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Antibacterial Activity of Benzimidazole Derivatives: A Mini Review

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Review Article

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ABSTRACT

Benzimidazole derivatives are of wide interest because of their presence in numerous categories of medicinal drugs; such as anticancer, anticoagulants, antihypertensives, anti-inflammatory, antimicrobials, antiparasites, antivirals, antioxidants, immunomodulators, proton pump inhibitors, hormone modulators, CNS stimulants as well as depressants, lipid level modulators, antidiabetics, etc., makes it a moiety of great importance in medicinal chemistry. Because of this great importance, it attracts the researchers to synthesize more effective benzimidazole derivatives for several biological activity screening. Many reviews and mini reviews on importance of benzimidazole nucleus for medicinal purpose are present. Present study is an attempt to review the antibacterial activity separately of benzimidazole nucleus containing compounds within the period from 2011 to 2017. This review will be helpful in development of effective benzimidazole derivatives.

INTRODUCTION

In 1943, Goodman and Nancy Hart published first paper on pharmacological properties of benzimidazole [1]. In 1944, Woolley published their work benzimidazoles and purins. He also reported the antibacterial activity of synthesized benzimidazoles against *E. coli* and *Streptococcus lactis* [2]. In 1949, Norman GB and Karl Folker obtained a new basic compound 5, 6-dimethyl benzimidazole from the acid hydrolysis of Vitamin B-12, as a degradation product [3]. Other degradation products like 5, 6-methylbenzimidazole and 1, 2-diamino- 4, 5-dimethylbenzene also exhibits vitamin B12-like growth activity [4]. After a long time of research, benzimidazole becomes an important heterocyclic system because the compounds containing benzimidazole nucleus exhibits a long rang of biological activity against a number of pathogens and physical disorders. Active involvement of benzimidazole nucleus reported in various therapeutic agents like antiparasitics, anticonvulsants, analgesics (Etonitazene), antihistaminics (astemizole), antihelmintics (albendazole, mebendazole, thiabendazole), antiulcers, antihypertensives (candesarten cilexitil, telmisartan), antiviral (enviradine), anticancers, antifungals (Benomyl, Carbendazim), anti-inflammatory agents, proton pump inhibitors (omeprazole, lansoprazole, pantoprazole) and anticoagulants [5].

Many researchers synthesis benzimidazole based compounds and screened them for antibacterial activity against several bacterial strains. But no one compound makes his way to clinic. This is still a failure in benzimidazole chemistry. Antibiotics resistance bacterial infection is a serious problem. Numbers of antibacterial drugs are no longer very useful against many bacteria due to bacterial resistance. Numbers of well identified examples are present for such antibiotics resistance of bacteria (identification year) - Penicillin resistance Staphylococcus (1940), Tetracycline resistance Shigella (1959). Methicillin resistance Staphylococcus (1962), Penicillin resistance Pnuemococcus (1965), Erythromycin resistance Streptococcus (1968), Gentamicin resistance Enterococcus (1979), Ceftazidime resistance Enterobacterlaceae (1987), Vancomycin resistance Enterococcus (1988), Levofloxacin resistance Pneumococcus (1996), Imipenem resistance Enterobacteriaceae (1998), linezolid resistance Tuberculosis (2000), Linezolid resistance Staphylococcus (2010), Vancomycin resistance Staphylococcus (2002), Deptomycin resistance Acinetobacter and Psuedomonas (2004/05), Ceftriaxone resistance Neisseria gonorrhoeae and Enterobacteriaceae (2009), Ceftaroline resistance Staphylococcus (2011) [6]. Recently a short summary was published on global priority list of antibiotic resistance bacteria by World health organization (WHO); and creates a priority list of bacteria's and divided them into three categories: Acinetobacter baumannii (carbapenem-resistant), *Pseudomonas aeruginosa* (carbapenem-resistant), Enterobacteriaceae (carbapenem-resistant, 3rd generation cephalosporin-resistant) comes under critical priority list; *Enterococcus faecium* (vancomycin-resistant), *Staphylococcus aureu* (methicillin-resistant, vancomycin intermediate and resistant) *Helicobacter pylori* (clarithromycin-resistant), *Campylobacter* (fluoroquinolone-resistant), Salmonella spp.(fluoroquinolone-resistant), *Neisseria gonorrhoeae* (3rd generation

