Pharmacophore

ISSN-2229-5402

Journal home page: http://www.pharmacophorejournal.com

SUBSTITUTED BENZIMIDAZOLES AS ANTIBACTERIAL AND ANTIFUNGAL AGENTS: A REVIEW

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ARTICLE INFO

Received:
29 Jan 2022
Received in revised form:
11 Apr 2022
Accepted:
14 Apr 2022
Available online:
28 Apr 2022

Keywords: Benzimidazole, Antimicrobial agents, Antibacterial activity, Antifungal activity

ABSTRACT

Microorganism-caused diseases are one of the greatest predicaments faced by the world. The disease conditions are worsened due to the development of microbial resistance against numerous antimicrobial agents like quinolones, vancomycin, macrolides, tetracyclines, β-lactam antibiotics, etc. There will always be a vital need to discover new chemotherapeutic agents to avert the emergence of resistance and ideally shorten the duration of therapy. There are various ways to overcome these problems, one of which is to properly utilize the marketed anti-microbials and the other is the synthesis of new antimicrobial compounds. In medicinal chemistry, one of the most potent and biologically active classes to be considered includes the Benzimidazoles. Different benzimidazoles analogues were synthesized by structure modifications. As a result, numerous types of benzimidazole analogues have been synthesized so far and for their chemotherapeutic importance, screened. The aforementioned review summarizes the chemistry of different benzimidazole derivatives formed by substitution at 1st and 2nd position and their applications as antimicrobial agents.

To Cite This Article: Kumar R, Singh G. Substituted Benzimidazoles as Antibacterial and Antifungal Agents: A Review. Pharmacophore. 2022;13(2):41-55. https://doi.org/10.51847/ySnvqCudRM

Introduction

One of the major issues in modern healthcare is the problems arising due to microbes. A variety of microorganisms hold pathological potential and tend to develop the resistance to antimicrobial agents being used against them and thus, making them more deteriorating [1]. This microbial resistance can be managed by systematic and effective use of available antimicrobial agents and by the development of novel molecules to cope with the changing trends. We can eradicate these issues by proper utilization of marketed antimicrobials or by developing new antimicrobial agents [2, 3]. This will also help in reducing the period of antimicrobial treatment.

For the development of new antimicrobial agents, heterocyclic compounds served as an important lead due to their affinity toward various enzymes and protein receptors [4, 5]. The modification of these heterocyclic moieties is a good synthetic approach for the discovery of novel antimicrobial drugs. In the previous couple of decades, benzimidazole and its subsidiaries have got considerable attention owing to their chemotherapeutical potential [4, 6, 7].

For medicinal chemists, benzimidazole (1) is a potential heterocyclic structure with therapeutic values. To plan the synthesis of benzimidazoles, 2-substituted compounds are of special interest as having better pharmacological properties in comparison to other benzimidazole analogues [8]. Various pharmacological and biochemical analyses showed that they have a broad spectrum of antimicrobial activities [9].

Benzimidazole has structural similarity to important heterocyclic structure Purine (2). The purine ring is formed by the fusion of the pyrimidine (3) and imidazole (4) rings as shown in **Figure 1**. Purine is an important component of microbial genetic material.

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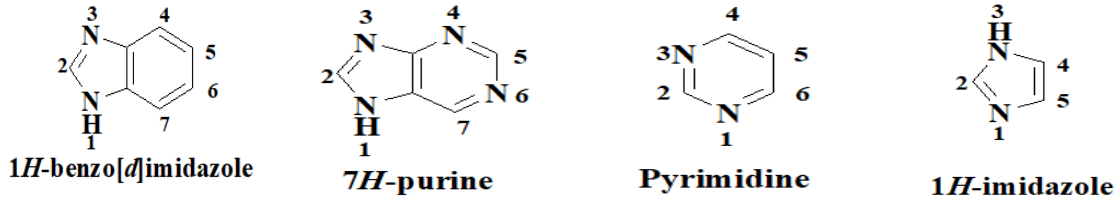


(1) (2) (3) (4)

Figure 1. Structure of benzimidazole, purine and its components

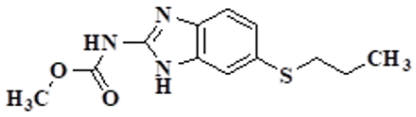
Due to their antimicrobial activities against various microorganisms, purine is considered one of the potentials leads for the development of novel antimicrobial agents.

Benzimidazoles show antimicrobial activity by competitively inhibiting nucleic acids and proteins synthesis of microbes, which can be attributed to their structural similarity with purine [10].

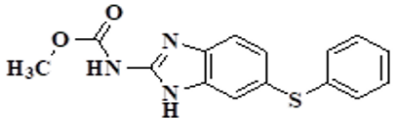
Imidazole and its fused derivatives possessed an important status in medicinal chemistry due to their important pharmacological properties [11]. Therefore, benzimidazoles have been investigated by medicinal chemists and observed to possess several biological applications of substituted benzimidazole compounds. Given the multipurpose core present in numerous compounds of benzimidazole, these derivatives have a wide range of activities [12].

The various kind of biological activities possessed by benzimidazole derivatives are antimicrobial [13, 14], pesticide [15, 16], cytotoxicity [17], anti-inflammatory [13], anthelmintic [18], HIV-RT inhibitor [13], ionotropic [13], antiviral [13], antihistaminic [13], antiparasitic [19], antiulcer [13], antiarrhythmic [20, 21], anticancer [13], antihypertensive [13], 5-HT antagonist [13], anxiolytics [13], anticonvulsant [22, 23], antiaggregant [13], and antipsychotic [24]. In this manner, the development of benzimidazole containing new compounds gives rise to numerous effective medicines that are presently available in the market **(Figure 2)**, like Albendazole **(5)**, Fenbendazole **(6)**, Mebendazole **(7)**, Flubendazole **(8)**, Lansoprazole **(9)**, Pantoprazole **(10)**, Omeprazole **(11)** Rabeprazole **(12)**, Antivir 1 **(13)** and Antivir 2 **(14)**. Thus, the development and synthesis of new benzimidazole derivatives leads to significant consideration in recent years.

