



REVIEW ARTICLE

OPEN ACCESS

Benzimidazole: A short review of their antimicrobial activities

*Namrata Singh, Annamalai Pandurangan, Kavita Rana, Preeti Anand, Arshad Ahmad, Amit Kumar Tiwari
Bharat Institute of Technology, School of Pharmacy, Bypass Road, Partapur, Meerut, Uttar Pradesh, India

ABSTRACT

Benzimidazole is the heterocyclic compound formed from benzene and imidazole ring containing nitrogen, oxygen sulphur and its derivatives are of wide interest because of their diverse biological activity and clinical applications, they are remarkably effective compounds both with respect to their inhibitory activity and their favourable selectivity ratio. Reported nucleus is a constituent of vitamin-B12. Benzimidazoles are regarded as a promising class of bioactive heterocyclic compounds that exhibit a range of biological activities like anti-microbial, anti-viral, anti-diabetic, anti-cancer activity, numerous anti-oxidant, anti-parasitic, anti-helminthics, anti-proliferative, anti-HIV, anti-convulsant, anti-inflammatory, anti-hypertensive, anti-neoplastic, proton pump inhibitor and anti-trichinellosis. Benzimidazoles exhibit significant activity as potential antitumor agents, smooth muscle cell proliferation inhibitors, a treatment for intestinal cystitis, and in diverse area of chemistry. Some of the important benzimidazole derivatives have been reported as thyroid receptor agonist gonadotropin releasing hormone receptor antagonists, non-nucleoside HIV-1 reverse transcriptase inhibitors and interestingly alkynylbenzimidazoles as modulators of metabotropic glutamate receptors. The imidazole core is a common moiety in a large number of natural products and pharmacologically active compounds. The synthesis of novel benzimidazole derivatives remains a main focus of medicinal research. This comprehensive overview summarizes the chemistry of different derivative of substituted benzimidazole along with their anti-microbial activity containing anti-malarial anti-fungal, anti-bacterial, anti-viral activities.

Key Words: benzimidazoles, anti-malarial, anti-fungal, anti-bacterial, anti-viral.

INTRODUCTION

Benzimidazole derivatives are of wide interest because of their diverse biological activity and clinical applications, they are remarkably effective compounds both with respect to their inhibitory activity and their favorable selectivity ratio (Ansari *et al.*, 2009, Kazimierczuk *et al.*, 2002, Grocer *et al.*, 2002). Looking at the importance of benzimidazole and oxadiazole nucleus, it was thought that it would be worthwhile to design and synthesize some new benzimidazole derivatives bearing oxadiazole moiety and screen them for potential biological activities. We have previously reported the synthesis of some new biologically active benzimidazoles. Resistance to number of anti-microbial agents (β -lactam antibiotics, macrolides, quinolones, and

vancomycin) among a variety of clinically significant species of bacteria is becoming increasingly important global problem. In particular, increasing drug resistance among Gram-positive a bacterium such as *staphylococci*, *enterococci*, and *streptococci* is a significant health matter. Benzimidazole ring displays an important heterocyclic pharmacophor in drug discovery. These compounds carrying different substituent's in the benzimidazole structure are associated with a wide range of biological activities including anti-cancer, anti-viral, anti-bacterial, anti-fungal, anti-helminthic, anti-inflammatory, anti-histaminic, proton pump inhibitor, anti-oxidant, Anti-hypertensive and anti-coagulant properties (Tuncbilek *et al.*, 2009). In 1960, Fort *et al.* reported the discovery of benzimidazole derivatives as proton pump inhibitors. Further, synthesis and evaluation of different substituted benzimidazole derivatives resulted in the discovery of omeprazole, lansoprazole, rabeprazole, and pantoprazole (Figure 1) (Patil *et al.*, 2008).

*Corresponding Author:

Namrata Singh
Bharat Institute of Technology
School of Pharmacy, Bypass Road, Partapur,
Meerut, Uttar Pradesh, India
E-mail: namrata.pharma85@gmail.com
Contact No.: 8881544437

The benzimidazole ring is an important pharmacophore in modern drug discovery. In recent years, attention has increasingly been given to the synthesis of benzimidazole derivatives. The synthesis of novel benzimidazole derivatives remains a main focus of medicinal research. Recent observations suggest that substituted benzimidazoles and heterocyclic, show easy interactions with the biopolymers, possess potential activity with lower toxicities in the chemotherapeutic approach in man (Haugwitz *et al.*, 1982).