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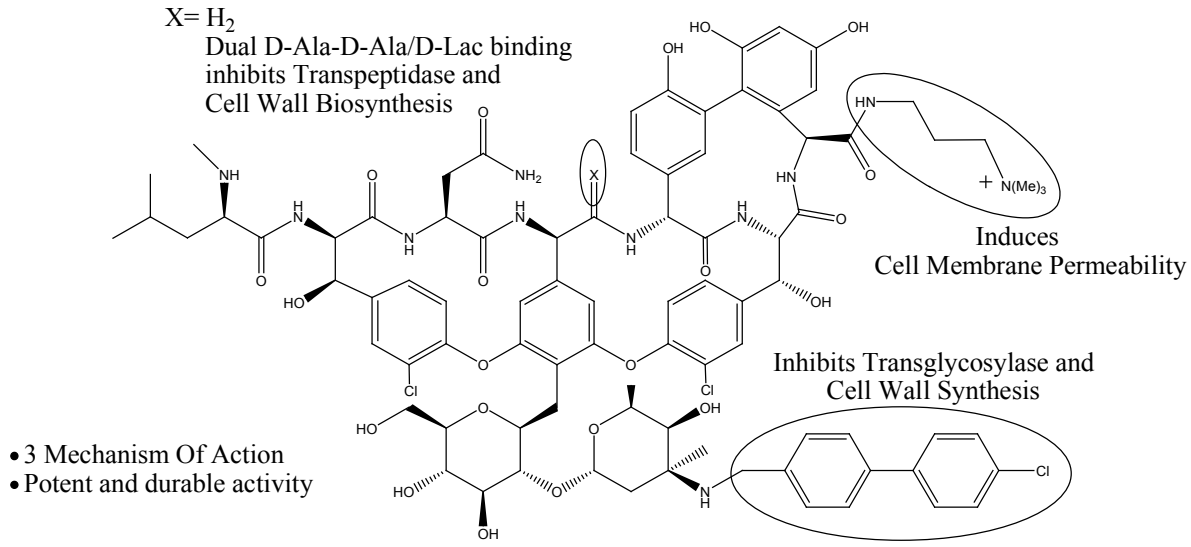
cephalosporin-resistant, fluoroquinolone-resistant) comes under high priority list and *Streptococcus pneumonia* (penicillin-non-susceptible), *Haemophilus influenzae* (ampicillin-resistant), Shigella spp., (fluoroquinolone-resistant) comes under medium priority list [7]. Literature suggests that overuse of antibiotics clearly drives the evolution of bacterial resistance. Previously, in 1945 Alexander Flaming raised the alarm regarding overuse of antibiotics. Problem of antibiotics resistance sparks the research on chemical compound that will potent against bacterial infection and benzimidazole derivatives also seems hopeful along with other organic/inorganic derivatives.

In the way of discovery of new antibiotics, Okano et al. makes research on vencomycin, and makes it durable, more potent antibiotics after peripheral and binding pocket modification on parent vencomycin. After modifications, compound 18 found more effective than others derivatives and there's three mechanism of action in modified vancomycin. There antibacterial potency followed a predictable trend of (Three>Two>One) mechanism of action [8]. This is also a way of antibiotic discovery suggested by Okano et al. in which researchers make studies and research on those antibiotic drugs against those bacteria developed their resistance ability.

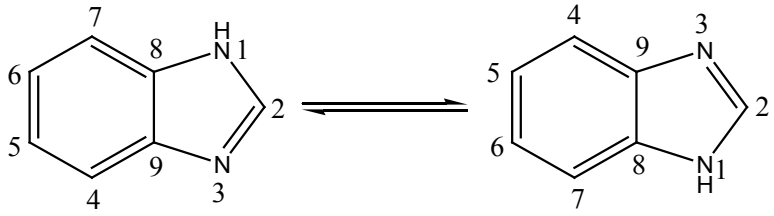


Compound 18, Summary of activity and Mechanism of action

In this review, we will cover the comparative study on antibacterial activity of different benzimidazole derivatives with optimization of substituent on benzimidazole moiety. It will helpful in the development of novel and more effective drugs based on benzimidazole nucleus against bacterial infection.

Chemistry

Benzimidazole is a fused aromatic heterocyclic system consists of a fusion of imidazole ring with benzene ring. Benzimidazole exhibit amphoteric nature, it can be protonated in presence of an acid and can be deprotonated in presence of a strong base like LiH. Benzimidazole exhibits tautomerism because of hydrogen attached to N-1 in imidazole ring can be shifted to N-3, and exhibit amine-imine tautomerism.



1*H*-benzo[*d*]imidazole

In 1872, Hoebrecker synthesized benzimidazole first time as 2, 5- or 2, 6-dimethylbenzimidazole (tautomers) through reduction of 2-nitro-4-methylacetanilide in presence of Sn/HCl reducing agent [9]. After Hoebrecker, in 1875 Ladenburg extensively explored the benzimidazole synthesis by condensation between O-amino aniline and carbonyl compounds (aldehyde and ketone)

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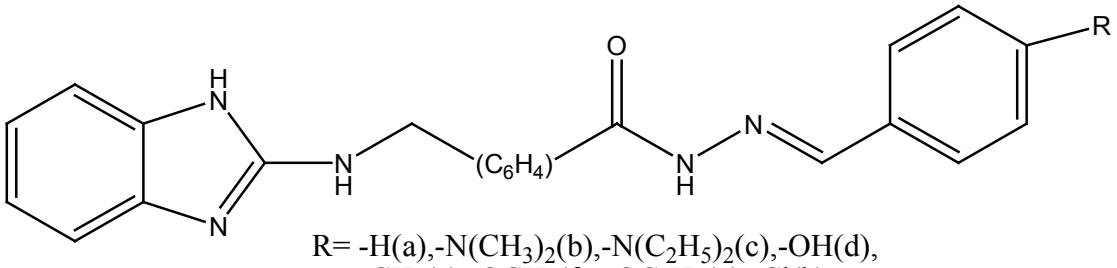
and others by using [10]. Subsequently, Phillips explored Ladenburg synthesis to the condensation between O-amino aniline and carboxylic acids (acetic acid). Hence the synthesis reaction of benzimidazole from O-amino aniline is known as Ladenburg synthesis or Phillips synthesis or Ladenburg – Phillips synthesis [11].