Benzimidazoles used as anthelmintic drugs:



(5)



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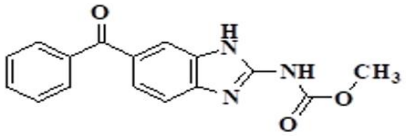

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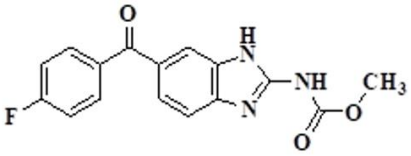
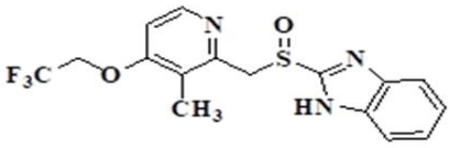


(8)

Benzimidazoles used as proton pump inhibitors:



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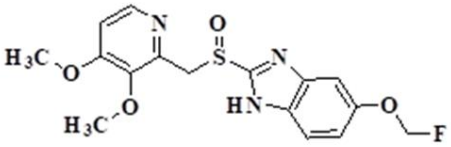

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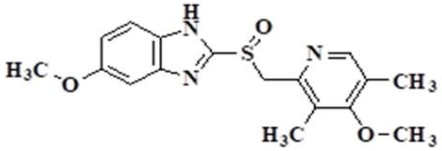

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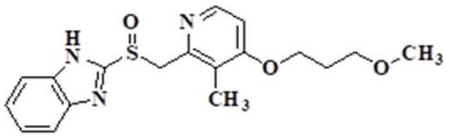


(12)

Benzimidazoles used as antiviral agent:

(13) (14)

Figure 2. Marketed benzimidazole drugs. (5-14)

Physico-chemical, pharmacokinetic and metabolic properties of most of the benzimidazole compounds are changed with the modification in functional group at the different positions on the benzimidazole ring. 2-phenylbenzimidazole is synthesized by the reaction of aromatic carboxylic acid and *o*-phenylenediamine **(Figure 3)**.

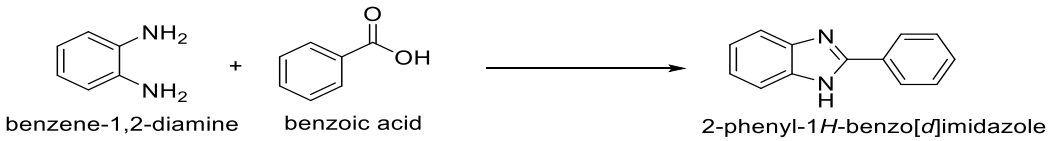


Figure 3. Synthesis of 2-phenyl imidazole

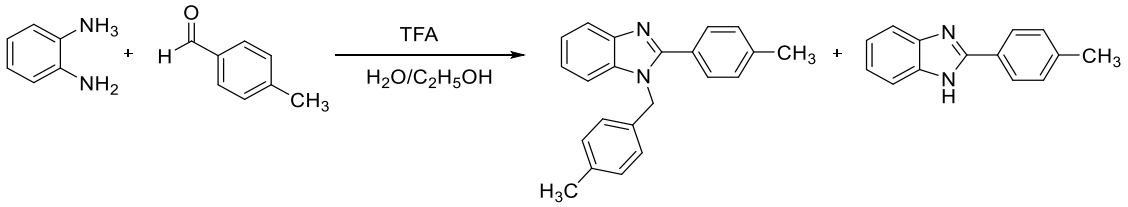
Looking into the importance of benzimidazole as antimicrobial agents, this review summarizes the benzimidazole derivatives in which substitution of different moieties has been done in 1st and 2nd positions specifically.

In today's world, human beings are in consistent contact with countless microorganisms which incidentally repress their body making a brief or everlasting network. Relations which are set up along these lines are different and exceptionally mind-boggling because sometimes this may be good for humans and many a time may lead to negative results. Microorganisms, whether present inside or outside the body, may cause disease due to the presence of some disease-causing elements in them. A lot of elements that empower effective penetration and harm of the host include poisons, contaminants, antigens and enzymes. An exceptionally complex interaction is set up; between the human and microorganism whose results are dependent upon the host's attributes and on the pathogen's qualities. Disease or illness caused by microorganisms can be counteracted, overseen and treated by using antimicrobial agents which are known as antibiotics. These compounds restrain the growth or destroy the microorganisms. Antibiotics are generally obtained from natural sources, but now they are synthesized in the labs.

In recent years, medicinal chemists focused on the synthesis of novel drugs bearing heterocyclic moieties, because heterocyclic compounds possess a broader spectrum of therapeutic activities. Especially, nitrogen-containing heterocyclic moieties possess potential medicinal values like Quinine, Morphine, metronidazole etc. The significance of nitrogen-containing heterocycles could be clarified by their accessibility in an assorted variety of pharmaceutical medications and in various herbs that have a wide scope of uses.

Furthermore, different nitrogen-containing heterocyclic compounds which are fused with other rings have been found to possess antimicrobial activities. So, the nitrogen-containing ring system seems, by all accounts, to be a standout amongst the most noticeable contender to investigate and assess their properties as antimicrobial agents. Among the N-heterocyclic rings Imidazole, benzimidazole, azetidinone and pyrazole give off an impression of being the most attractive ones.

Recently Marinescum reported the synthesis of hybrid derivatives of Benzimidazole and pyrazole which are effective against different types of microbes [25]. Some benzimidazole derivatives when used with colistin show a synergistic effect against gram-negative bacteria [26]. Schiff base of benzimidazole also possesses good antimicrobial activities [27]. In addition to that hybrid derivatives of benzimidazole with azetidinone show good activity against the microorganisms [28]. Substituted 2-phenyl benzimidazoles (**15** and **16**) were synthesized by the reaction of o-phenylenediamine with aromatic aldehydes at an ordinary temperature when catalyst trifluoroacetic acid (TFA) is present **(Figure 4)** [29].

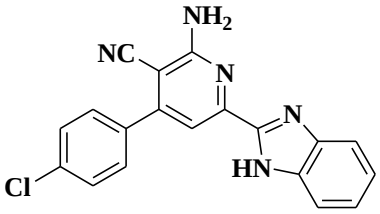
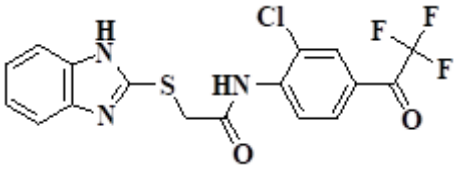
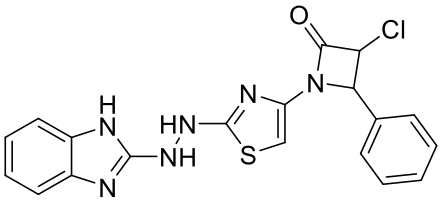
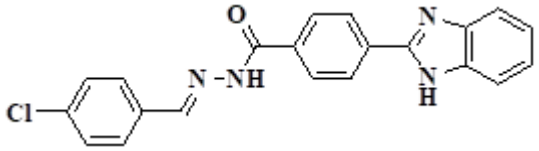
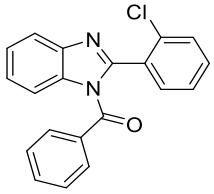
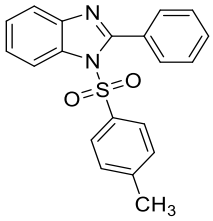
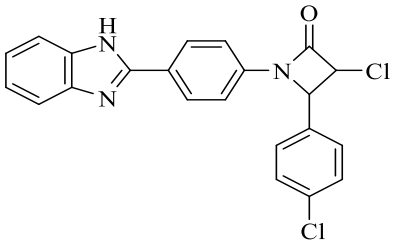