BIOLOGICAL ACTIVITY OF BENZIMIDAZOLE

Antimalarial activity

Malaria caused 350-500 million clinical episodes annually and result in over one million deaths, most of which affect children under 5 years old in sub Saharan Africa. Malaria is the fifth cause of death from infectious diseases worldwide (after respiratory infections, HIV/AIDS, diarrhoeal diseases and tuberculosis). Recent estimates so that as many as 3.3 billion people live in areas at risk of malaria in 109 countries. In addition to its health toll, malaria puts a heavy economic burden on endemic countries and contributes to the cycle of poverty people face in many countries. Malaria mortality and morbidity began to increase in the 1980s due to a combination of factors such as increase in parasite and vector resistance to the current anti-malarial drugs and insecticides, the weakening of traditional malaria control programs, rapid decentralization and integration into deteriorating primary health service, and the development of humanitarian crisis situations in many malaria-endemic areas. This dramatic increase led to a compelling and urgent necessity for new malarial, with mechanisms of action different from the existing ones, and to identify new drug targets. Chloroquine has recently been shown to inhibit hemozoin formation within the parasite food vacuole. This process is also thought to be the molecular target of other quinoline anti-malarial. Hemozoin was originally considered to be formed by the polymerization of heme, but has now been demonstrated to be a crystalline cyclic dimer of ferriprotoporphyrin IX. Thus, hemozoin synthesis, a process unique to the malaria parasite, offers a logical and valuable potential target for new anti-malarial drug development. New drugs that attack the same vital target of chloroquine but that

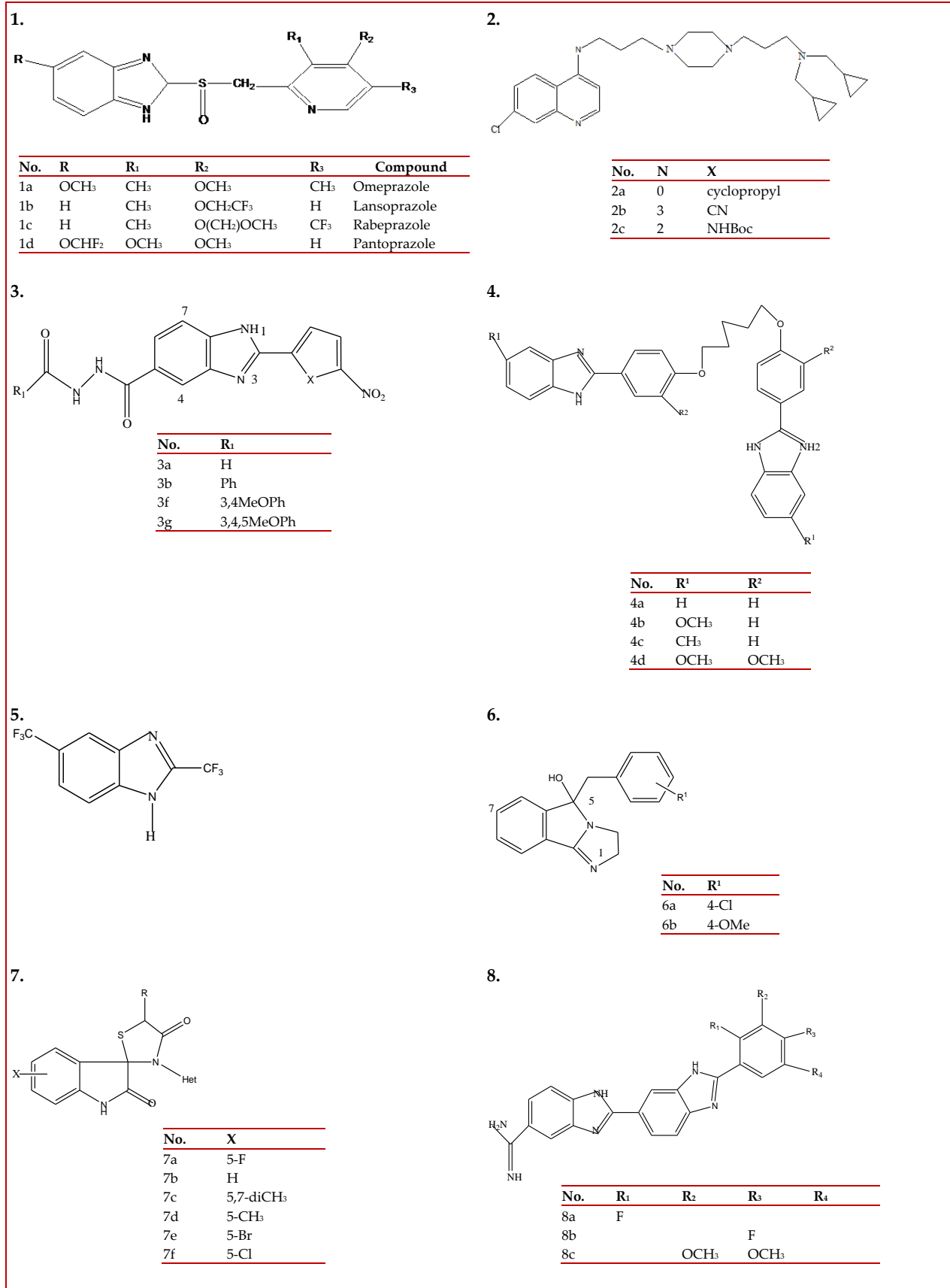
are not subject to the same resistance mechanism would be highly desirable (Camacho *et al.*, 2011).

