result gave 30% or greater reduction in non injected paw volume compared to control together with the result for indomethacin (Evans et al., 1996).



(76)

R= H, R'= 4-$ClC_6H_5$, R''= OMe

R= H, R'= 4-$ClC_6H_5$, R''= OH

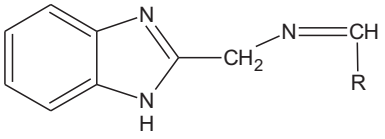


R=Me, R'= 4-$ClC_6H_5$, R''= -(OMe)Me

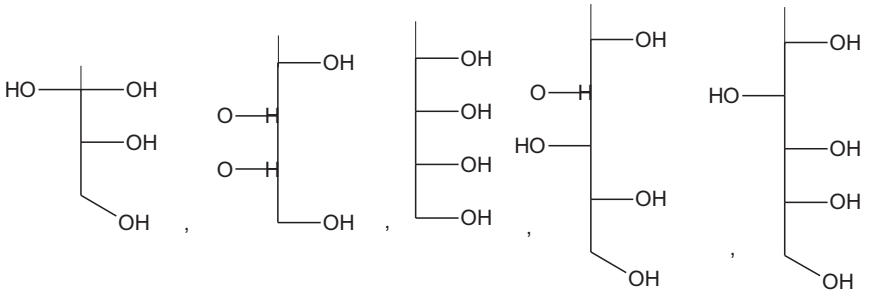
Some imino sugars of methylbenzimidazole (**77**) have been prepared and anti-inflammatory activity of the compounds was studied by employing the cotton pellet granuloma bioassay in rats using indomethacin as reference standard. The granuloma% inhibition values were determined for each compound (Taha, 2005).

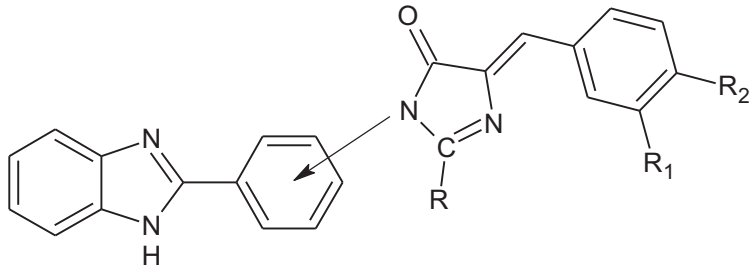
1-[2,3-(2-Phenylbenzimidazole)]2-methyl/phenyl-4-(3,4-disubstituted benzylidine)-5-oxoimidazoles (**78**) have been synthesized by condensing 2-(2/3 aminophenyl)benzimidazoles with appropriate 2-methyl/phenyl-4-(3,4-disubstituted) oxazoline-5-ones in dry pyridine and screened anti-inflammatory activity against carrageenan induced oedema (Mohan et al., 1984).

A series of novel 5-substituted-1-(phenylsulphonyl)-2-methylbenzimidazole derivatives (**79**) have been synthesized. Compounds were evaluated for their anti-inflammatory and analgesic activities as well as gastric ulcerogenic effects by carrageenan-induced rat paw edema and acetic acid-induced writhing in mice using indomethacin as standard (Gaba et al., 2010).



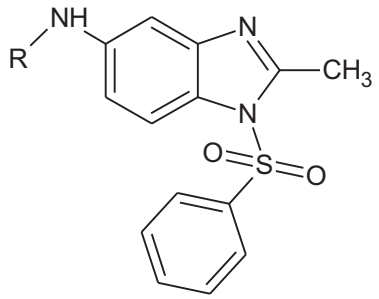
(77)

R= 



(78)

R=$CH_3$, $C_6H_5R_1$= H, $OCH_3R_2$= H, $OCH_3$



(79)

R= *o*-$NH_2C_6H_4$, *p*-$NH_2C_6H_4$, p-$NH_2C_7H_6$

## 7. Conclusion

The new classes of reviewed substituted benzimidazole have a wide variety of biological activities. The 2-substituted-1-[{(5-substituted-alkyl/aryl)-1,3,4-oxadziazolyl-2-yl}] 3-cyano-2,3di hydropyrolo[1,2-a]benzimidazole-1(H)-one has good antibacterial and antifungal activities respectively. The significant antiviral and anticancer activities are shown by 7-(aryl-amidoalkyl)-3,4-diphenyl-isoquinolinyl-[1,5-c]-benzimidazole and benzimidazole substituted Schiff bases, but they are associated with some drawbacks like side effect, toxicity. So for minimizing these drawbacks there is a need to synthesize some new chemical compounds with better results.