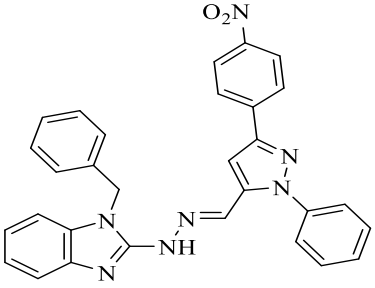
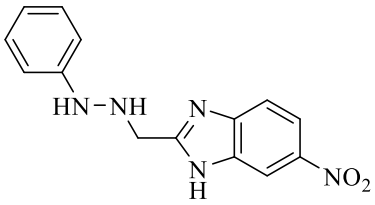
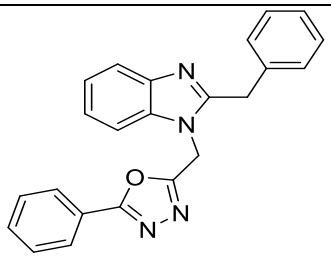
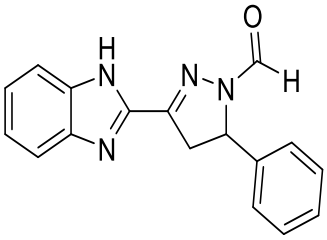
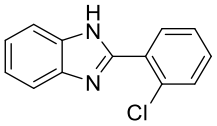
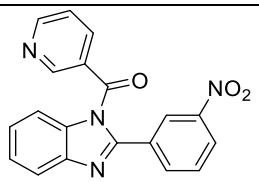
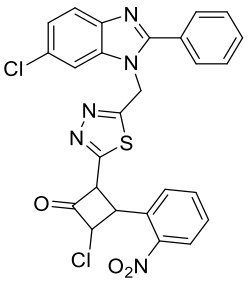
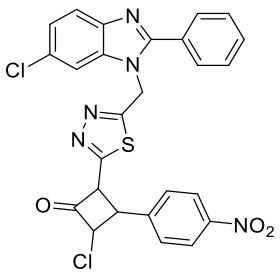
(15) (16)

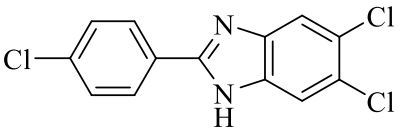
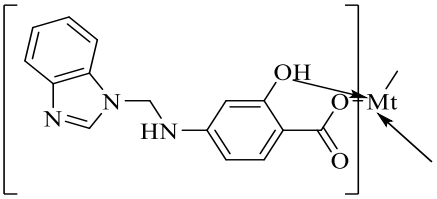
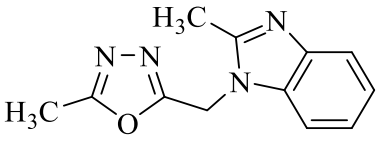
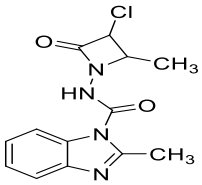
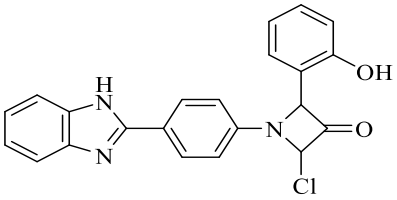
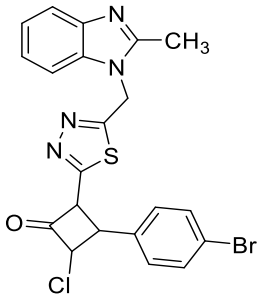
Figure 4. Synthesis of substituted 2-phenylbenzimidazoles.

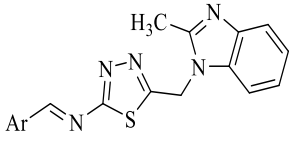
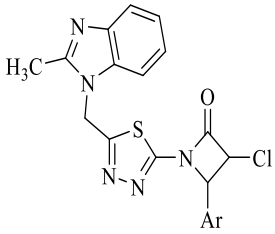
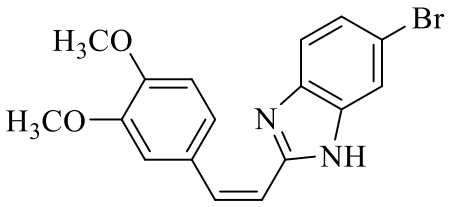
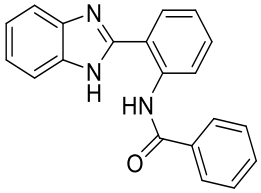
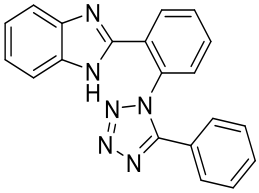
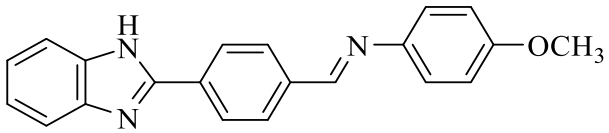
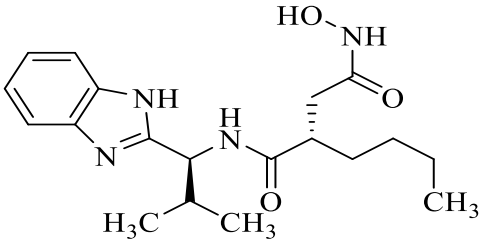
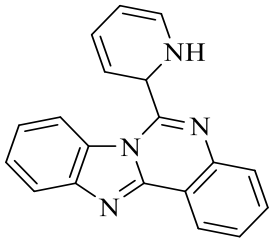
Number of medicinal chemists synthesized novel derivatives of benzimidazole by modifying the first and second position. This has led to generation of novel antimicrobial agents. These studies done by various scientists have been compiled in **Table 1** below.