Ryckebusch *et al.* (2005) reported the synthesis of the activity of new N1-(7-chloro-4-quinolyl)-1, 4-bis (3-aminopropyl) piperazine derivatives against a chloroquine-resistant strain of *Plasmodium falciparum* in which compound 1 is active showing best anti-malarial activity. Camacho *et al.* (2011) reported a series of N-substituted-2-(5-nitrofuran or 5-nitrothiophen-2-yl)-3H-benzo[d]imidazole-5-carbohydrazide derivatives and screened for their anti-malarial efficacy in rodent *Plasmodium berghei*. Gomez *et al.* (2008) reported a series of ten novel hybrids from benzimidazole tested *in vitro* against the protozoa *Trichomonas vaginalis*, *Giardia lamblia*, *Entamoeba histolytica*, *Leishmania mexicana*, and *Plasmodium berghei* showed good anti-malarial activity. Vázquez *et al.* (2006) substituted a series of 2-(trifluoromethyl)-1H-Benzimidazole derivatives and shows good anti-malarial activity. Olmo *et al.* (2011) reported synthesis of several series of imidazo [2, 1-a] isoindol-5-ol derivatives and evaluated against *Plasmodium falciparum*.

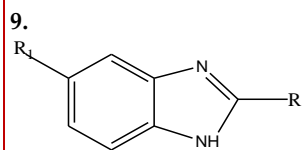
Antifungal activity

Infectious diseases have been serious and growing threatens to human health during the past few decades. The decrease of sensibility to anti-microbial agents in current use has also been increasing for a great variety of pathogens and the resistance to multiple drugs is more and more prevalent for several microorganisms, especially for Gram-positive bacteria and some intractable fungi. Their inhibitory properties as regard representative fungi have been extensively exploited. Especially, it is worthy to note that Fluconazole, the first -line triazole-anti-fungal drug Recommended by World Health Organization (WHO) has established an exceptional therapeutic record for *Candida* infections, and become the first choice in the treatment of infections by *Candida albicans* and *Cryptococcus neoformans* due to its potent activity, excellent safety profile, and favorable pharmacokinetic characteristics. However, Fluconazole is not effective against invasive aspergillosis and is not fungicidal. In addition, extensive clinical use of Fluconazole has resulted in the increasing Fluconazole-resistant *C. albicans* isolates (Fang *et al.*, 2010).

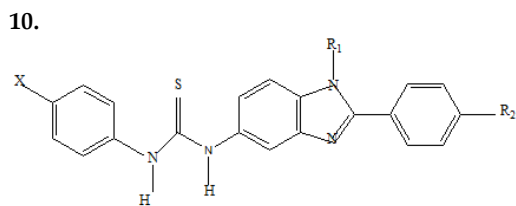
Figure 1: Structures of some established benzimidazole derivatives as antiulcer agents.



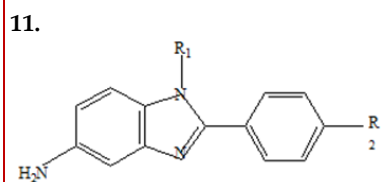
Continued....



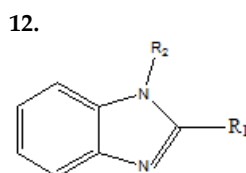
No.	R ₁	R
9a	NO ₂	
9b	NO ₂	
9c	Cl	
9d	Cl	



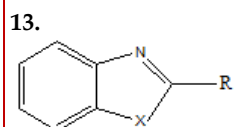
No.	R ₁	R ₂	X
10	-C ₃ H ₇	F	Cl



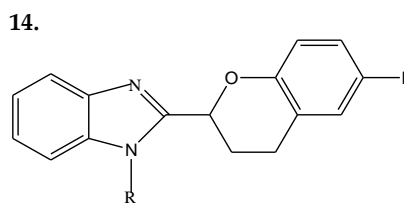
No.	R ₁	R ₂
11	C ₃ H ₇	F



Compound	R ₁	R ₂
12a	CH ₃	H
12b	CH ₃	C ₆ H ₅ -CH ₂
12c	CH ₃	4-CH ₃ -C ₆ H ₄ -CH ₂
12d	CH ₃	4-Cl-C ₆ H ₄ -CH ₂
12e	CH ₃	C ₆ H ₅ -CO
12f	CH ₃	4-CH ₃ -C ₆ H ₄ -CO
12g	CH ₃	4-Cl-C ₆ H ₄ -CO
12h	NH ₂	H
12i	NH ₂	C ₆ H ₅ -CH ₂
12j	NH ₂	4-CH ₃ -C ₆ H ₄ -CH ₂
12k	NH ₂	4-Cl-C ₆ H ₄ -CH ₂
12l	NH ₂	C ₆ H ₅ -CO
12m	NH ₂	4-CH ₃ -C ₆ H ₄ -CO
12n	NH ₂	4-Cl-C ₆ H ₄ -CO

