Annals of Phytomedicine 11(2): 102-113, 2022

DOI: http://dx.doi.org/10.54085/ap.2022.11.2.11

Annals of Phytomedicine: An International Journal

http://www.ukaazpublications.com/publications/index.php

Print ISSN : 2278-9839 Online ISSN : 2393-9885

Review Article : Open Access

Benzimidazole as promising antimicrobial agents: A systematic review

Mohd Anas, Arun Kumar◆, Kuldeep Singh, Syed Misbahul Hasan, Shom Prakash Kushwaha, Shubham Kumar Maurya, Priyanka Yadav and Suprabha Nishad

Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Integral University, Kursi Road, Lucknow-226026, Uttar Pradesh, India

Article Info

Article history

Received 10 October 2022

Revised 29 November 2022

Accepted 30 November 2022

Published Online 30 December-2022

Keywords

Heterocyclic compound

Benzimidazole derivatives

Antibacterial activity

Antifungal activity

Antiviral activity

Abstract

Benzimidazole is an aromatic heterocyclic organic molecule which contains nitrogen. The benzene ring is fused with the imidazole ring to form this bicyclic compound. It is an essential pharmacophore and favoured structure in pharmaceutical chemistry with antibacterial, antitubercular, antiulcer, antihypertensive, analgesic, antiviral, antifungal, antipsychotic, antioxidant, antiinflammatory, antiprotozoal, anticancer and antihistaminic properties. These categories of medications encourage the creation of more effective and significant pharmaceuticals.The current article extensively covers various procedures for synthesis of 2-substituted benzimidazole and its analogues using various reactants, catalysts, solvent conditions and microwave irradiation to obtain an economical, eco-friendly, less time-consuming procedure that ensures good yield and quick isolation of the pure product and their antimicrobial activities.

1. Introduction

Benzimidazoles are heterocyclic aromatic organic molecules with broad pharmacophore appeal in pharmaceutical chemistry. One of the most beneficial scaffolds for the discovery and synthesis of new medicinal compounds is the benzimidazole ring (Tewari *et al.*, 2006; Mishra *et al.*, 2006). Benzimidazole is a six-membered bicyclic heteroaromatic molecule in which the benzene ring is fused to the 4- and 5-positions of the imidazole ring. The benzimidazole ring contains two amphoteric nitrogen atoms in positions 1 and 3 that show both acidic and basic characteristics (Wright *et al.*, 1951). This nitrogen-containing heterocyclic moiety exhibited antibacterial, anticancer, anthelmintic, anticonvulsant, antioxidant (Singh *et al.*,2016) antiinflammatory, antifungal, antipsychotic, antihistaminic and antiviral effects (Alaqeel *et al.*, 2016; Shatha Ibrahim *et al.*, 2016). The benzimidazole ring occurs in two tautomeric forms, with the hydrogen atom positioned on one of the two nitrogen atoms (Phillip *et al.*, 1951).

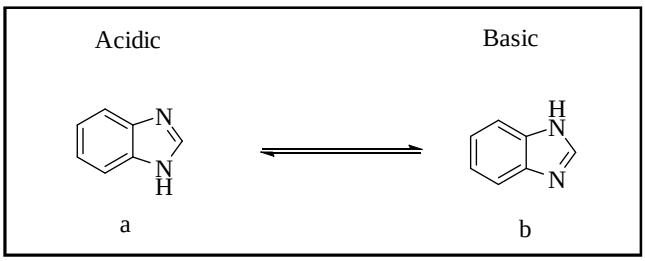


Figure 1: Structure of benzimidazole.

Corresponding author: Dr. Arun Kumar

Associate Professor, Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Integral University,Kursi Road, Lucknow-226026, Uttar Pradesh, India

E-mail: arun@iul.ac.in, arun.mpharm@gmail.com

Tel.: +91-7985489405

Table 1: Properties of benzimidazole

IUPAC name	1*H*-1,3-Benzimidazole
Molecular formula	$C_7H_6N_2$
Molar mass	118.139 g·mol^{-1}
Melting point	170 to 172°C (338 to 342°F; 443 to 445 K)
Boiling point	360°C
Appearance	Whitish
Odour	Characteristics

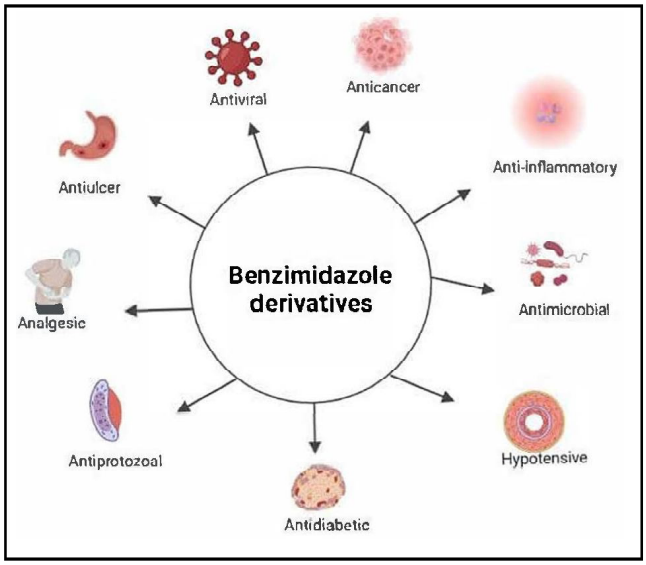


Figure 2: Biological activities of benzimidazole derivatives.

Numerous research has been undertaken in recent years that have generated highly exciting findings about the chemistry, structure-activity connection and biological activities of numerous benzimidazole-based compounds. The numerous biological actions of molecules containing the benzimidazole nucleus have encouraged scientists (Fahim *et al.*, 2017) all around the world to develop and synthesise eco-friendly (Sudha *et al.*, 2020) and readily available (Punit *et al.*,2019) efficacious (Thakur *et al.*, 2020) many benzimidazole derivatives. A series of latest released patents on the benzimidazole nucleus are given below (Bansal *et al.*, 2012; Silakari *et al.*, 2012).

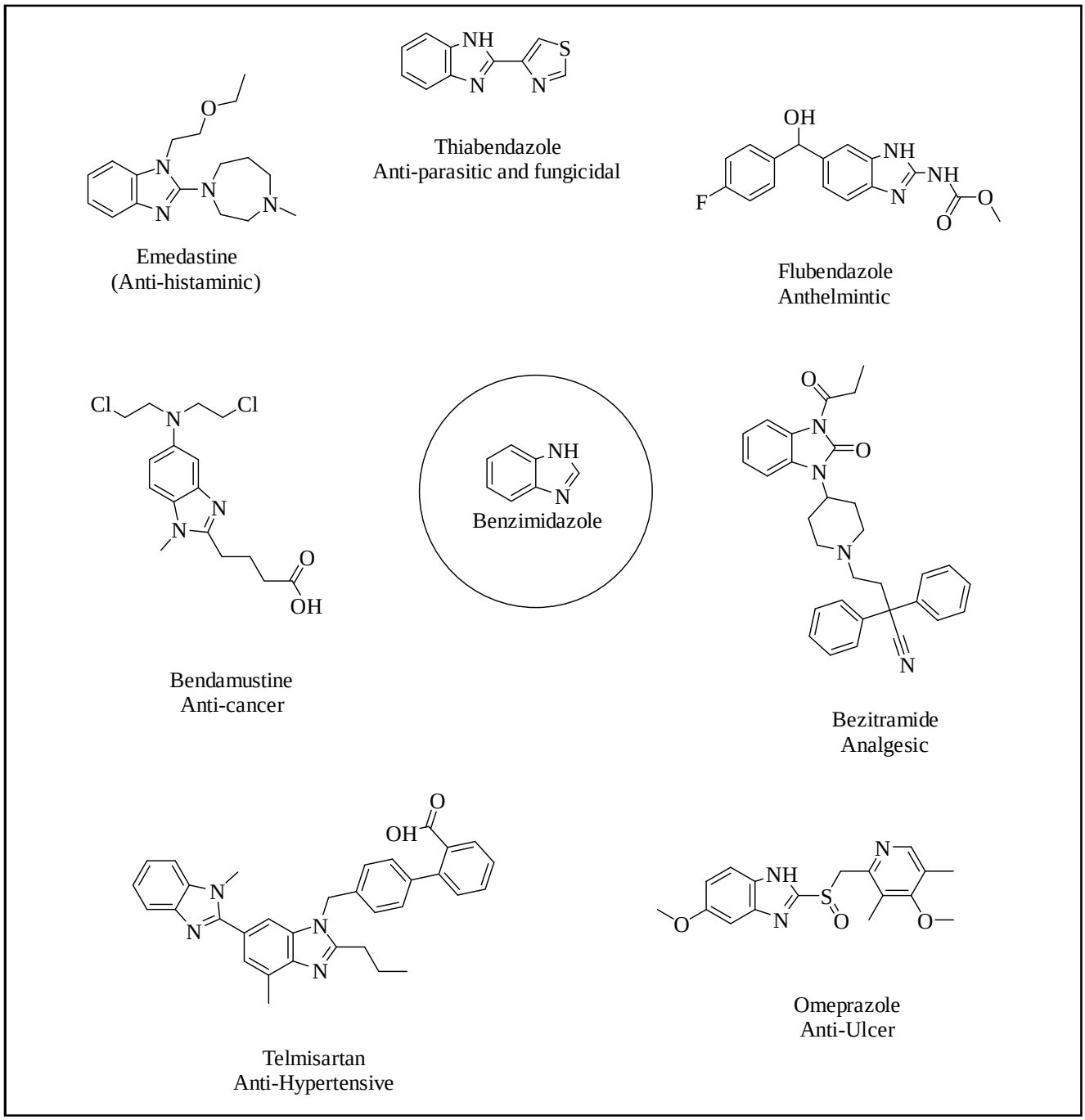
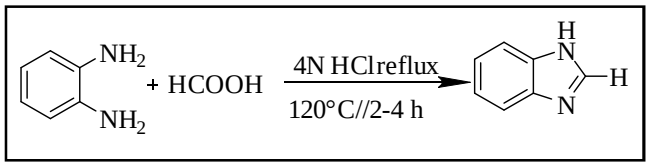


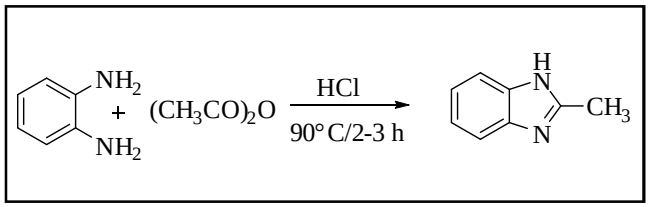
Figure 3: Some marketed drugs containing benzimidazole.