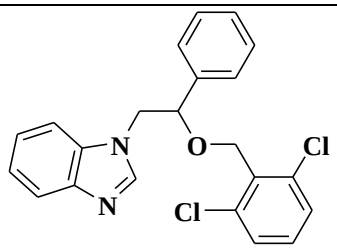
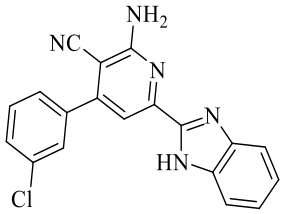
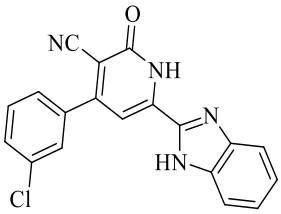
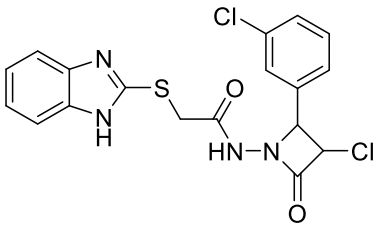
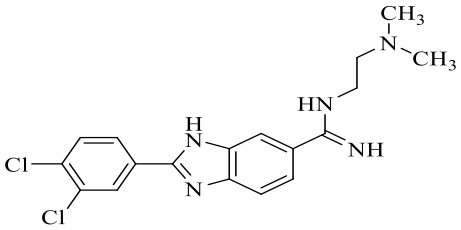
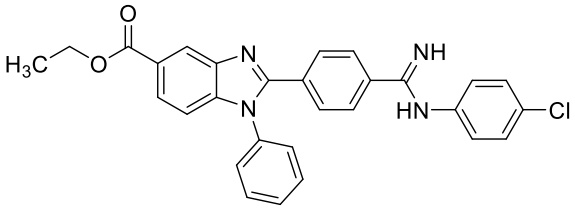
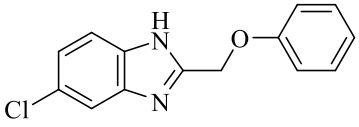
Table 1. Benzimidazole derivative showing antimicrobial activity.

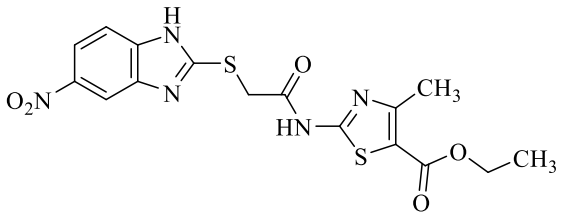
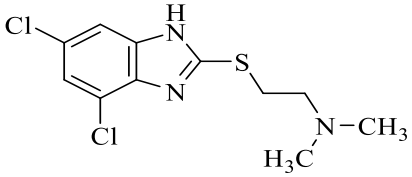
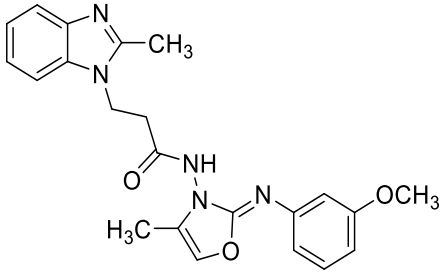
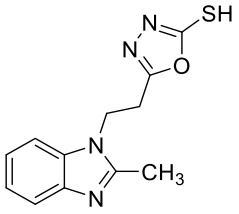
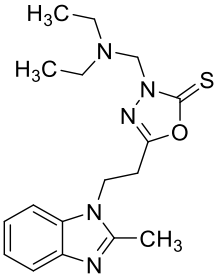
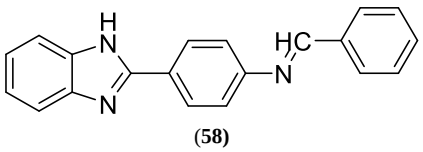
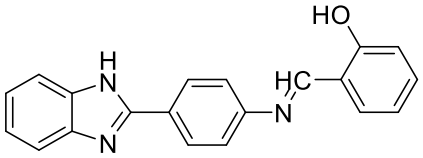
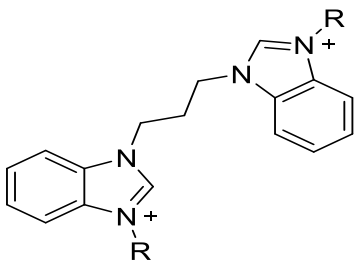
S. No	Author	Structure of compound	Finding
1	Yadav, J. S. and Srivastava, Y. K	 **(17)**	Yadav and his coworker synthesized novel derivatives of benzimidazole bearing nicotinonitrile moeityand assessed for *in vitro* antibacterial and antifungal activity. The structure of the newly synthesized compound **(17)** was elucidated using IR, NMR and mass spectral techniques. *In vitro* antimicrobial activity was checked against selected bacterial and fungal strains with reference to standard cifuroxacin HCl and fluconazole respectively [30].
2	Goud, V. M.; Sreenivasulu, N.; Rao, A. S.; Chigiri	 **(18)**	A variety of benzimidazole analogues were prepared which are linked to different derivatives of phenylacetamide at position 2nd through sulphydryl linkage and the antibacterial activity of synthesized analogues was checked by determining the zone of inhibition. Compound **(18)** had shown moderate antibacterial activity against selected strains of microorganisms regarding standard ciprofloxacin [31].
3	Singh, V.; Kumar, A.; Bhati, S.; Kumar, A	 **(19)**	Another study reported the synthesis of various benzimidazole azetidinone derivatives. Compound **(19)** shows good antibacterial activity among all the synthesized derivatives against *Staphylococcus aureus* (*S. aureus*) and *E. coli* against the standard chloramphenicol [32].
4	Alasmary, F.; Snelling, A.; Zain, M.; Alafeefy, A.; Awaad, A.; Karodia, N	 **(20)**	A new series of novel 2-phenyl benzimidazole compounds bearing hydrazone moiety were synthesized. Compound **(20)** had shown good activity against *Salmonella typhi* (*S. typhi*), *S. aureus*, *B. subtilis*, *E. coli* and *P. aeruginosa* by measuring the MIC (µg/mL) values with reference to standard chloramphenicol [8].
5	Gupta, S.; Pancholi, S.; Gupta, M.; Agrawal, D.; Khinchi, M.	 **(21)**  **(22)**	Another study reported the synthesis of *N*-substituted benzimidazole **(21)** and 2-phenyl benzimidazoles **(22)**. *N*-Substituted benzimidazole derivatives were produced by reacting tosyl chloride with benzoyl chloride. The synthesized derivatives showed good antibacterial activity against *E. coli*, *P. aeruginosa* and *S. aureus* [33].
6	Shanmugapandiyan, P.; Densching, K.; Ilavarasan, R.; Anbalagan, N.; Nirmal, R	 **(23)**	Schiff base of 2-phenyl substituted benzimidazole azetidinone derivatives showed good antimicrobial activities. The compound **(23)** had shown potent Antimicrobial activity by measuring the Zone of inhibition(mm) with reference to standard cefaclor [34].