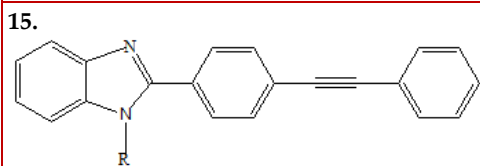


No.	X	R
13a	O	
13b	O	

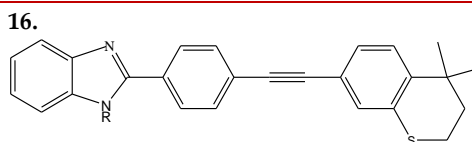


No.	R	No.	R
14a	Methyl	14h	-SO ₂ -CF ₃
14b	Ethyl	14i	-SO ₂ -Phenyl
14c	Propyl	14j	-SO ₂ -C ₆ H ₄ -Me- <i>p</i>
14d	<i>n</i> -Butyl	14k	-Benzyl
14e	-CO-O-Ethyl	14l	<i>p</i> -Fluorobenzyl
14f	-CO-O- <i>tert</i> Butyl	14m	<i>p</i> -Bromobenzyl
14g	-CO-Phenyl	14n	<i>p</i> -Methylbenzyl
		14o	<i>p</i> - <i>tert</i> -Butylbenzyl

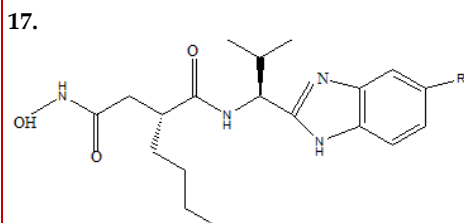
Continued....



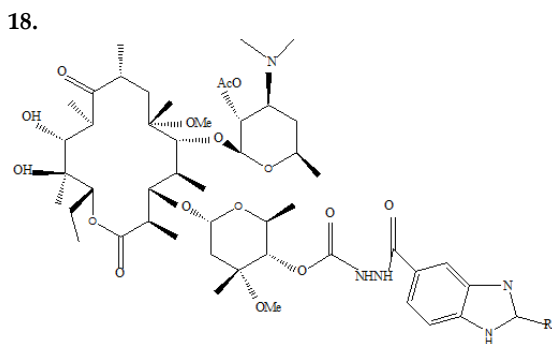
No.	R
15	4-Methylphenylsulfonyl



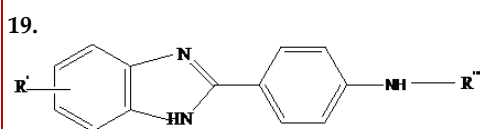
No.	R
16a	Methyl
16b	Ethyl
16d	Butyl
16e	Methyloxycarbonyl



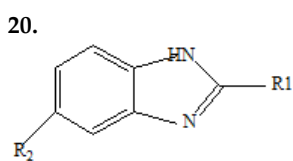
No.	R
17a	H
17b	CH ₃
17c	OCH ₃



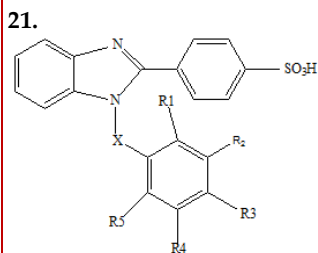
No.	R ³
18a	Phenyl
18b	2-methoxyphenyl
18c	3-methoxyphenyl
18d	2-chlorophenyl
18e	3-chloro-2-hydroxyphenyl



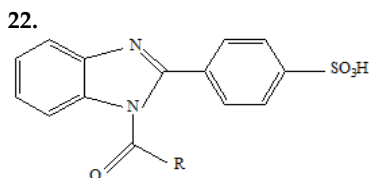
No.	R'	R''
19a	5-NO ₂	H
19b	5-NO ₂	CH ₃ CO
19c	5,6-DiCl	CH ₃ CO



No.	R ₁	R ₂
20a		
20b		
20c		

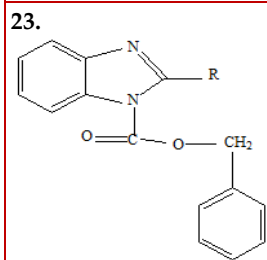


No.	R1	R2	R3	R4	R5	X
21	H	H	OCH ₃	H	H	C=O

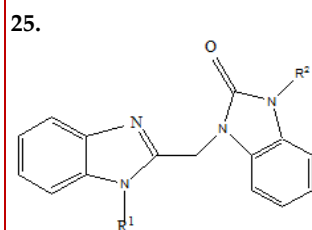


No.	R
22	-CH ₂ -(CH ₂) ₆ -CH=CH-(CH ₂) ₇ -CH ₃

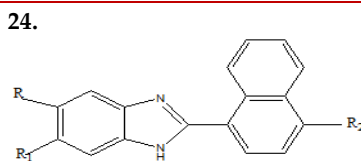
Continued....