2. Material and Methods

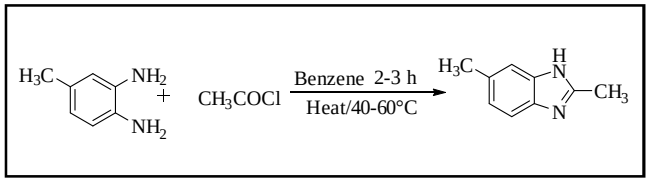
Method 1: Carboxylic acid reaction and its derivatives: By refluxing o-phenylenediamine and formic acid in acidic conditions (4NHCl) at 120ºC for 2 to 4 h to achieve 75% yield of benzimidazole. This is a typical laboratory technique for producing benzimidazole (Wundt *et al.*, 1878).



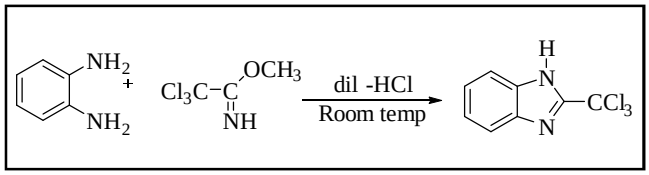
Method 2: Using acidic anhydride: O-phenylenediamine was condensed with acetic anhydride for 2 to 3 h at 90ºC in the presence of diluted HCl. The yield of 2-methyl benzimidazole was determined to be 68% (Wagner *et al.*, 1946).



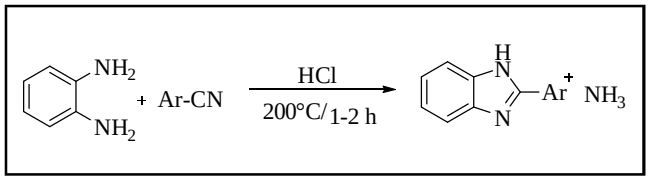
Method 3: Using acetyl chloride: The yield of 2,6-dimethyl benzimidazole is 71% when condensed with acetyl chloride and 5-methyl-1, 2-diaminophenyl are combined at 40 to 60ºC for 2 to 3 h in benzene (Park *et al.*, 2014).



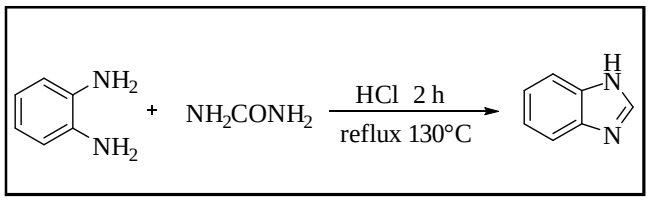
Method 4:Using imino-ethers imidates: When o-phenylene diamine and trichloro-acetimidate were combined at room temperature with dilute hydrochloric acid, 81% of 2-trichloromethyl benzimidazole was produced (Vishwanath *et al.*, 2015).



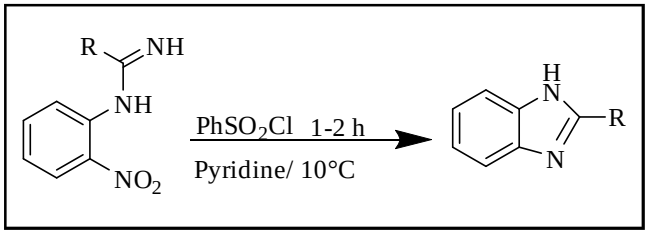
Method 5: Nitrile-related reaction: By combining substituted nitrile with o-phenylenediamine at 200ºC for 1-2 h it produced 2-substituted benzimidazole with a 77% yield (Singh *et al.*, 2019).



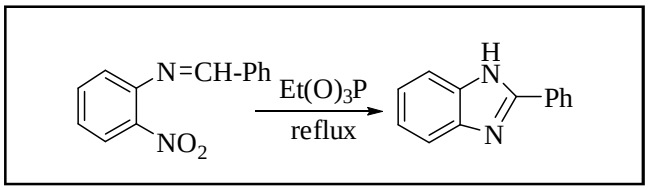
Method 6: Using urea: Benzimidazole is produced with a 78% yield when o-phenylene-diamine and urea are refluxed at 130ºC for 2 h while being in the presence of hydrochloric acid (Shibinskya *et al.*, 2010).



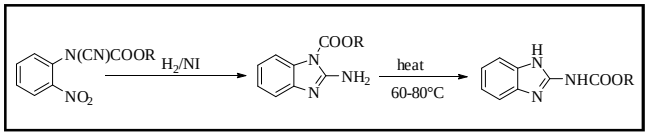
Method 7: By amidine: At 10ºC for 1 to 2 h the derivative of amidine interacts with the phenylsulfonyl-chloride in pyridine to produce an 81% yield of 2-substituted benzimidazole (Rathod *et al.*, 2013).



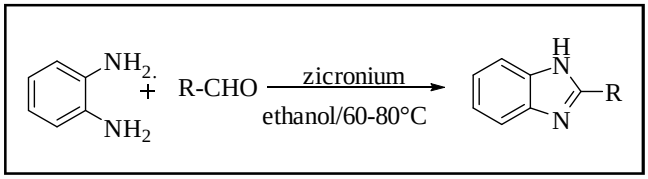
Method 8: *Via* o-substituting N-benzamidineanilines: When N-benzyl-2-nitroaniline is refluxed at 80 to 100ºC for 2 h with the reducing agent triethyl phosphate, 89% of 2-phenyl benzimidazoles are produced (Chiyanzu *et al.*, 2005).



Method 9: Derived from ortho nitroarylamines and ortho-dinitroarenes: Benzimidazoles are created by reducing ortho-nitroarylamines with a reducing agent such as nickel. Following reduction, ortho-nitroarylamines are transformed into 1-alkyl-2-amino-benzimidazole, which is subsequently heated to 60-80°C to generate a good yield of 2-substituted benzimidazole. Because of the high yield of this method, it is used in industry to produce large quantities of benzimidazole (Panneerselvam *et al.*, 2010).

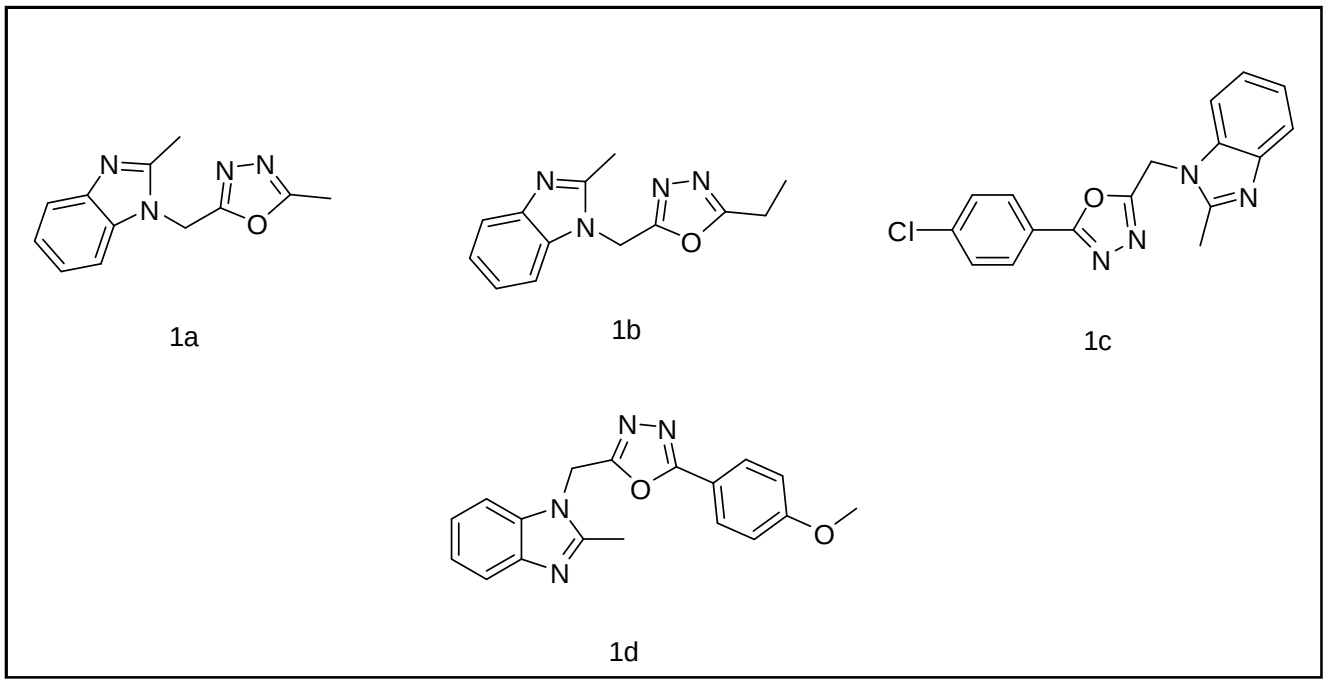


Method 10: Green synthesis of benzimidazole: o-phenylene-diamine with substituted aldehydes or ketone heated under the influence of greenish zirconium catalyst for 3-4 h at 60-80°C. These methods provide roughly 82% of the product yield while being economical and environment friendly (Sriram *et al.*, 2013).