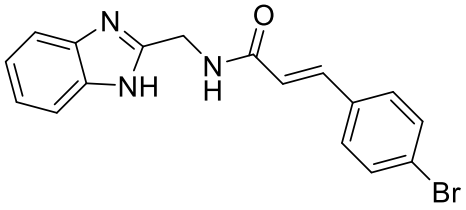
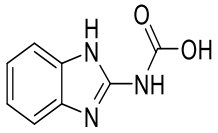
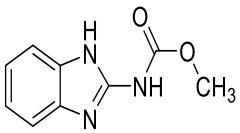
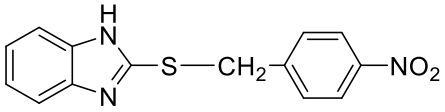
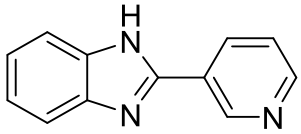
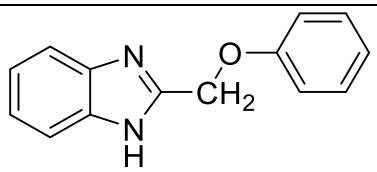
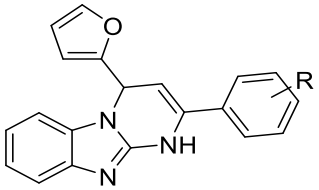
7	Patil, S. B.; Goudgaon, N. M.	 **(24)**	A variety of benzimidazole Schiff bases were produced by the reaction of 1-(1-benzyl-1*H*-benzimidazole-2-yl)hydrazine with substituted pyrazole-4-carbaldehydes. The resultant compounds were produced by the cyclization of Schiff base using Zinc chloride and thioglycolic acid. All compounds showed good antibacterial activity but compound (**24)** had shown good activity against selected bacteria strains with regard to standard gentamycin [35].
8	Venkataramana, H.; Singh, A.; Tiwari, A.; Tiwari, V	 **(25)**	Benzimidazole derivatives linked with phenylhydrazine were synthesized by the reaction between o-phenylenediamine and chloroacetic acid, which gave 2-chloromethyl benzimidazole. It further undergoes halide replacement with phenylhydrazines to give the corresponding *N, N'*-disubstituted hydrazines. The newly formed analogues were checked for antimicrobial properties against *S. aureus*, *Enterobacter cocci* (*E. cocci*) and *E. coli*. The compound **(25)** had shown better activity among the synthesized compounds [36].
9	Gowda, J.; Khadar, A.; Kalluraya, B.; Kumari, N. S	 **(26)**	A variety of 2-Substitutedbenzimidazole compounds were synthesized which is further substituted at 1 position by 1,3,4-oxadiazole. All newly formed derivatives have shown good antimicrobial properties but compound **(26)** had shown potent activity with regards to standard nitrofurazone [37].
10	Rajora, J.; Yadav, J.; Kumar, R.; Srivastava, Y. K.	 **(27)**	A new analogue of 2-substituted benzimidazole with 5-phenylpyrazole-1-carbaldehyde **(27)** was synthesized and screened for antibacterial activity against *P. aeruginosa*, *E. coli*, *K. pneumonia* and *B. subtilis* with regard to standard ciprofloxacin [38].
11	Sharma, D.; Narasimhan, B.; Kumar, P.; Jalbout, A	 **(28)**  **(29)**	Sharma and his coworker in the year 2009, synthesized various new benzimidazole derivatives like 2-(chlorophenyl)benzimidazole **(28)** and [2-(3-nitrophenyl)benzimidazol-1-yl]pyridin-3-yl-methanone **(29)**. The synthesized analogues had shown good antimicrobial activity [12].
12	Dhakad, A.; Sharma, M.; Chaturvedi, S.; Sharma, S	 **(30)**  **(31)**	Another study reported the synthesis of novel 2-phenyl benzimidazole substituted with 1,3,4-thiadiazol-2-ylazetidin-2-one derivatives (**30** & **31**) which are checked for their antimicrobial activities. All the new formed derivatives had shown good activity when compared with standard norfloxacin and clotrimazole [39].

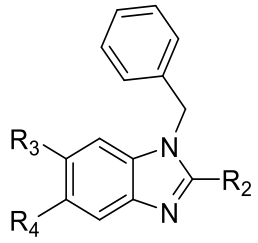
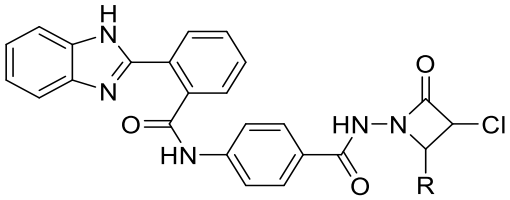
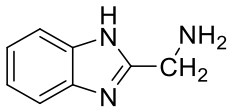
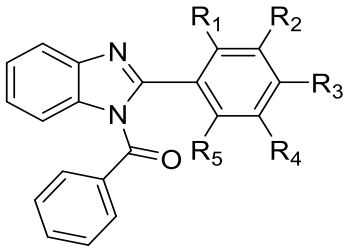
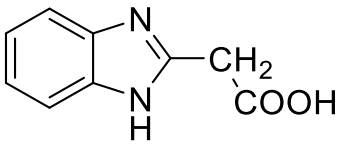
13	Tunçbilek, M.; Kiper, T.; Altanlar, N	 **(32)**	Tuncbilek also carried out the synthesis of some new 2-substituted benzimidazole analogues and checked for antimicrobial activity. Compound (**32)** had shown good antibacterial activity than standard ciprofloxacin [40].
14	Patel, K. V.; Singh, A	 BI-SA Metal Chelates Where Mt: $Cu^{2+,}$ Co^{2+}, Ni^{2+}, Mn^{2+}, Zn^{2+} and Fe^{3+} **(33)**	BI-SA Metal Chelates were prepared by the reaction of formaldehyde with 4-aminosalicylic acid. The synthesized analogues were represented as 4-{(Benzimidazole-1-yl)methyl}xamino-2-hydroxybenzoic acid (BI-SA) **(33)**. The various metals were used to form a transition metal complex with BI-SA. Almost all synthesized derivatives showed good antimicrobial activity [41].
15	Ansari, K.; Lal, C	 **(34)**	Analogues of 2-substituted benzimidazole were prepared which was further substituted at 1st position with the 5-methyl-1,3,4-oxadiazole-2-ylmethyl group. All compounds had shown good antibacterial activity but Compound **(34)** was more potent as compared to standard ampicillin [42].
16	Ansari, K.; Lal, C	 **(35)**	In another study, a new series of acetamide linked 2-methyl benzimidazole derivatives **(35)** were synthesized and tested for their antibacterial activities. The disc diffusion method was used to evaluate the antimicrobial activity of the synthesized derivatives [43].
17	Baviskar, B.; Baviskar, B.; Chuadhary, S.; Parwani, K.; Balani, P.; Salode, V.; Patil, S.; Khadabadi, S	 **(36)**	1-[4-(Benzoimidazol-2-yl)phenyl]-3-chloro-4-phenylazetidin-2-one **(36)** were synthesized from *o*-phenylenediamine. The compounds were assessed for their antimicrobial activity against selected bacterial and fungal strains. All of the analogues had shown antimicrobial activity [44].
18	Sharma, M.; Kohli, D.; Sahu, N.; Sharma, S.; Chaturvedi, S	 **(37)**	QSAR study on a series of 1,3,4-Thidiazol-2-yl azetidine-2-one as antibacterial agents were performed with the help of Chem Office ultra-7.01. To derive QSAR models, a multiple linear regression analysis was performed. Further, the relationship is assessed for activity prediction. The best QSAR model was chosen with a correlation coefficient (r^2) of 0.8040 and a cross-validated correlation coefficient (Q^2) of 0.6189. MIC (µg/mL) value of compound **(37)** against *B. Subtilis* was 500 [45].