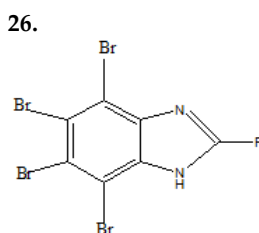
No.	R
23	-CH ₂ -O-C ₆ H ₅ Cl ₂



No.	R ¹	R ²
25a	CH ₂ CH ₂ CH(CH ₃) ₂	CH ₂ -4-C ₆ H ₄ -P(O)(OH) ₂
25b	CH ₂ CH ₂ CH(CH ₃) ₂	CH ₂ -2-C ₆ H ₄ -SO ₃ H
25c		
25d	CH ₂ CH ₂ CH(CH ₃) ₂	
25e	CH ₂ CH ₂ CH(CH ₃) ₂	
25f		Iso-Propyl



No.	R	R ₁	R ₂
24a	CH ₃	CH ₃	H
24b	Cl	H	NH ₂
24c	Cl	Cl	NH ₂



No.	R
26a	NH ₂
26b	
26c	

Dandia *et al.* (2006) reported synthesis of a series of novel spiro [indole-thiazolidinones and screened *in vitro* for anti-fungal activity against *Rhizoctonia solani*, *Fusarium oxysporum* and *Collectotrichum*. Alp *et al.* (2009) reported synthesis of series of 20-arylsubstituted-1H, 10H-[2, 50] - bisbenzimidazolyl-5-carboxamidines and evaluated for their anti-fungal activity. Sharma *et al.* (2009) reported synthesis of a series of novel 2-substituted benzimidazoles, tetrahydrobenzimidazoles and imidazoles and screened there *in vitro* anti-bacterial anti-fungal activities. Kilcigil *et al.* (2006) reported synthesis of a series of novel benzimidazole derivatives and evaluated for anti-fungal activity. Cvetkovic *et al.* (2011) reported Lipophilicity and anti-fungal activity of some 2-substituted benzimidazole derivatives against yeast *Saccharomyces cerevisiae*. Elnima *et al.* (1981) reported for Anti-bacterial and Anti-fungal Activities of Benzimidazole and Benzo-

xazole Derivatives against standard strains and 59 clinical Isolate and compound 13a and 13b is active.

Antibacterial activity

The increase in bacterial resistance has attracted considerable interest in the discovery and development of new classes of anti-bacterial agents. The new agents should preferably consist of chemical characteristics that clearly differ from those of existing agents. Actinonin was first isolated from a Malayan strain of *Actinomyces* and found to show a weak inhibitory activity against Gram-positive and Gram-negative bacteria. However, recently actinonin has been proven to have anti-proliferative effects on human tumor cells. The action mechanism of actinonin is believed to be the inhibition of the peptide deformylase that is a new class of metalloenzyme which is essential for bacterial survival. The hydroxamate group of actinonin, which can

complex with the metal ion in the active pocket of the peptide deformylase, is necessary for its activity. Nevertheless, actinonin lacks *in vivo* efficacy, due to the poor bioavailability (Zhang *et al.*, 2009). Second-generation macrolides such as clarithromycin (CAM) and azithromycin (AZM) (Figure 1) have enjoyed widespread clinical use for the treatment of upper and lower respiratory tract infections as well as genital infections due to their superior antibacterial activity, pharmacokinetic properties and fewer gastrointestinal side (GI) effects compared with first-generation macrolides such as erythromycin (EMA) which is its acid instability, leading to consequential degradation products responsible for its poor pharmacokinetic profile and GI side effects. Their mechanism of action has been elucidated that the macrolides bind reversibly to the nucleotide A2058 in domain V of the 23S rRNA in the ribosomal 50S subunit and block protein synthesis. However, the therapeutic utility of the macrolides has been severely compromised by the emergence of widespread bacterial resistance which has become a serious medical problem worldwide. The predominant mechanism of resistance involves the methylation of A2058 by a ribosomal methylase encoded by the *erm* gene, which confers a high level of resistance to MLSB (macrolide-lincosamide-streptogramin B) antibiotics. Third-generation macrolides known as ketolides such as telithromycin and cethromycin were developed to overcome *erm*-resistant bacteria through interacting with a secondary ribosomal binding site A752 directly in domain II of the 23S rRNA by their C-11-12 carbamate or C-6 side chains in addition to the main interaction of the drugs in domain V (Cong *et al.*, 2011).