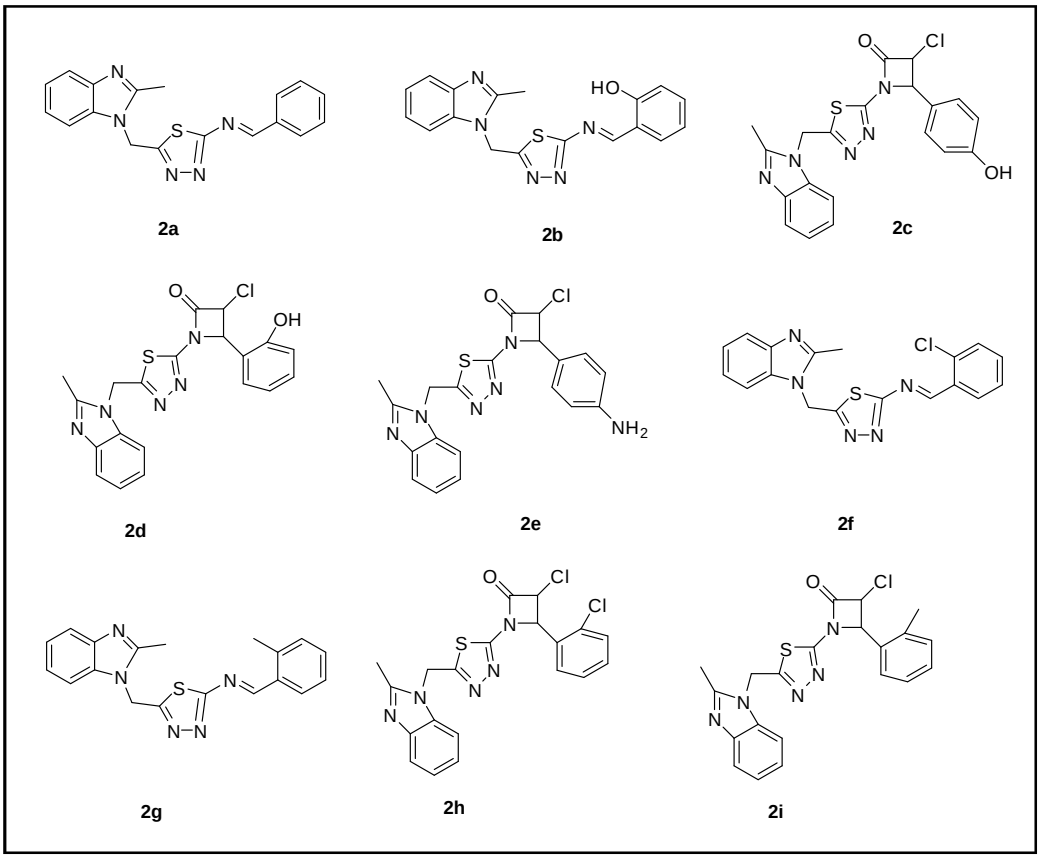


3. Antimicrobial activity

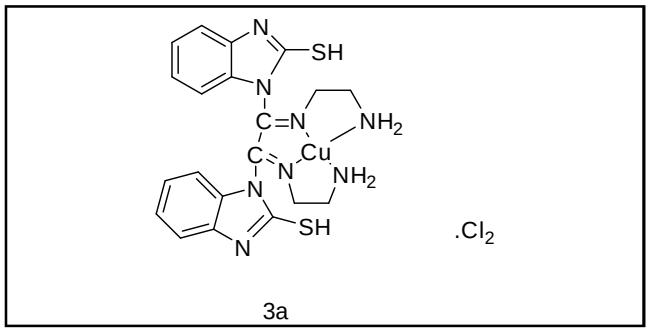
Ansari *et al.* (2009) used nucleophilic substitution reactions to create 2-substituted 1H-benzimidazole derivative and tested their antimicrobial activity as opposed to various microbes. Compound 1a, 1b,1d demonstrated strong bacterial resistance, while compound 1c demonstrated strong action against fungi. According to SAR studies, increasing the number of side-chain carbon atoms atposition-2 of the oxadiazole moietyand the para-substituted phenyl nucleus increases antimicrobial effectiveness against *C. albicans, B. subtilis, S. aureus.*



Ansari *et al*. (2009) reported number of 2-mercaptobenzimidazole derivative, their *in vitro* antibacterial effectiveness is determined by the cup-plate agar diffusion technique to wards *C. albicans, A. flavus, B. subtilis, E. coli* and *A. niger*. Studies of the relationships between structure and activity identified compounds with ortho chloro, ortho-methyl, hydroxide and para amine (2b, 2c, and 2d). It became evident a group present in the phenyl ring, similar to that in the unsubstituted compound 2a, demonstrated high antibacterial activity potential as reference drugs.

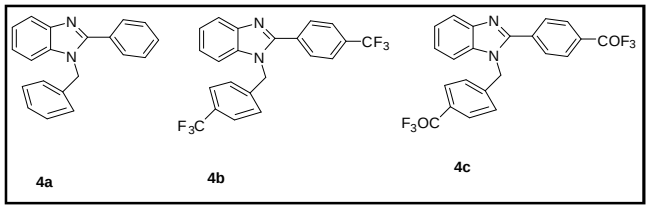


Arjmand *et al* .(2005). By condensation of 2-mercaptobenzimidazole and diethyl oxalate, a novel Cu (II) complex benzimidazole derivatives was created. It was then tested for its antibacterial activity towards *S. aureus, E. coli* and *A. niger*. Compound 3a has the strongest antibacterial and antifungal effects.



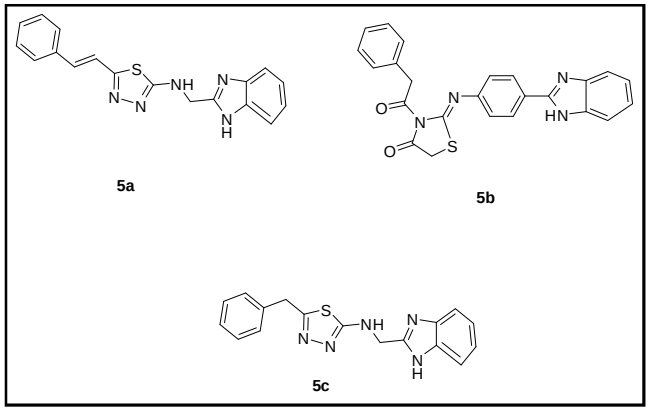
3a

Bandyopadhyay *et al.* (2011) Al_2O_3-Fe_2O_3 nanocrystals were used as heterogeneous catalysts in the mild reaction conditions for the synthesis of a new class of 1,2-disubstituted benzimidazole derivatives for antimicrobial effectiveness towards *S. aureus, S. dysenteriae, B. cereus, V. cholerae,* and *E. coli.* The activity was evaluated (Kirby-Bauer disc diffusion method). When compared to conventional ciprofloxacin, compounds 4a, 4b, and 4c displayed good action whereas ciprofloxacin killed these bacteria after 48 h, compounds 4a-4c produced 100% bactericidal effectiveness towards tested microbes within 24 h.



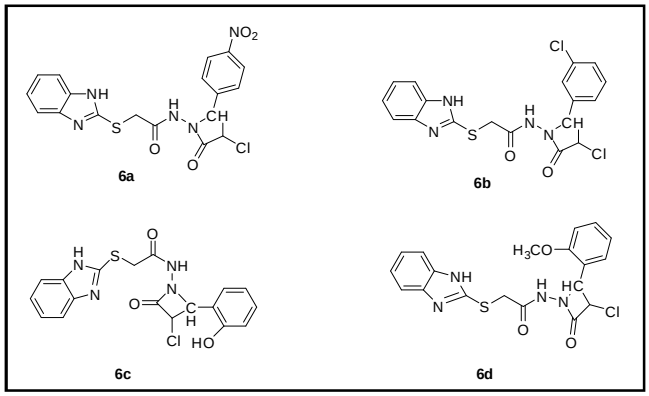
4a 4b 4c

Barot *et al*. (2017) created novel benzimidazole derivatives and tested them against *C. albicans, E. faecalis, P. aeruginosa, B. cereus, E. coli, K. pneumoniae, S. aureus, A. niger,* and *F. oxyspora*. Compounds 5a and 5b showed strong antibacterial activity, compound 5c showed strong antifungal activity.