19	Ansari, K.; Lal, C	 **(38)**  **(39)**	Another study reported the synthesis of new azetidinone benzimidazole derivatives. The resultant compounds were synthesized by the reaction of 5-[(2-methyl benzimidazole-1-yl)methyl]-1,3,4-thiadiazol-2-amine with different aromatic aldehydes to produce 5-[(2-methyl benzimidazole-1-yl)methyl]-*N*-[(substituted) phenyl methylidene]-1,3,4-thiadiazol-2-amine **(38)** which undergo cyclization with chloroacetyl chloride and triethylamine to form 3-chloro-1-{5-[(2-methyl-1*H*-benzimidazole-1-yl)methyl]-1,3,4-thiadiazol-2-yl}-4-(substituted)phenylazetidin-2-one **(39)**. Chemical structures of newly formed derivatives were confirmed with the help of spectral analysis. All the compounds had shown good antibacterial activity [46].
20	Shingalapur, R. V.; Hosamani, K. M.; Keri, R. S.	 **(40)**	A new compound, 5-Bromostyryl-2-benzimidazoles was prepared by the reaction of cinnamic acids and 5-Bromo-1,2-phenylenediamine in the presence of ethylene glycol. The antimicrobial properties of synthesized compounds were assessed against different bacterial and fungal strains. Compound (**40)** had shown good antimicrobial activity with reference to standard ciprofloxacin and fluconazole [47].
21	Jafar, A. A.; Vijayakumar, K. N.; Venkatraman, B. R.; Venkatesh, G	 **(41)**  **(42)**	Ahamed and his co-worker performed the synthesis of a variety of new benzimidazole analogues and evaluated them for antimicrobial properties using the disc diffusion method. Compounds **41** and **42** possessed potent antimicrobial activities [48].
22	Chhonker, Y.; Veenu, B.; Hasim, S.; Kaushik, N.; Kumar, D.; Kumar, P	 **(43)**	Cycloaddition reaction is also used for the synthesis of 2-phenylbenzimidazole analogues Compound (**43)** had shown well *in vitro* antibacterial activity [49].
23	Zhang, D.; Wang, Z.; Xu, W.; Sun, F.; Tang, L.; Wang, J.	 **(44)**	In the year 2009, a novel series of benzimidazole linked with actinonin moiety was prepared. The chemical structures of all newly formed derivatives were checked by NMR, Mass and IR spectroscopic methods. Almost every compound had shown well *in vitro* antimicrobial activity against the standard drug cefoperazone. The compound **(44)** with no substitution on benzimidazole showed potent antimicrobial activity [50].
24	Rohini, R.; Shanker, K.; Reddy, P. M.; Ho, Y.-P.; Ravinder, V.	 **(45)**	Another study reported the synthesis of some new mono-2-*o*-arylidene-aminophenyl benzimidazoles. The target benzimidazole-quinazoline analogues were prepared by the cyclization of the product obtained by the reaction of 2(-aminophenyl)benzimidazole and mono carbonyl compounds. The structure of all products was confirmed with the help of spectroscopic techniques. The antimicrobial properties of synthesized quinazolines derivatives were screened against different bacterial strains. The compound **(45)** had shown remarkable antimicrobial activity [51].

25	Güven, Ö. Ö.; Erdoğan, T.; Göker, H.; Yıldız, S	 **(46)**	Benzimidazole analogues substituted by benzyl ethers were synthesized in the year 2007 and their antimicrobial activity was assessed against selected strains of bacteria and fungi. Compound (**46)** had shown the most potent antimicrobial activity against standards ampicillin and fluconazole [52].
26	Rida, S. M.; El-Hawash, S. A.; Fahmy, H. T.; Hazzaa, A. A.; El-Meligy, M. M.	 **(47)**  **(48)**	Novel benzimidazole derivatives were prepared by using an isostere approach like 2-acetylbenzimidazole and 2-cyanomethylbenzimidazole. The prepared derivatives were checked for anti-HIV1, anticancer and antimicrobial activity. Compounds **47 and 48** showed good antimicrobial activity [53].
27	Desai, K. G.; Desai, K. R	 **(49)**	Another study reported the synthesis of new benzimidazole derivatives by the reaction of 2-(benzimidazole-1-yl-thio)-*N'*-2-substituted phenylhydrazide, chloroacetylchloride and triethylamine. Under microwave conditions, this reaction produced a good yield in a short duration. The structure of new heterocyclic compounds was elucidated with the help of spectral analysis. Every new analogue was assessed for its antimicrobial activity. The compound **(49)** showed remarkable antibacterial activity amongst the newly formed compounds against the standard streptomycin [54].
28	Göker, H.; Alp, M.; Yıldız, S	 **(50)**	Novel 2-phenylbenzimidazole substituted with *N*-alkylated-5-carboxamidine was synthesized and the synthesized compounds were assessed for antibacterial activity. The compound **(50)** had shown good antimicrobial activity against the standard ampicillin [55].
29	Özden, S.; Atabey, D.; Yıldız, S.; Göker, H	 **(51)**	Synthesis of alkyl esters of benzimidazole-5-carboxylic acid substituted with amide or amidine moiety having methyl or phenyl groups present at the C-2 position was reported in the year 2005. The synthesized compounds were screened for antimicrobial activity. The results indicate that compound **(51)** had shown good inhibitory activity with reference to standard ampicillin [56].
30	Yildiz-Oren, I.; Yalcin, I.; Aki-Sener, E.; Ucarturk, N	 **(52)**	Another study reported the synthesis of the ether of 2-substituted benzimidazoles and evaluation of their antimicrobial properties. The compound **(52)** had shown potent antimicrobial activity against the standards ampicillin and amoxicillin [57].