Kumar *et al.* (2006) reported synthesis of some novel 2-(6-fluorochroman-2-yl)-1-alkyl/acyl/aryloxy-1H-benzimidazoles and compounds exhibited promising anti-bacterial activity against *Salmonella typhimurium*. Kumar *et al.* (2008) reported synthesis of a series of novel and functionalized benzimidazole derivatives by the condensation of OPDA with 4-bromobenzoic acid and screened for their potential anti-bacterial. Zhang *et al.* (2009) reported synthesis of a series of novel actinonin derivatives containing a benzimidazole heterocyclic linked as amide isostere and evaluated *in vitro* against *Staphylococcus aureus*, *Klebsiella pneumoniae*, and *Sarcina*

lutea. Cong *et al.* (2011) reported synthesis of Novel 400-O-benzimidazolyl clarithromycin derivatives & evaluated for their *in vitro* anti-bacterial activities.

Antiviral activity

Chronic infection with the hepatitis C virus (HCV) is a major risk factor for developing cirrhosis and hepatocellular carcinoma. Approximately 3% of the worldwide population is chronically infected with HCV (Alter and Seeff, 2000; Bialek and Terrault, 2006). A preventive vaccine has not been developed and limits of current therapeutics include serious side effects and therapy usually lasting 48 weeks with only a 50% sustained virological response rate (Bowen and Walker, 2005; De Francesco and Migliaccio, 2005; Fried *et al.*, 2002; Houghton and Abrignani, 2005). A recent major advance was the development of an infectious virus system based on the transfection of human hepatoma cells with genomic HCV RNA (JFH1) isolated from a patient with fulminant hepatitis (Kato *et al.*, 2001; Lindenschmidt *et al.*, 2005; Wakita *et al.*, 2005; Zhong *et al.*, 2005). This cell culture model allows all stages of the HCV life cycle to be studied (Liu *et al.*, 2011). Antiviral properties of various benzimidazole derivatives have been reported in a variety of studies using different virus strains, such as human cytomegalovirus (HCMV), human immunodeficiency virus, and hepatitis B and C virus. Also, amidino-substituted benzimidazoles, such as bis(5-amidino-2-benzimidazolyl) methane (BABIM), showed ability to block respiratory syncytial (RS) virus induced cell fusion. In addition, introducing amidino moiety to benzimidazole ring was shown to possess potent antimicrobial and anti-protozoal activity.

Liu *et al.* (2011) reported Major progress has been made in developing infectious HCV cell culture systems and these systems have been useful in identifying novel HCV anti-viral. Starcevic *et al.* (2007) prepared a set of heterocyclic benzimidazole derivatives bearing amidino substituent at C-5 of benzimidazole ring, by introducing various heterocyclic nuclei (pyridine, N-methyl-pyrrole or imidazole) at C-2, and evaluated their anti-tumor and anti-viral activities. Yadav *et al.* (2010) reported synthesis of a series of 4-[1-(substituted aryl/alkyl carbonyl)-benzimidazol-2-yl]-benzene sulphonic acids and evaluated for anti-fungal activity and

compounds 4-[1-(4-Nitrobenzoyl)-1H-benzimidazol-2-yl] benzenesulfonic acid and 4-(1-octadec-9-enoyl-1H-benzimidazol-2-yl)-benzenesulfonic acid was found to be the most active ones. Gupta *et al.* (2010) reported synthesis of benzimidazoles by refluxing o-phenyldiamine with corresponding carbo-xylic acids and evaluated for anti-viral activity against PRSV on plant *chenopodium amranticular*. Vitale *et al.* (2008) reported a new series of 2-arylbenzimidazoles and evaluated them for anti-viral activity as well as anti-proliferative. Compounds were tested in cell-based assays against viruses' representative of: i) two of the three genera of the *Flaviviridae* family, i.e. *Flaviviruses* and *Pestiviruses*; ii) other RNA virus families, such as *Retroviridae*, *Picornaviridae*, *Paramyxoviridae*, *Rhabdoviridae* and *Reoviridae*; iii) two DNA virus families (*Herpesviridae* and *Poxviridae*). Compounds 24a, 24b and 24c resulted moderate activity only against Yellow Fever Virus. Yu *et al.* (2006) proposed Water-soluble benzimidazol-2-one derivatives with anti-viral activity *in vivo* in the cotton rat model of RSV infection following administration as a small particle aerosol. The acidic compounds 25a, 25b, 25c, 25d, 25e and 25f demonstrated potent anti-viral activity in cell culture. Budow *et al.* (2009) reported a series of benzimidazole derivatives and substituted benzimidazole β -L- and β -D-2'-deoxyribonucleosides and evaluated for anti-viral activity against selected RNA and DNA viruses including HIV-1, BVDV, YFV, DENV-2, WNV, HBV, HCV and human RSV.

CONCLUSION

Benzimidazoles are regarded as a promising class of bioactive heterocyclic compounds that exhibit a range of biological activities like anti-microbial, anti-viral, anti-diabetic, and anti-cancer activity. This comprehensive overview summarizes the chemistry of different derivative of substituted benzimidazole along with their anti-microbial activity.