## References


Afaf, H.E., Fahmy, H.H., Abdelwal, S.H., 2000. Molecules 5, 1429.

Amari, M., Fodili, M., Nedjar-kolli, B., 2002. Reactivity studies on 4-aminopyrones: Access to benzimidazole and benzimidazolone derivatives. J. Heterocycl. Chem. 39, 811.

Ansari, K.F., Lal, C., 2009a. Synthesis and evaluation of some new benzimidazole derivatives as potential antimicrobial agents. Eur. J. Med. Chem. 44, 2294.

Ansari, K.F., Lal, C., 2009b. Synthesis, physicochemical properties and antimicrobial activity of some new benzimidazole derivatives. Eur. J. Med. Chem. 44, 4028.

Bansal, R.K., 2002. Herocyclic Chemistry, third ed. Publisher, New Delhi, New Age International, 401 pp.

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

Bistrzycki, Ulffers, 1980. Ueber Diacyl-*o*-Diamine. Ber. 23, 1876.

Campbell, W.C., Denham, D.A., 1983. Chemotherapy. In: Campbell, W.C. (Ed.), Trichinilla and Trichinosis. Plenum Press, USA and London, UK, 340 pp.

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

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

Fischer, Veiel., 1905. The chemistry of benzimidazoles. Ber. 38, 320.

Gaba, M., Sing, D., Singh, S., Sharma, V., Gaba, P., 2010. Synthesis and pharmacological evaluation of novel 5-substituted-1-(phenyl-sulfonyl)-2-methylbenzimidazole derivatives as anti-inflammatory and analgesic agents. Eur. J. Med. Chem. 45, 2245.

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

Ghoneim, K.M., Essawi, M.Y.H., Mohamed, M.S., Kamal, A.M., 1998. 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.

Gomez, H.T., Nunez, E.H., Rivera, I.L., Alvarez, J.G., Rivera, R.C., Puc, R.M., Ramos, R.A., Guttirez, M.C.R., Bacab, M.J.C., Vazquez, G.N., 2008. Design, synthesis and in vitro antiprotozoal activity of benzimidazole-pentamidine hybrids. Bioorg. Med. Chem. Lett. 18, 3147.

Gowda, J., Khadar, A.M.A., Kalluraya, B., Kumari, N.S., 2010. Microwave assisted synthesis of 1,3,4-oxadiazoles carrying benzimidazole moiety and their antimicrobial properties. Ind. J. Chem. 49B, 1130.

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

Hranjec, M., Starcevic, K., Pavelic, S.K., Lucin, P., Pavelic, K., Zamola, G.K., 2011. Synthesis, spectroscopic characterization and antiproliferative evaluation *in vitro* of novel Schiff bases related to benzimidazoles. Eur. J. Med. Chem. 46, 2274.

Ismail, M.A., Brun, R., Wenzler, T., Tanious, F.A., Wilson, W.D., Boykin, D.W., 2004. Dicationic biphenyl benzimidazole derivatives as antiprotozoal agents. Bioorg. Med. Chem. 12, 5405.

Kaghtara, P.R., Shah, N.S., Doshi, R.K., Parekh, H.H., 1999. Synthesis of 2,5-disubdtituted 1,3,4-oxadiazoles as biologically active heterocycles. Ind. J. Chem. 38B, 572.

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

Kelly, Day., 1945. Preparation of 2-phenylnaphth [1,2] imidazole and 2-methylnaphth [1,2] imidazole. J. Am. Chem. Soc. 67, 1074.

Khalafallh, A.K., Selim, M.A., Abu, R.M., Elmaghraby, M.A., Soleiman, H.A., Raslan, M.A., 1995. Novel synthesis of some new fused/spiro heterocyclic compounds and their biological activity. Ind. J. Chem. 34B, 1066.

Khan, S.A., Nandan, S.A., 1997. 2-Substituted benzimidazoles as anti-inflammatory and analgesic agents. Indian J. Heterocycl. Chem. 7, 55.

Kohler, P., 2001. The biochemical basis of anthelmintic action and resistance. Int. J. Parasitol. 31, 336.