31	uran-Zitouni, G.; Demirayak, Ş.; Özdemir, A.; Kaplancıklı, Z. A.; Yıldız, M. T	 **(53)**	Various new derivatives of benzimidazole linked with thiazole moiety were synthesized by the reaction between 4-methyl-2-(chloroacetylamino)thiazole analogues with benzazol-2-thiole in the presence of acetone and K_2CO_3. The structures of the synthesized analogues were confirmed by spectral data. The compound **(53)** had shown potent antimicrobial activity against the standard chloramphenicol [58].
32	Kazimierczuk, Z.; Upcroft, J. A.; Upcroft, P.; Górska, A.; Starosciak, B.; Laudy, A.	 **(54)**	New derivatives of benzimidazole were synthesized which are substituted at the second position. Compound **(54)** had shown potent activity as compared to that of metronidazole against both gram-positive and gram-negative bacterial strains [59].
33	Fahmy, H. H.; El-masry, A.; Ali Abdelwahed, S. H.	 **(55)**	2-Methylbenzimidazole derivatives were also synthesized which is further attached with several heterocyclic moieties at the first position through ethyl or carbamoyl ethyl groups. Also, semicarbazides and thiosemicarbazides linked with 3-(2-methyl benzimidazole-l-yl)propanoic acid hydrazide were prepared and assessed for their antibacterial activities. The compound **(55)** had shown potent antimicrobial activity by measuring the zone of inhibition against the standard ampicillin [60].
34	El-masry, A.; Fahmy, H.; Ali Abdelwahed, S.	 **(56)**  **(57)**	A novel series of 2-methyl benzimidazole derivatives were synthesized in which benzimidazole is further substituted at first positions by heterocyclic moieties and checked their antimicrobial properties. Compounds **(56)** and **(57)** had shown good antibacterial activity with respect to gentamycin and ampicillin as standard [61].
35	Alam, S.; Ahmad, T.; Nazmuzzaman, M.; Rahman, S.; Ray, S.; Sharifuzzaman, M.; Karim, M.; Alam, M.; Ajam, M.; Maitra, P.	 **(58)**  **(59)**	Another study reported the synthesis of Schiff base of 2-phenylbenzimidazole. The compounds were formed by the reaction of *p*-aminobenzoic acid with benzene-1,2-diamine in the presence of xylene and polyphosphoric acid. The resultant compounds were further treated with different aldehydes to produce the Schiff base of benzimidazole. The tube dilution method was used to check the antibacterial activity of the Schiff base. The compounds (**58)** and (59**)** have better antibacterial activity as compared to vancomycin [62].
36	KÜÇÜKBAY, H.; YILMAZ, Ü.; ŞİRECİ, N.; GÜVENÇ, A. N	 **(60)**	New bis-benzimidazoles **(60)** compounds bearing different groups were also synthesized. Chemical structures of all newly formed derivatives compounds were ascertained by spectroscopic methods. The disk diffusion method was used to evaluate the *in vitro* antimicrobial activity of synthesized analogues. Most of the synthesized derivatives had shown potent antimicrobial properties as compared to the standard drug, cefozine and nystatin [63].

37	Rajput, P. B.; Phadke, S. A.; Bandiwadekar, P. V	 **(61)**	2-Acetylated benzimidazole linked with chalcone showed different biological activities. So, various 2-acetylated benzimidazole chalcone analogues were synthesized and characterized with the help of IR and ^{1}HNMR spectroscopic data. Every synthesized derivative was screened for antifungal activity against *Candida albicans* (MTCC 227). Compounds (**61)** have shown good antifungal activity [64].
38	Ravishankara, D. K.; Chandrashekara, P. G and Maxwell, W.; Brody, G.	 **(62)**  **(63)**	2-Phenylsubstituted benzimidazole derivatives were synthesized by reacting different benzimidazoles with phenyl sulphonyl chloride. All the synthesized derivatives were assessed for antibacterial activity with reference to the standard drug chloramphenicol [65]. 2-Benzimidazole carbamic acid and their esters showed potent antimicrobial activity as compared to benlate. Compounds **(62) and (63)** were the degradation product of (butyl carbamoyl)-2-benzimidazole carbamic acid and their methyl esters [66].
39	Shahnaz, M.; Kaur, P.; Parkash, J.; Parsad, D.	 **(64)**	Another study reported the synthesis of various novel 2-{(4-nitrobenzyl)thio}-1*H*-benzo[d]imidazole **(64)** which were synthesized by reaction of different amine derivatives of benzene-1,2-diamine and carbon disulphide. The structure of all synthesized compounds was elucidated by spectral techniques and the purity of compounds was checked by the chromatography method (TLC). The microbiological assay showed that almost every compound had shown promising antibacterial activity against ciprofloxacin as the reference standard [67].
40	Kumar, K.; Pathak, D.	 **(65)**	The microwave irradiation technique was used for the synthesis of novel benzimidazole compounds which were substituted at the second position with different substituents. For this different carboxylic acid (aliphatic, aromatic and heterocyclic) and 2-nitroaniline were reacted to produce the required compounds. The structure of synthesized analogues was identified by spectroscopic techniques. All synthesized derivatives were assessed for antimicrobial properties by the agar well diffusion method. compound **(65)** has shown potent antimicrobial activity [68].
41	Arora, G.; Sharma, S.; Sahni, T.; Sharma, P	 (**66)**	New benzimidazole and 2-phenyl-1*H*-indoles derivatives were prepared and assessed for antimicrobial activity against *Bacillus sp.* (Gram-positive) and *Pseudomonas sp., Enterobacter sp.* (Gram-negative). Compound (**66)** had shown good antibacterial activity [69].
42	Arora, G.; Sharma, S.; Sahni, T.; Sharma, P	 **(67)**	Synthesis of various derivatives of pyrimido[1,2-a]benzimidazole **(67)** was carried out by refluxing 2-aminobenzimidazole with chalcones in the presence of n-butanol. Every synthesized analogue was checked for its antibacterial properties against different strains of bacteria [70].