REFERENCES

- Alp, M., Goker, H., Brun, R., Yıldız, S. (2009). Synthesis and anti-parasitic and anti-fungal evaluation of 20- arylsubstituted-1H, 10H-[2, 5] bisbenzimidazolyl-5-carboxamidines. *Eur. J. Med. Chem.* 44:2002–2008. [DOI](#) PMID:19010569
- Ansari, K.F., Lal, C (2009). Synthesis, physicochemical properties and anti-microbial activity of some new benzimidazole derivatives. *Eur. J. Med. Chem.* 44: 4028–4033. [DOI](#) PMID:19482384
- Budow, S., Kozłowska, M., Gorska, A., Kazimierczuk, Z., Eickmeier, H., Colla, P.L., Gosselin, G., Seela, F. (2009). Substituted benzimidazoles: anti-viral activity and synthesis of nucleosides. *ARKIVOC* iii: 225- 250.
- Camacho J., Barazarte A., Gamboa N., Rodrigues J., Rojas R., Vaisberg A., Gilman R., Charris J. (2011). Synthesis and biological evaluation of benzimidazole-5-Carbohydrazide derivatives as anti-malarial, cytotoxic and anti-tubercular agents. *Bioorg. & Med. Chem.* 19: 2023–2029. [DOI](#)
- Cong, C., Wang, H., Huc, C., Liu, C., Ma, S., Li, X., Cao, J., Ma, S. (2011). Synthesis and anti-bacterial activity of novel 400-O-benzimidazolyl clarithromycin Derivatives. *Eur. J. Med. Chem.* 46:3105-3111. [DOI](#) PMID:21524827
- Cvetkovic, S.O.P.K.D.D. (2011). Lipophilicity and anti-fungal activity of some 2-substituted benzimidazole derivatives. *Chem. Ind. & Chem. Eng. Quart.* 17 (1):9-15. [DOI](#)
- Dandia, A., Singh, R., Merienne, C., Morgant, G., Loupy, A. (2006). Efficient microwave Enhanced regioselective synthesis of a series of benzimidazolyl/triazolyl spiro [indole-thiazolidinones] as potent anti-fungal agents and crystal structure of spiro[3H-indole-3, 20- thiazolidine]-30(1, 2,4-triazol-3-yl)- 2,40(1H)-dione. *Bioorg. & Med. Chem.* 14: 2409–2417. [DOI](#)
- Elnima, E.I., Zubair, M., Badar, A.A. (1981). Anti-bacterial and antifungal activities of benzimidazole and benzoxazole derivatives. *Antimicrob. Agents Chemother.* 19(1):29-32. PMID:7247359 PMID:181352
- Fang, B., Zhou, C.H., Rao, X.C. (2010). Synthesis and biological activities of novel amine-derived bis-azoles as potential anti-bacterial and anti-fungal agents. *Eur. J. Med. Chem.* 45: 4388-4398. [DOI](#) PMID:20598399
- Gomez H.T., Nunez E.H., Rivera I.L., Alvarez J.G., Rivera R.C., Puc R.M., Ramos A.R., Gutierrez, M.D.R., Bacab, M.J.C. Vazquez, G.N. (2008). Design, synthesis and *in vitro* anti-protozoal activity of benzimidazole- pentamidine hybrids. *Bioorg. & Med. Chem. Lett.* 18: 3147–3151. [DOI](#)
- Grocer, H., Kus, C., Boykin, D.W., Yildiz, S., Altanlar, N. (2002). Synthesis and Anti-fungal Properties of Some Benzimidazole Derivatives. *Bioorg. Med. Chem.* 10:2589–2596. PMID:12057648
- Grocer, H., Kus, C., Boykin, D.W., Yildiz, S., Altanlar, N. (2002). Synthesis and Anti-fungal Properties of Some Benzimidazole Derivatives. *Bioorg. Med. Chem.* 10:2589–2596. PMID:12057648
- Gupta, H.C., Jaiswal, V. (2010). Synthesis and Anti-viral Activity of Some New benzimidazoles. *J. Ind. Council Chem.* 27(2):159-162.
- Haugwitz, R.D. (1982). Anti-parasitic agents Synthesis and anti-helmintic activities of novel 2-substituted isothiocyanatobenzoxazoles and benzimidazole. *J. Med. Chem.* 25: 969-974. [DOI](#) PMID:7120286