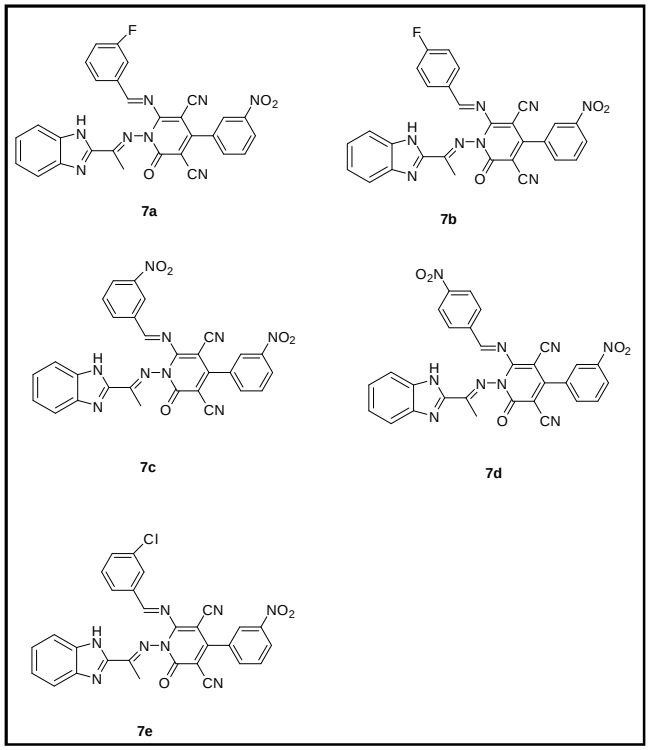
5a 5b 5c

Desai *et al.* (2006) synthesised some 2-mercapto benzimidazole and β-lactam segment derivative containing -CONH- and their antimicrobial effectiveness was examined through Kirby-Bauer disc diffusion technique and *in vitro* antibacterial capability was examined towards standard tested strains using streptomycin and fluconazole. Compound 7a demonstrated excellent inhibited behaviour to wards *B. subtilis*, compound 7b demonstrated significant efficacy to wards *S. aureus*, *E. coli* and compound 7c demonstrated significant inhibitory behaviour to wards *A. niger*. Compound 7d demonstrated excellent efficacy to wards *C. krusei***.**



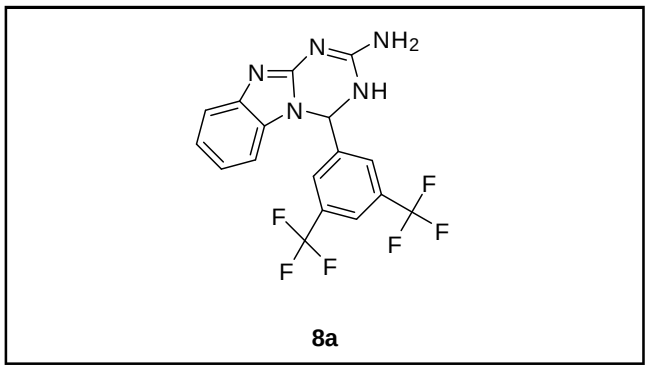
6a 6b 6c 6d

Desai *et al*. (2014) identified new 2-pyridone-containing benzimidazoles that were tested by the traditional broth dilution method for their antibacterial efficacy towards *A. clavatus, C. albicans, S. pyogenes, E. coli, P. aeruginosa, S. aureus, A. niger* compared to chloramphenicol, the produced compounds 7a, 7b, 7c, and 7d with electron-withdrawing group (nitro) at meta position had higher antimicrobial effectiveness, compound 7e showed the best antifungal action as compared to ketoconazole.



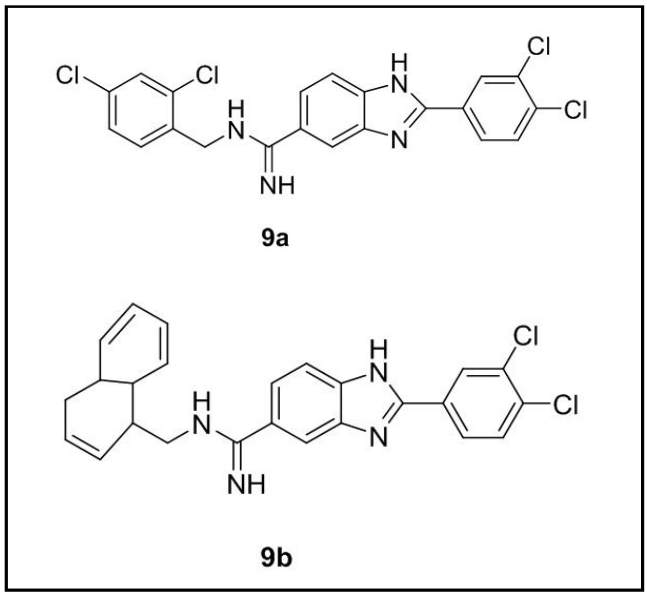
7a 7b 7c 7d 7e

Dolzhenko *et al.* (2005) by using the two fold serial dilution procedure, new benzimidazole compound was created and examine their *in vitro* for antimicrobial effectiveness. When compared to common medication tetracycline, compound 8a showed good antibacterial activity.



8a

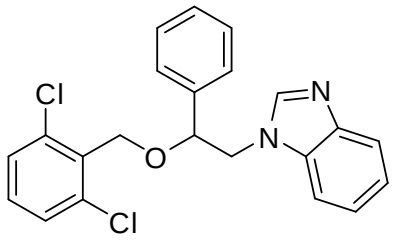
Goker *et al*. (2005) by using the tube dilution method, newly synthesised substituted benzimidazole carboxamidine compounds were tested for their antibacterial efficacy against a selection of microorganisms. The antibacterial activity of compounds 9a and 9b was substantial and comparable to that of conventional medications (ampicillin and sultamicillin).



9a

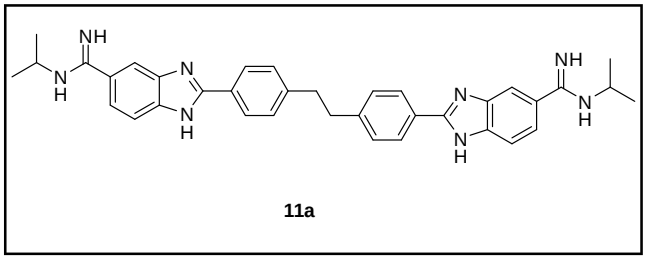
9b

Guven *et al.* (2007) identified some phenyl-substituted benzyl ethers and benzimidazoles and assessed their antibacterial efficacy against a number of microbial species. Compound 10 a is produced derivative which has a good antimicrobial effect and is compared tooriginal medication.



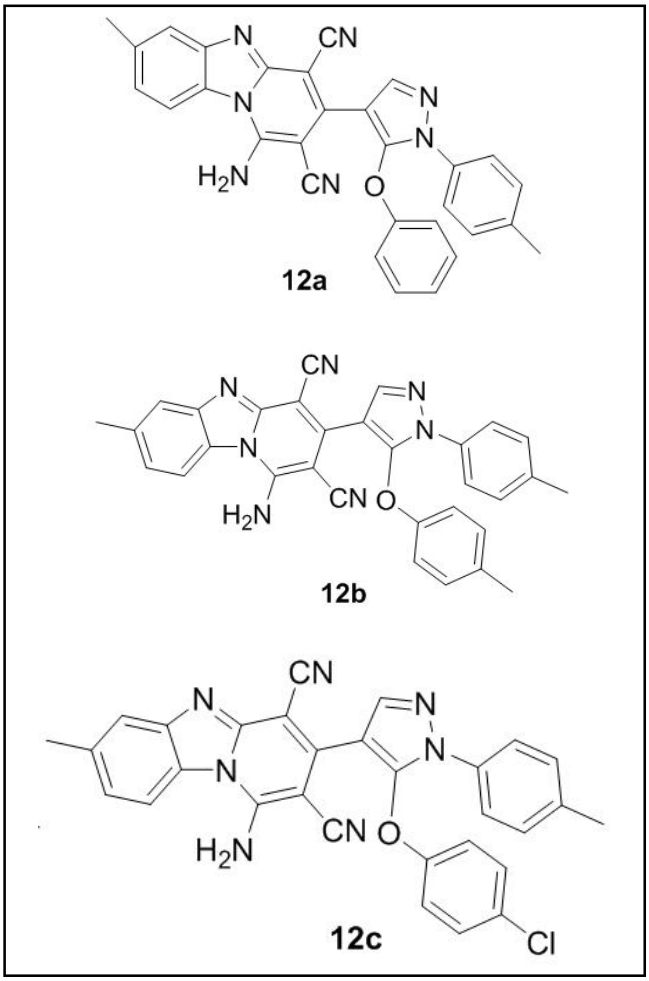
10a

Hu *et al.* (2009) created compounds containing bis-benzimidazole diamidine, their effectiveness against test species and existing treatments were evaluated (penicillin G, vancomycin and ciprofloxacin). Vancomycin was outperformed in terms of compound 11a as powerful antibacterial action.



11a

Jardosh *et al*. (2013) developed apyrido[1,2-a] benzimidazole derivative using the broth microdilution technique and tested their *in vitro* antimicrobial activity towards *C. albicans, V. cholerae, S. typhi, B. subtilis, S. pneumoniae, C. tetani, A. fumigatus,* and *E. coli*. Compounds 12a-12c from the produced derivatives showed good antibacterial efficacy when compared to conventional medications.

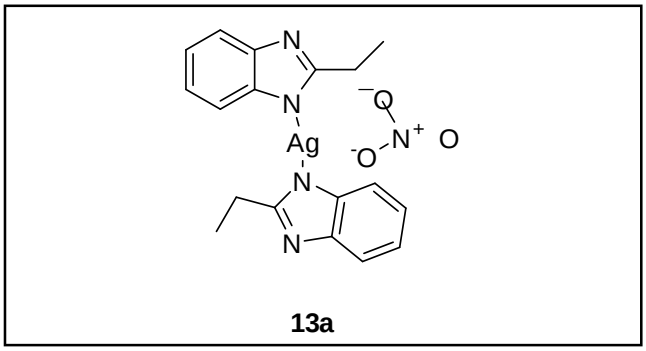


12a

12b

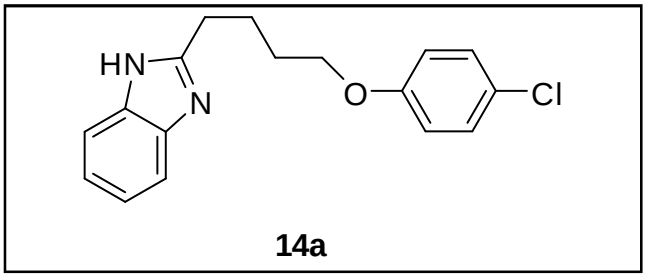
12c

Kalinowska-Lis *et al.* (2014) created synthetic benzimidazole silver (I) complexes and tested them towards *C. albicans, S. aureus* and *S. epidermidis* for antibacterial activity. Comparing compound 13a to the conventional medications $AgNO_3$ and silver sulfadiazine, compound 13a showed good antifungal but modest antibacterial action.