43	Podunavac-Kuzmanović, S.; Cvetković, D.	 **(68)**	Another method that is used for the synthesis of some new derivatives of benzimidazole by the reaction of 1-benzylbenzimidazole derivatives **(68)** with $ZnCl_2$. Every synthesized analogue was assessed for antimicrobial properties against different strains of microorganisms. It was observed that every tested derivative had shown good activity towards gram-positive than gram-negative bacteria [71].
44	Mehta, P.; Davadra, P.; Pandya, J. R.; Joshi, H. S.	 **(69)**	Synthesis of some new benzimidazole derivatives linked with 2-azetidinone moiety **(69)** was reported in 2014. The cup and plate methods were adopted to check the antimicrobial activity. Every compound had shown moderate to good antimicrobial activity [72].
45	Ajani, O. O.; Aderohunmu, D. V.; Olorunshola, S. J.; Ikpo, C. O.; Olanrewaju, I. O.	 **(70)**	Ajani and his coworker, synthesized various derivatives of benzimidazole substituted at the 2nd position using an ameliorable pathway by the reaction of different amino acids with benzene-1,2-diamine. All analogues were assessed for their antimicrobial activity with regard to gentamicin as a standard drug. Compound **(70)** had shown the best antimicrobial activity among all the derivatives [73].
46	Sharma, D.; Narasimhan, B.; Kumar, P.; Judge, V.; Narang, R.; De Clercq, E.; Balzarini, J	 **(71)**	In 2009, the synthesis of a series of [2-(substitutedphenyl)-benzoimidazol-1-yl]-methanone derivatives **(71)** was carried out and screened for antimicrobial activity. The outcome of the antimicrobial assessment is that none of the newly formed analogues had shown antibacterial activity. Some of the compounds had shown a little bit of antifungal activity [74].
47	Chandhrasekar, S.	 **(72)**	A new series of benzimidazole analogues were synthesized and evaluated for antimicrobial potential. Synthesis involves the reaction between different dicarboxylic acid and benzene-1,2-diamine to produce substituted benzimidazoles. This was further treated with benzoyl chloride in the presence of sodium hydride to produce the required derivatives. Chemical structures were elucidated by using spectral data. Antibacterial activity was studied against *Pseudomonas aeruginosa* using the disc diffusion method. Compound **(72)** had shown potent activity with respect to standard ciprofloxacin [75].

A novel series of benzimidazole analogues were prepared, having different groups at 2nd position. For the synthesis of these compounds' benzene-1,2-diamine was reacted with a different carboxylic acid in presence of polyphosphoric acid. Chemical structures of newly formed derivatives were confirmed by spectral data. The cup and plate method was adopted to check the *in-vitro* antibacterial activity against different strains of microorganisms [76].

A novel method emerged for the synthesis of benzimidazole derivatives by treating citronellal when ethanol is present with o-phenylenediamine **(Figure 5)**. The structure of resultant compounds was elucidated with the help of FTIR and NMR. Antibacterial activity of newly synthesized derivatives was checked with the help of the agar diffusion technique using Gentamicin as a standard drug [77].

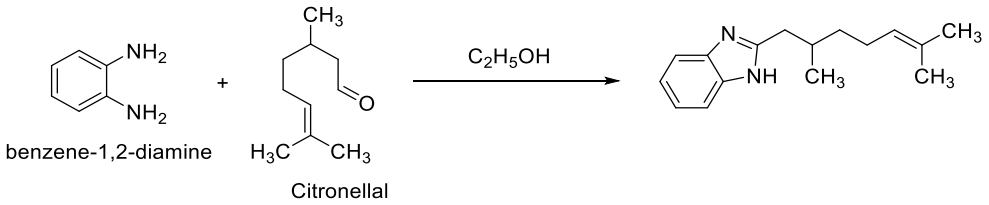


Figure 5. Synthesis of benzimidazole from Citronellal and *o*-phenylenediamine

Another study reported the synthesis of acetamide linked benzimidazole with substituted phenyl ring. For this, substituted anilines analogues were treated with chloroacetyl chloride to produce chloroacetamide. This was further reacted with benzimidazole in the presence of dimethylformamide to give the resultant compounds **(Figure 6)**. ^{1}HNMR and FTIR techniques were used to confirm the structure of synthesized derivatives. Most of the synthesized compounds show good antibacterial activity [78].

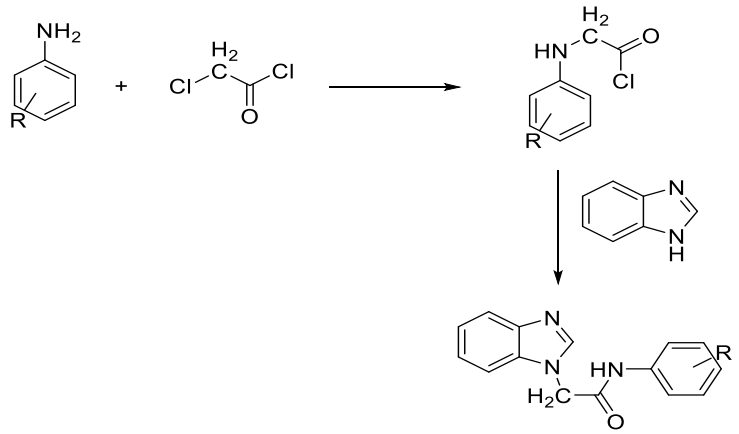


Figure 6. Synthesis of acetamide linked benzimidazole with a substituted phenyl ring

Conclusion

The benzimidazole nucleus is structurally related to purine nucleoside bases, thereby it interacts with all types of the biological macromolecules and it is found in some natural products, such as vitamin B_{12}, marine natural products namely makaluvamins. Further, the literature survey reports have revealed that the 1 or 2- substituted benzimidazole has been reported to possess antibacterial and antifungal activity. So, it is possible to synthesize different benzimidazole derivatives having antimicrobial activity by the structural modification of benzimidazole moiety.

Acknowledgments: The authors are thankful to School of Pharmaceutical Sciences, Lovely Professional University, Phagwara for providing the necessary facilities and atmosphere.

Conflict of interest: None

Financial support: None

Ethics statement: None

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