- Kazmierczuk, Z., Upcroft, J.A., Upcroft, P., Gorska, A., Starosciak, B., Laudy, A. (2002). Synthesis and antiprotozoal activity of some 2-(trifluoromethyl)-1H-benzimidazole bioisosteres. *Acta.Biochim.Pol.* 49: 185–195. PMID:12136939
- Kilcigil, G.A., Altanlar. (2006). Synthesis and anti-fungal properties of some benzimidazole derivatives. *Turk J. Chem.* 30:223-228.
- 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-1H-benzimidazoles. *Eur. J. Med. Chem.* 41:599–604. DOI PMID:16527375
- Kumar, R.V., Vaidya, S.D., Kumar, B.V.S., Bhise, U.N., Bhirud, S.B., Mashelkar, U.C. (2008). Synthesis, anti-bacterial, anti-asthmatic and anti-diabetic activities of novel N-substituted-2-(4-phenylethynyl-phenyl)-1H-benzimidazoles and N-substituted 2[4-(4, 4-dimethylthiochroman-6-yl-ethynyl)-phenyl]-1Hbenzimidazoles. *Eur. J. Med. Chem.* 43:986-995. DOI PMID:17825955
- Liu, S., Nelson, A.C., Xiao, L., Lu, L., Seth, P.P., Davis, D.R., Hagedorn, C.H. (2011). Measuring antiviral activity of benzimidazole molecules that alter IRES RNA structure with an infectious hepatitis C virus chimera expressing Renilla luciferase. *Anti-viral Res.* 89:54–63. DOI PMID:3018537
- Olmo, E.D., Barboza, B., Chiaradia, L.D., Moreno, A., Lerida, J.C., Pacanowska, D.G., Victoria, M., Perez, J.L.L., Giménez, A., Benito, A., Martinez, A.R., Perez, L.M.R.A., Feliciano, A.S. (2011). Anti-malarial activity of imidazo [2, 1- a] isoindol-5-olderivatives and related compounds. *Eur. J. Med. Chem.* 46:5379- 5386. DOI PMID:21940072
- Patil, A., Ganguly, S., Surana, S. (2008). A systemic review of benzimidazole derivatives as an antiulcer agent. *Rasayan Journal of Chemistry*, 1(3): 447-460.
- Ryckebusch A., Fontaine M.A.D., Mouray E., Grellier P., Sergheraerta C., Melnyk P. (2005). Synthesis and anti-malarial evaluation of new N1-(7-chloro-4-quinolyl)-1, 4-bis (3-aminopropyl)-piperazine derivatives. *Bioorg. & Med. Chem. Lett.*15: 297–302. DOI
- Sharma, S., Gangal, S., Rauf, A. (2009). Convenient one-pot synthesis of novel 2-substituted benzimidazoles, tetrahydrobenzimidazoles and imidazoles and evaluation of their *in vitro* antibacterial and antifungal activities. *Eur. J.Med.Chem.* 44:1751-1757. DOI PMID:18472189
- Starcevic, K., Kralj, M, Ester, K., Sabol, I., Grce, M., Pavelic, K., Zamola, G.K. (2007). Synthesis, anti-viral and anti-tumor activity of 2-substituted-5-amidino-benzimidazoles. *Bioorg. & Med. Chem.*15:4419– 4426. DOI
- Tuncbilek, M., Kiper T., Altanlar, N. (2009). Synthesis and *in vitro* anti-microbial activity of some novel substituted benzimidazole derivatives having potent activity against MRSA. *Eur. J. Med. Chem.* 44:1024–1033. DOI PMID:18718694
- Vazquez, G.N, Vilchis, M.D.M.R., Mulia, L.Y., Meléndez, V., Gerena, L., Campos, A.H., Castillo, R., Lui, F.H. (2006). Synthesis and anti-protozoal activity of some 2-(trifluoromethyl)-1H- benzimidazole bioisosteres. *Eur. J. Med. Chem.* 41: 135–141. PMID:16260067
- Vitale, G., Carta, A., Loriga, M., Paglietti, G., Colla, P., Busonera, B., Collu, D., Loddo, R. (2008). 2-Arylbenzimidazoles as Anti-viral and Anti-proliferative Agents-Part 1. *Med. Chem.* 4:605-615. DOI PMID:18991746
- Yadav, S., Kumar, P., Clercq, E.D., Balzarini, J., Pannecouque, C., Dewan, S.K., Narasimhan, B. (2010). 4-[1-(Substituted aryl/alkyl carbonyl)-benzimidazol-2-yl]-benzenesulfonic acids: Synthesis, anti-microbial activity, QSAR studies, and anti-viral evaluation. *Eur. J. Med. Chem.* 45:5985-5997. DOI PMID:20971531
- Yu, K.U., Wang, X.A., Civiello, R.L., Trehan, A.K., Pearce, B.C., Yin, Z., Combrink, K.D., Gulgeze, H.B., Zhang, Y., Kadow, K.F., Cianci, C.W., Clarke, J., Genovesi, E.V., Medina, I., Lamb, L., Wyde, P.R., Krystal, M., Meanwell, N.A. (2006). Respiratory syncytial virus fusion inhibitors. Part 3: Water-solub benzimidazol-2-one derivatives with anti-viral activity *in vivo*. *Bioorg. & Med. Chem. Lett.* 16:1115–1122. DOI
- Zhang, D., Wang, Z., Xu, W., Sun, F., Tang, L., Wang, J. (2009). Design, synthesis and anti-bacterial activity of novel actinonin derivatives containing benzimidazole heterocycles. *Eur. J. Med.Chem.* 44:2202- 2210. DOI PMID:18617291