Kopanska, K., Najda, A., Zebrowska, J., Chomicz, L., Piekarczyk, J., Myjak, P., Bretner, M., 2004. Synthesis and activity of 1*H*-benzimidazole and 1*H*-benzotriazole derivatives as inhibitors of *Acanthamoeba castellanii*. Bioorg. Med. Chem. 12, 2617.

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

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

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

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

Mavrova, A.T., Vuchev, D., Anichina, K., Vassilev, N., 2010. Synthesis, antitrichinnellosis and antiprotozoal activity of some novel thieno[2,3-*d*]pyrimidin-4(3H)-ones containing benzimidazole ring. Eur. J. Med. Chem. 45, 5856.

Mohan, R.R., Agarwal, C., Agarwal, R., Misra, V.S., 1984. CNS, anthelmintic and antiinflammatory activities of some 1-[2/3-(2-phenyl benzimidazole)]2-methyl/phenyl-4-(3,4-disubstituted benzylidene)5-oxo-imidazoles. Pharma-col. Res. Commun. 16, 321.

O'Neil, M.J., Smith, M., Heckelman, 2001. The Merck Index, 13th ed. Merck & Co Inc., P-1785, 10074.

Padilla, D.V., Morales, S.R., Campos, A.H., Luis, F.H., Mulia, L.Y., Contraras, A.T., Castillo, R., 2009. Synthesis and antiprotozoal activity of novel 1-methylbenzimidazole derivatives. Bioorg. Med. Chem. 17, 1724.

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

Philips, 1928. The formation of 2-substituted benziminazoles. J. Chem. Soc. 2393.

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

Shaharyar, M., Abdullah, M.M., Bakht, M.A., Majeed, M., 2010. Pyrazoline bearing benzimidazoles: Search for anticancer agent. Eur. J. Med. Chem. 45, 114.

Shetgiri, N.P., Kokitkar, S.V., 2001. Synthesis and biological activity of new benzimidazoles. Ind. J. Chem. 40B, 163.

Sondhi, S.M., Rani, M., Sigh, J., Roy, P., Agrawal, S.K., Saxena, A.K., 2010. Solvent free synthesis, anti-inflammatory and anticancer activity evaluation of tricyclic and tetracyclic benzimidazole derivatives. Bioorg. Med. Chem. Lett. 20, 2306.

Taha, M.A.M., 2005. Synthesis and antiinflammatory evaluation of some imino-sugars of methylbenzimidazole. J. Ind. Chem. Soc. 82, 180.

Thimmegowda, N.R., Swamy, S.N., Kumar, C.S.A., Kumar, Y.C.S., Chandrappa, S., Yip, G.W., Rangappa, K.S., 2008. Synthesis, characterization and evaluation of benzimidazole derivative and its precursors as inhibitors of MDA-MB-231 human breast cancer cell proliferation. Bioorg. Med. Chem. Lett. 18, 432.

Valdez, J., Cedillo, R., Campos, A.H., Yepez, L., Luis, F.H., Vazquez, G.N., Tapia, A., Cortes, R., Hernandez, M., Castillo, R., 2002. Synthesis and antiparasitic activity of 1*H*-benzimidazole derivatives. Bioorg. Med. Chem. Lett. 12, 2221.

Vashi, B.S., Mehta, D.S., Shah, V.H., 1996. Synthesis of 2,5-disubstituted-1,3,4-oxadiazole, 1,5-disubstituted-2- mercapto-1,3,4-triazole and 2,5-disubstituted-1,3,4-thiadiazole derivatives as potential antimicrobial agents. Ind. J. Chem. 35B, 111.

Vazquez, G.N., Cedillo, R., Campos, A.H., Yepez, L., Luis, F.H., Valdez, J., Morales, R., Cortes, R., Hernandez, M., Castillo, R., 2001. Synthesis and antiparasitic activity of 2-(Trifluoromethyl)benzimidazole derivatives. Bioorg. Med. Chem. Lett. 11, 187.

Vazquez, G.N., Vilehis, M.M.R., Mulia, L.Y., Melendez, V., Gerena, L., Campos, A.H., Castillo, R., Luis, F.H., 2006. Synthesis and antiprotozoal activity of some 2-(trifluoromethyl)-1*H*-benzimidazole bioisosteres. Eur. J. Med. Chem. 41, 135.

Yadav, L.D.S., Pal, D.R., 1996. 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, 748.