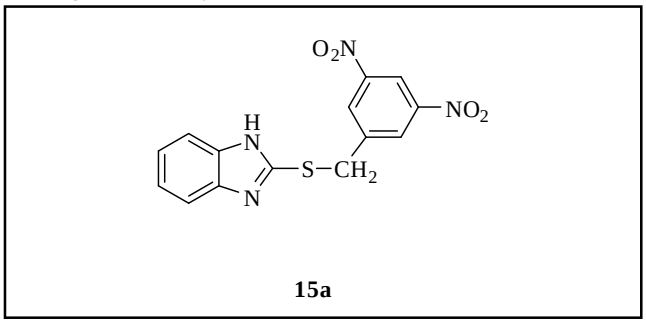
13a

Khalafi-Nezhad *et al.* (2005) developedchloro aryloxyalkyl benzimidazole derivativesusing the disc diffusion method and examined their *in vitro* antimicrobial efficacy towards *S. aureus* and *S. typhi*. Compound 14a effectively combated the indicated microbial species when evaluated for bacterial activity.



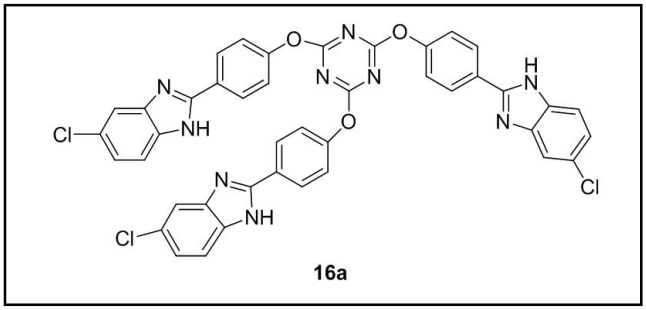
14a

Klimesova *et al.* (2002) produced some 2-alkylsulphanyl benzimidazoles and tested their *in vitro* against a number of different species of mycobacteria and fungi using isoniazid and ketoconazole as standards. Among the produced substances, 15a had notable antifungal and antimycobacterial effects.

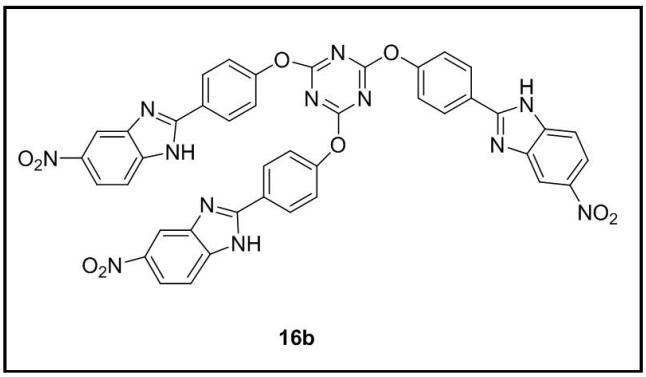


15a

Koc *et al.*(2010) developed some tripodal-benzimidazole derivatives using the standard disc diffusion method and tested their antimicrobial efficacy towards *E. coli, B. subtilis and S. aureus*. Compounds 16a-16b showed promising antimicrobial activity as gen-tamycin a reference.

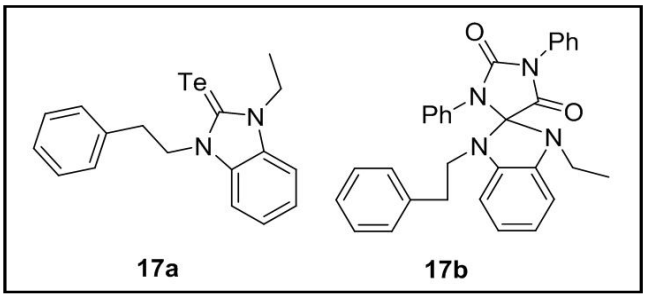


16a



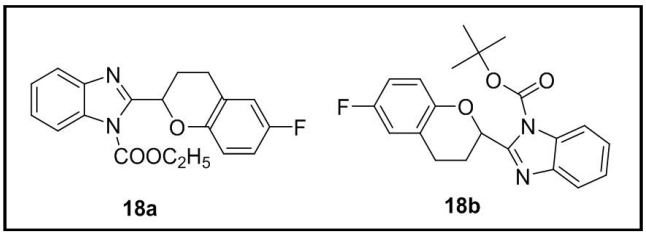
16b

Kucukbay *et al.*(2003) created novel electron-rich olefin benzimidazole derivatives and assessed for their *in vitro* antibacterial efficacy against *C. tropicalis* and *C. albicans*. Compound 17a-17b, were discovered to be the most successful antibacterial activity as standard medication.



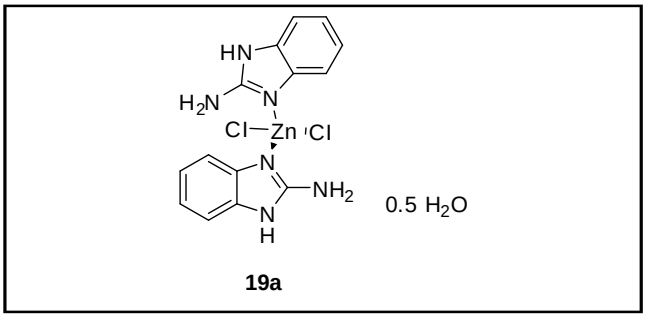
17a 17b

Kumar *et al.* (2006) produced some substituted benzimidazole scaffolds and tested them towards *S. typhimurium* and *S. aureus* for their *in vitro* antibacterial properties, and contrasted them to the gold standard cephalexin. Compounds 18a and 18b displayed dismal antibacterial efficacy.



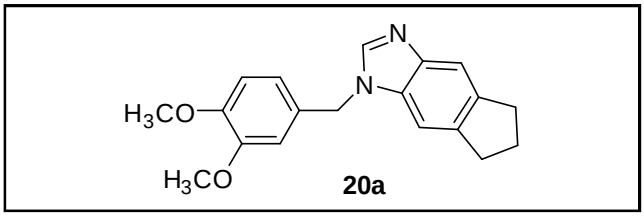
18a 18b

Lopez-Sandoval *et al.* (2008) presented variety of benzimidazole with complexes of cobalt (II), zinc (II) and assessed their antibacterial activity through disc diffusion and antibiotic microbiological tests towards *S. aureus, P. vulgaris, P. aeruginosa, S. Typhi, E. coli* and *M. luteus*. Complex 19a, one of the produced compounds showed good antibacterial efficacy.



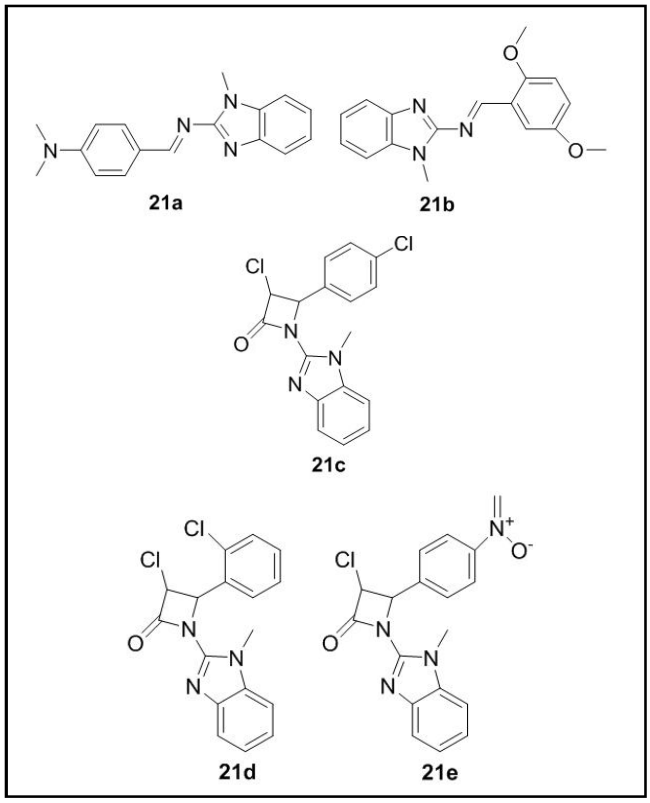
19a

Mehboob *et al*. (2015) identified some second-generation benzimidazole derivatives and tested them against *F. tularensis, E. coli* and MRSA for their antibacterial activity. The synthesised substance 20 a showed effective antibacterial action against particular bacterial strains.

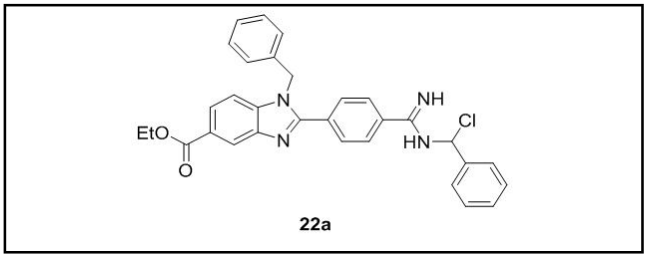


20a

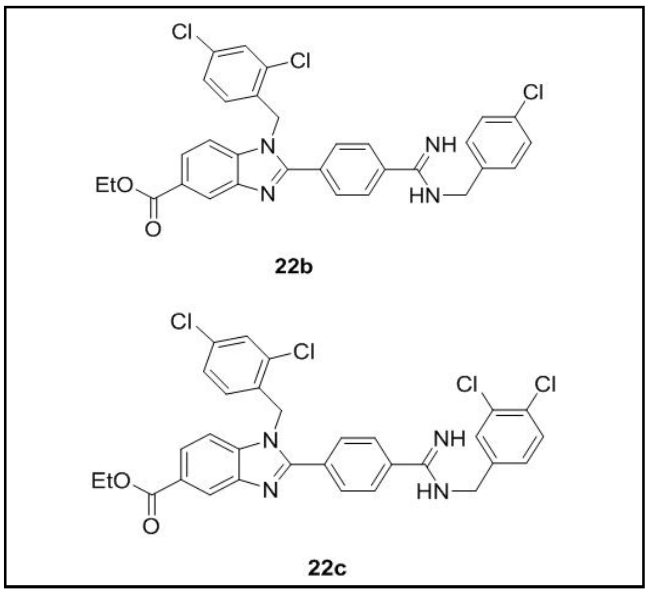
Noolvi *et al.* (2014) produced some 1H-benzimidazole azetidine-2-one scaffolds using an agar diffusion technique and examined their antibacterial activity against *P. aeruginosa, E. coli, B. pumillus,* and *S. aureus*. Compounds 21a-21e demonstrated good antimicrobial efficacy as standard ampicillin.



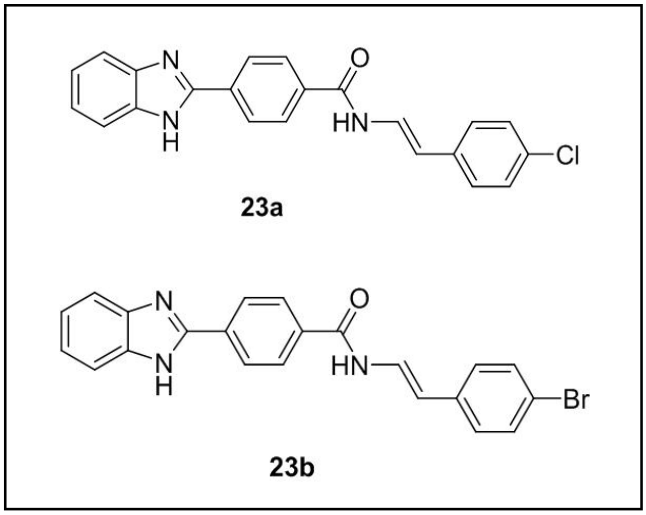
Ozden *et al.* (2005) created some benzimidazole-5-carboxylic acid alkyl esters and tested their antibacterial effectiveness against methicillin-resistant *C. albicans, S. aureus, S. faecalis* and *E. coli*. Compound 22a, 22b, and 22c revealed potential antibacterial activity as reference medicines.



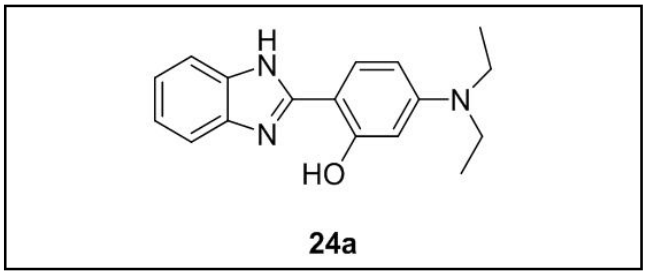
22a



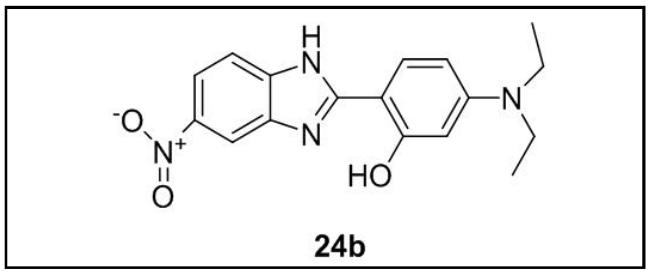
Ozkay *et al*. (2010) developed number some benzimidazole compound with hydrazone moiety and tested their *in vitro* antibacterial activity towards *P. aeruginosa, L. cytogenes, E. faecalis, B. subtilis, E. coli* ATCC 35218, *S. aureus, K. pneumoniae, E. coli* ATCC 25922, *etc*. Comparing these compounds to conventional medicines (chloramphenicol and ketoconazole) 23a and 23b in this series shown potential antibacterial and antifungal properties.



Padalkar *et al*. (2016) developed novel class of benzimidazole derivatives, using serial dilution technique and they were examined towards *S. aureus, C. albicans, E. coli* and *A. niger*. Compounds 24a and 24b shown substantial activity as conventional medicines.

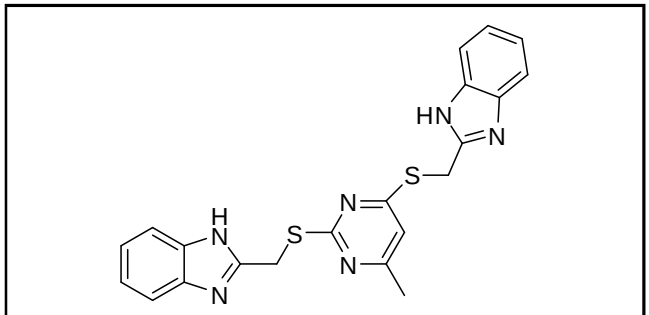


24a



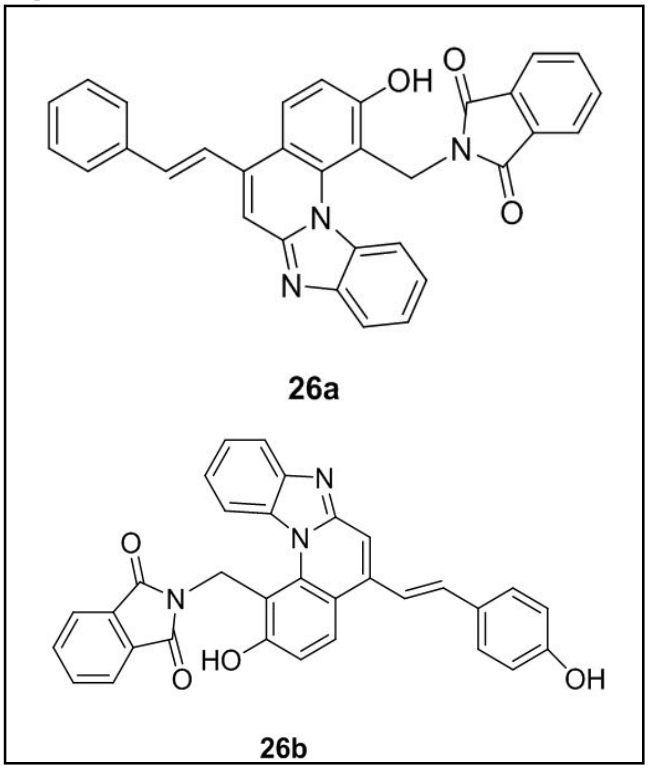
24b

Seenaiah *et al.* (2014) developed some benzimidazole derivatives using broth dilution and agar well diffusion (ZI) techniques and tested towards microbial species for their antibacterial efficacy. Compound 25 a showed potential activity as compared to conventional medicines.



25a

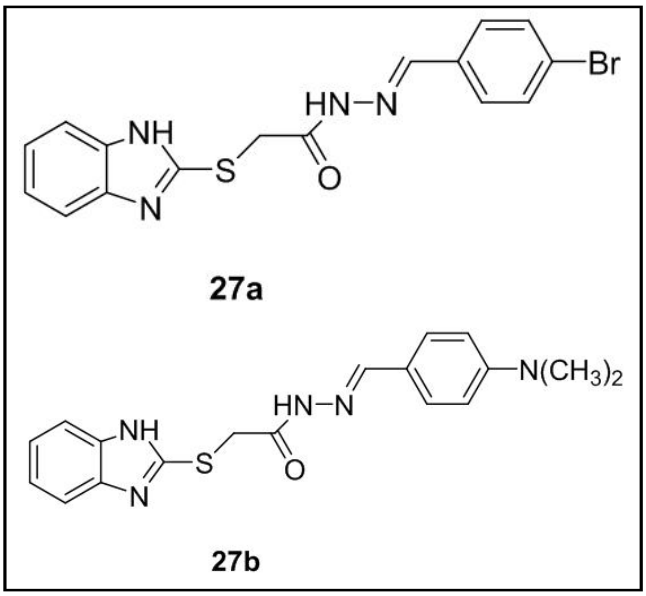
Tiwari *et al.* (2007) created some benzimidazole scaffolds using agar plate method and tested their *in vitro* for antifungal potential towards *A. niger* and *A. flavus*. Compounds 26a and 26b from the synthesised derivatives demonstrated excellent antimicrobial activity against amphotericin B.



26a

26b

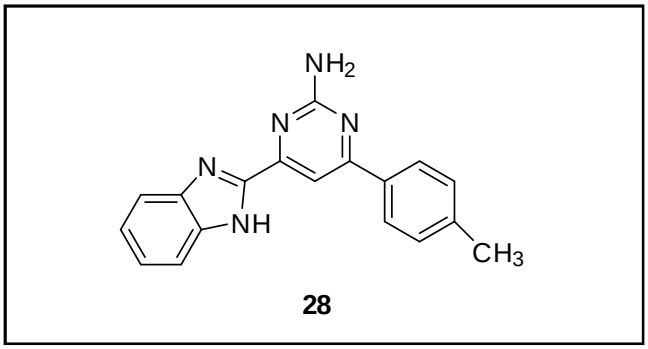
Yadav *et al.* (2018) synthetically produced 2-substituted benzimidazole derivatives and tested towards microbial species for their antimicrobial efficacy. Compound 27a shown excellent antimicrobial activity when compared to standard cefadroxil while as compound 27b demonstrated the highest antimicrobial potential against *A. niger* (MIC = 0.018 mM).



27a

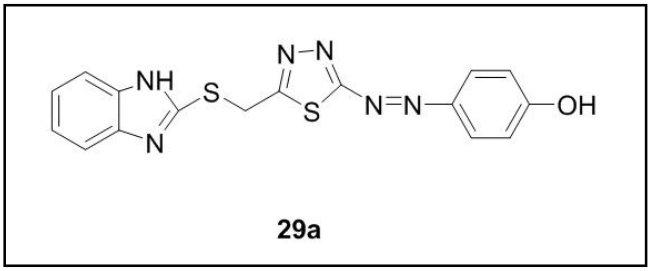
27b

Liu *et al.* (2018) developed some aminopyrimidinyl benzimidazoles as antibacterial agents and tested towards methicillin resistant *S. aureus, A. flavus* and *E. coli.* Compound 28 demonstrated good antibacterial activity than the usual medications chloromycin, norfloxacin and fluconazole.

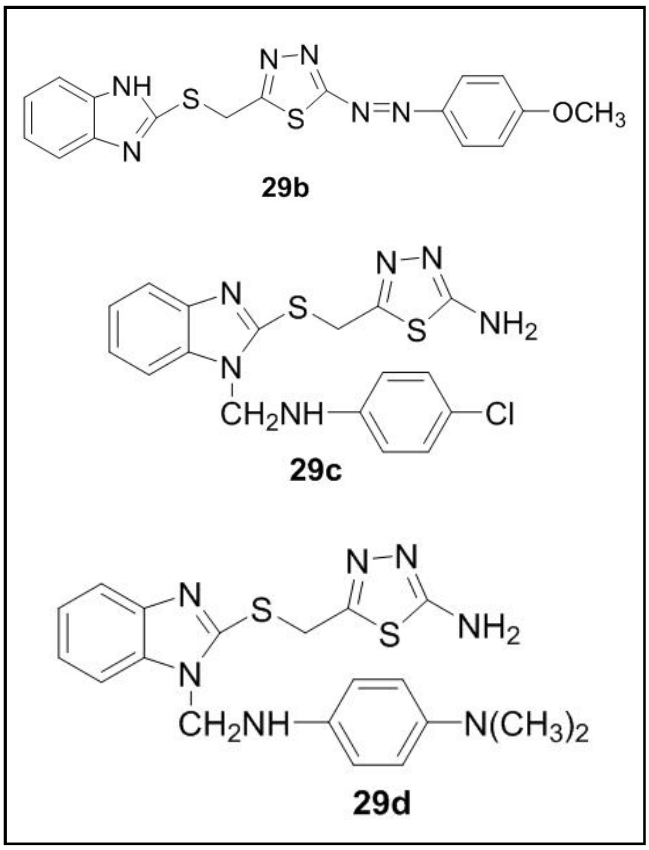


28

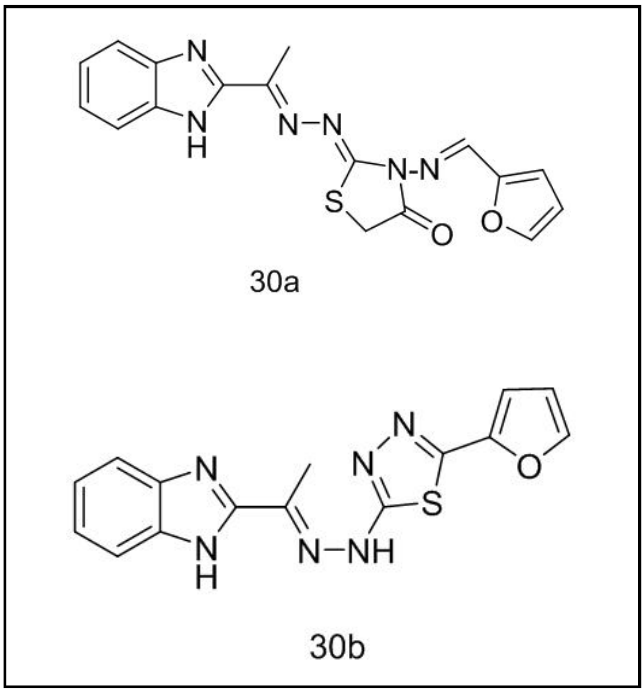
Mahmoud *et al* .(2020) produced several possible antibacterial benzimidazole derivatives having1,3,4-thiadiazole ring and azo moiety and tested towards *P. aeruginosa, S. aureus, E. coli* and *B. subtilis.* Compound 29a, 29b, 29c, 29d shown good action as standard ciprofloxacin and amoxicillin.



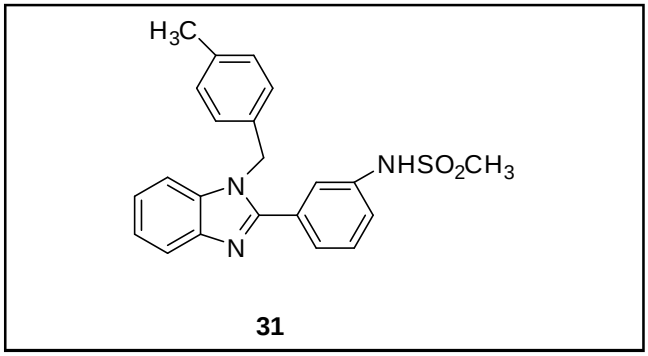
29a



Abdel-Motaal *et al.* (2020) produced some substituted benzimidazole -2yl derivatives and tested towards *B. pumilus*,*E. coli*, and *S. aureus*. Compounds 30a and 30b which included thiadiazole and thiazolone moieties, demonstrated good antimicrobial efficacy to normal gentamicin.



Dokla *et al.* (2020) developed benzimidazole derivativewith colistin and tested towards *K. pneumoniae*, *E. coli*, *P. aeruginosa* and *A. baumannii*. Compound 31 demonstrated a potential synergistic effect with MICs ranging from 8 to 16 µg/ml.



4. Conclusion

After analysing the literature reports, we concluded that benzimidazoles is recognised as a potential class of bioactive heterocyclic compounds which demonstrated variety of biological actions, such as antimicrobial, antiviral, antidiabetic, and anticancer activity.

Researchers looking to synthesise new molecules with the benzimidazole nucleus, which have a great deal of potential for further investigation into new therapeutic possibilities, may find the current review which only focuses on the antimicrobial activity of reported benzimidazole derivatives, to be a useful source of information.

Acknowledgments

The authors are grateful to the Faculty of Pharmacy, Integral University, Lucknow. The authors acknowledge that they received the manuscript number and MCN is IU/R&D/2022-MCN0001759.

Conflict of interest

The authors declare no conflicts of interest relevant to this article.

References

Abdel-Motaal, M.; Almohawes, K. and Tantawy, M. A. (2020). Antimicrobial evaluation and docking study of some new substituted benzimidazole-2yl derivatives. Bioorg. Chem., **101**(8):1-41.

Alaqeel, Shatha Ibrahim (2016). Synthetic approaches to benzimidazoles from O-phenylenediamine: A literature review. J. Saudi Chem. Soc., **21**(2):229-237.

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

Ansari, K.F. and Lal, C. (2009). Synthesis, physicochemical properties and antimicrobial activity of some new benzimidazole derivatives. Eur. J. Med. Chem., **44**:4028-4033

Arjmand, F.; Mohani, B. and Ahmad, S. (2005). Synthesis, antibacterial, antifungal activity and interaction of CT-DNA with a new benzimidazole derived Cu (II) complex. Eur. J. Med. Chem., **44**:1103-1110.

Bandyopadhyay, P.; Sathe, M.; Ponmariappan, S.; Sharma, A.; Sharma, P.; Srivastava, A.K. and Kaushik, M.P. (2011). Exploration of *in vitro* time point

quantitative evaluation of newly synthesized benzimidazole and benzothiazole derivatives as potential antibacterial agents. Bioorg. Med. Chem. Lett., **21**:7306-7309

Bansal, Y. and Silakari, O. (2012). The therapeutic journey of benzimidazoles: A review. Bioorg. Med. Chem., **20**:6208-6236.

Barot, K.P.; Manna, K.S. and Ghate, M.D. (2017). Design, synthesis and antimicrobial activities of some novel 1,3,4-thiadiazole, 1,2,4-triazole-5-thione and 1,3-thiazolan-4-one derivatives of benzimidazole. J. Saudi. Chem. Soc., **21**:S35-S43.

Chiyanzu, I.; Clarkson, C.; Smith, P.J. and Lehman, J. (2005). Design, synthesis and antiplasmodial evaluation *in vitro* of new 4-aminoquinoline isatin derivatives. Bioorg. Med. Chem. Lett., **13**:3249-3261.

Desai, K.G. and Desai, K.R. (2006). Green route for the heterocyclization of-mercaptobenzimidazole into *β*-lactum segment derivatives containing –CONH– bridge with benzimidazole: screening in vitro antimicrobial activitywith various microorganisms. Bioorg. Med. Chem. Lett., **14**:8271-8279.

Desai, N.C.; Shihory, N.R. and Kotadiya, G.M. (2014). Facile synthesis of benzimidazole bearing 2-pyridone derivatives as potential antimicrobial agents. Chin. Chem. Lett., **25**:305-307.

Dokla, E. M. E.; Abutaleb, N. S.; Milik, S. N.; Li, D.; El-Baz, K. and Shalaby, M. W. (2020). Development of benzimidazole based derivatives as antimicrobial agents and their synergistic effect with colistin against gram-negative bacteria. Eur. J. Med. Chem., **186**(1):1-26.

Dolzhenko, A.V.; Chui, W.K.; Dolzhenko, A.V. and Chan, L.W. (2005). Synthesis and biological activity of fluorinated 2-amino-4-aryl-3,4-dihydro [1, 3, 5]triazino[1,2-*a*] benzimidazoles. J. Fluorine. Chem., **126**:759-763.

Fahim, M.; Shrivastava, B.; Shrivastava, A.K.; Ibrahim, M.; Parveen, R. and Ahmad, S.(2017). Review on extraction methods, antioxidant and antimicrobial properties of volatile oils. Ann. Phytomed., **6**(2):5-46,

Goker, H.; Ozden, S.; Yildiz, S. and Boykin, D.W. (2005). Synthesis and potent antibacterial activity against MRSA of some novel 1,2-disubstituted-1*H*-benzimidazole- *N*-alkylated-5-carboxamidines. Eur. J. Med. Chem., **40**:1062-1069.

Guven, O.O.; Erdogan, T.; Goker, H. and Yildiz, S. (2007). Synthesis and antimicrobial activity of some novel phenyl and benzimidazole substituted benzyl ethers. Bioorg. Med. Chem. Lett., **17**:2233-2236.

Hu, L.; Kully, M.L.; Boykin, D.W. and Abood, N. (2009). Synthesis and *in vitro* activity of dicationic bis-benzimidazoles as a new class of anti-MRSA and anti-VRE agents. Bioorg. Med. Chem. Lett., **19**:1292-1295.

Jardosh, H.H.; Sangani C.B.; Patel, M.P. and Patel, R.G; (2013). One step synthesis of pyrido[1,2 *a*]benzimidazole derivatives of aryloxypyrazole and their antimicrobial evaluation. Chin. Chem. Lett., **24**:123-126.

Kalinowska, Lis. U.; Felczak, A.; Checinska, L.; Lisowska, K. and Ochocki, J. (2014). Synthesis, characterization and antimicrobial activity of silver (I) complexes of hydroxymethyl derivatives of pyridine and benzimidazole. J. Organomet. Chem., **749**:394-399.

Khalafi, Nezhad. A.; Rad, M.N.S.; Mohabatkar, H.; Asrari, Z. and Hemmateenejad, B. (2005). Design, synthesis, antibacterial and QSAR studies of benzimidazole and imidazole chloroaryloxyalkyl derivatives. Bioorg. Med. Chem. Lett., **13**:1931-1938.

Klimesova, V.; Koci, J.; Pour, M.; Stachel, J.; Waisser, K. and Jarmila, K. (2002). Synthesis and preliminary evaluation of benzimidazole derivatives as antimicrobial agents. Eur. J. Med. Chem., **37**:409-418.

Koc, Z.E.; Bingol, H.; Saf, A.O.; Torlak, E. and Coskun, A. (2010). Synthesis of novel tripodal-benzimidazole from 2,4,6-tris(*p*-formylphenoxy)-1,3,5-triazine: structural, electrochemical and antimicrobial studies. J. Hazard. Mater., **183**:251-255.

Kucukbay, H.; Durmaz, R.; Orhan, E. and Gunal, S. (2003). Synthesis, antibacterial and antifungal activities of electron-rich olefins derived benzimidazole compounds. Il. Farmaco., **58**:431-437.

Kumar, B.V.S.; Vaidya, S.D.; Kumar, R.V.; Bhirud, S.B. and 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**:599-604.

Liu, H. B.; Gao, W. W.; Tangadanchu, V. K. R.; Zhou, C. H. and Geng, R. X. (2018). Novel aminopyrimidinyl benzimidazoles as potentially antimicrobial agents: design, Synthesis and biological evaluation. Eur. J. Med. Chem., **143**:66-84.

Lopez, Sandoval. H.; Londono, Lemos. M.E.; Garza, Velasco. R.; Poblano, Melendez. I. Granada, Macias. P.; Gracia, Mora. I. and Barba, B. N. (2008). Synthesis, structure and biological activities of cobalt (II) and zinc (II) coordination compounds with 2-benzimidazole derivatives. J. Inorg. Biochem., **102**:1267-1276.

Mahmoud, M. A.; Ibrahim, S. K. and Rdaiaan, M. A. (2020). Antibacterial evaluation of Some New Benzimidazole Derivatives. Ijpr., **12**:282-287.

Mehboob, S.; Song, J.; Hevener, K.E.; Su, P.C.; Boci, T.; Brubaker, L.; Truong, L.; Mistry, T.; Deng, J.; Cook, J.L.; Santarsiero, B.D.; Ghosh, A.K. and Johnson, M.E. (2015). Structural and biological evaluation of a novel series of benzimidazole inhibitors of *Francisella tularensis* enoyl-ACP reductase (FabI). Bioorg. Med. Chem. Lett., **25**:1292-1296.

Noolvi, M.; Agrawal, S.; Patel, H.; Badiger, A.; Gaba, M. and Zambre, A.; (2014). Synthesis, antimicrobial and cytotoxic activity of novel azetidine-2-one derivatives of 1*H*-benzimidazole. Arabian. J. Chem., **7**:219-226.

Ozden, S.; Atabey, D.; Yildiz, S. and Goker, H. (2005). Synthesis and potent antimicrobial activity of some novel methyl or ethyl 1*H*-benzimidazole- 5-carboxylates derivatives carrying amide or amidine groups. Bioorg. Med. Chem., **13**:1587-1597.

Ozkay, Y.; Tunali, Y.; Karaca, H. and Isikdag, I. (2010). Antimicrobial activity and SAR study of some novel benzimidazole derivatives bearing hydrazone moiety. Eur. J. Med. Chem., **45**:3293-3298.

Padalkar, V.S.; Borse, B.N.; Gupta, V.D.; Phatangare, K.R.; Patil, V.S.; Umape, P.G. and Sekar, N. (2016). Synthesis and antimicrobial activity of novel 2-substituted benzimidazole, benzoxazole and benzothiazole derivatives. Arabian. J. Chem., **9**:1125-1130.

Panneerselvam, P.; Reddy, R.S.; Murali, K. and Kumar, N.R. (2010). Synthesis, analgesic, antiinflammatory, and antimicrobial activities of 5-sustituted isatin derivatives. Der. Pharm. Chem., **2**(1):28-37.

Park, S.; Jung, J. and Cho, E. Jin. (2014). Visible-light-promoted synthesis ofbenzimidazoles.Eur. J. Org. Chem., pp:4148-4154.

Phillip, M. (1951).The formation of 2-substituted benzimidazolesJ. Chem. Soc., **73**:1143-1145.

Punit, R.; Pandya, B.; Kajal.; Patel. B.; Urvesh.; Modi, D.; Chirag, M.; Harshad. and Javia, B. (2019). Antidiabetic, antioxidant and anti-inflammatory activity of medicinal plants collected from nearby area of Junagadh, Gujarat. Ann. Phytomed., **8**(2):75-84.

Rathod, C.P.; Rajurkar, R. M. and Thonte, S.S.; (2013). Synthesis and biological evaluation of some novel benzene sulfonamide derivatives. Indo. Am. J. Pharm. Res., **3**(2):2323-2329.

Seenaiah, D.; Reddy, P.R.; Reddy, G.M.; Padmaja, A.; Padmavathi, V. and Siva, K. N. (2014). Synthesis, antimicrobial and cytotoxic activities of pyrimidinyl benzoxazole, benzothiazole and benzimidazole. Eur. J. Med. Chem., **77**:1-7.

Shibinskya, M.O.; Lyakhov, S.A.; Mazepa, A.V. and Andronati, S.A. (2010). Synthesis, cytotoxicity, antiviral activity and interferon inducing ability of 6-(2aminomethyl)-6H-indolo [2, 3-b] quinoxalines. Eur. J. Med. Chem., **45**:1237-1243.

Singh, H.B.; Maurya, A.; Sadagopan, S.; Kesavan, P.K.; Acharya, S. and Arumugam, S.N. (2016). Immunomodulatory and antimicrobial activity of a polyherbal composition, panchatulasi drops, derived from essential oils of five species of basil. Ann. Phytomed., **5**(2):130-139.

Singh, V. K. and Amrita, P. (2019). The intriguing benzimidazole: a review.Int.J. Pharm. Sci. Res., **10**(4):1540-1552.

Sriram, D.; Yogeeswari, P. and Gopal, G. (2013). Synthesis, anti-HIV and antitubercular activity of lamivudine prodrugs. Eur. J. Med. Chem., **40**:1373-1376.

Sudha, B; Sumathi, S and Swabna, V; (2020). Enzyme mediated synthesis and characterization of silver nanoparticles using keratinase enzyme producing micro-organisms. Ann. Phytomed., **9**(1):147-153

Tewari, A.K. and Mishra, A. (2006). Synthesis and antiviral activities of N-substituted-2-substituted- benzimidazole derivatives Indian. J. Chem. Sect. B: Org. Chem. Inc. Med. Chem., **45**:489-493.

Thakur, K.; Mol, P.; Gawhankar, M.; Gupta, H.; Pati, P. and Thakur, M. (2020). Physicochemical characterization and antimicrobial properties of Mahamanjishthadi kadha: An ayurvedic formulation. Ann. Phytomed., **9**(1):78-90.

Tiwari, A.K.; Mishra, A.K.; Bajpai, A.; Mishra, P.; Singh, S.; Sinha, D. and Singh, V.K. (2007). Synthesis and evaluation of novel benzimidazole derivative and its radio/biological studies. Bioorg. Med. Chem. Lett., **17**:2749-2755.

Vishvanath, D.P. and Ketan, P.P. (2015). Synthesis of benzimidazole and benzoxazole derivatives catalyzed by nickel acetate as organometallic catalyst. Int. J. Chemtech Res., pp:457-465.

Wagner, E.C. (1946). The chemistry of formic acid and its simple derivatives, Org. Synthesis, **2**:65.

Wright, J.B. (1951). The chemistry of the benzimidazoles, research laboratories, The upjohn company, Kalamazoo, Michigan, January 29.

Wundt, E. (1878). The reaction of o-phenylenediamine with formic acid. Chem. Ber., **11**:826.

Yadav, S.; Narasimhan, B.; Lim, S. M.; Ramasamy, K.; Vasudevan, M. and Shah, S. A. A. (2018). Synthesis and evaluation of antimicrobial, antitubercular and anticancer activities of benzimidazole derivatives. Egypt. J. Basic Appl. Sci., **5**:100-109.

Citation **Mohd Anas, Arun Kumar, Kuldeep Singh, Syed Misbahul Hasan, Shom Prakash Kushwaha, Shubham Kumar Maurya, Priyanka Yadav and Suprabha Nishad (2022). Benzimidazole as promising antimicrobial agents: A systematic review. Ann. Phytomed., 11(2):102-113. http://dx.doi.org/10.54085/ap.2022.11.2.11.**