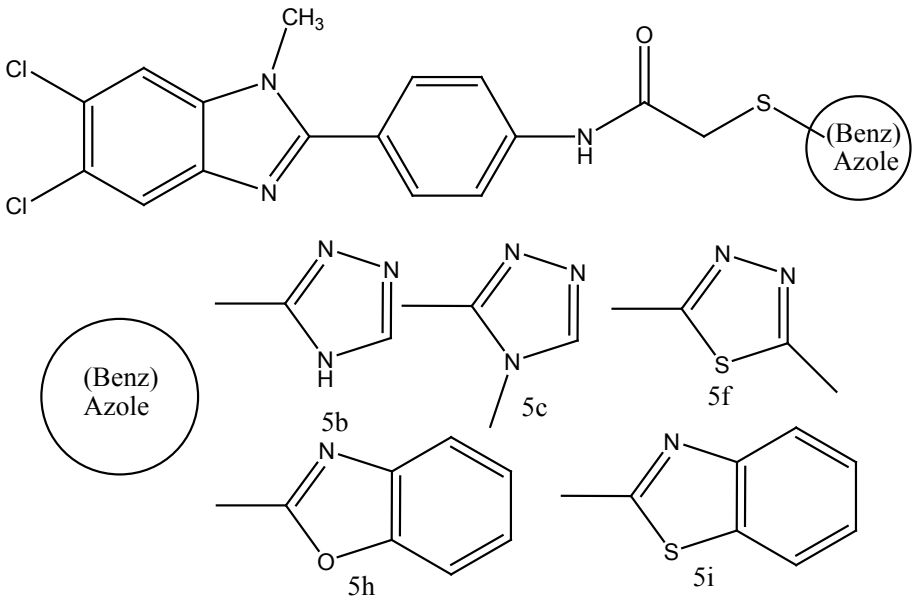
Antibacterial activity

In 2011, Özkay et al. screened a new series of 14 novel benzimidazole derivatives for antimicrobial activity. They used 9 bacterial strains of following bacteria *E. coli* 35218, *E. coli* 25922, *P. vulgaris, S. thyphimurium, K. pneumoniae, L. monocytogenes, S. aureus, E. faecalis* and *B. subtilis*. Unfortunately synthesized benzimidazole-hydrazones compounds were inactive against antibacterial activity. However all of the synthesized compounds indicate moderate antibacterial activity against *E. coli* [12]. Again a new series of benzimidazole derivatives bearing various (benz)azolylthio moieties were synthesized by the same group of researcher and screened them for their antimicrobial activity by using *E. coli* 35218, *E. coli* 25922, *P. vulgaris, S. thyphimurium, K. pneumoniae, P. aeruginosa, L. monocytogenes, S. aureus, E. faecalis,* and *B. subtilis* bacterial strain. Compound 5b show more potent antibacterial activity against *E. coli* 35218 having MIC of 6.25 (µg/mL) less than the reference drug chloramphenicol having MIC value of 12.5 (µg/mL). Compound 5b, 5c, 5f, 5h and 5i show more potent antibacterial activity against *P. vulgaris* having MIC value of 12.5(µg/mL), 25(µg/mL), 25(µg/mL), 25(µg/mL), 12.5 (µg/mL) respectively which is also less than the reference drug chloramphenicol with 50 (µg/mL) MIC value [13].



R= -H(a),-N(CH_3)$_2$(b),-N(C_2H_5)$_2$(c),-OH(d),
-CH_3(e),-OCH_3(f), -OC_2H_5(g),-Cl(h),
-Br(i),-F(j),-NO_2(k),-CF_3(l),-CN(m),-COOH(n)

4-(1H-benzimidazol-2-yl-aminomethyl)-N'-(4-substituted benzylidene) benzohydrazides



2-[4-[2-[(benz)azolylsulfanyl]acetylamino]phenyl]-5,6-dichloro-1-methyl-1H-benzimidazole

Trimethylsilyl substituted benzimidazole derivatives were synthesized by Yılmaz et al. and synthesized compounds were tested against standard strains of Gram (+) *E. faecalis* and *S. aureus* and Gram (-) *E. coli* and *P. aeruginosa* bacteria. Compounds I exhibits maximum antibacterial activity against all the bacterial strain but always show higher MIC value in comparison of reference drug ampicillin. Except I, compound 2 and compound 4 also exhibit better antibacterial activity against gram (+) *E. faecalis* and *S. aureus*) with MIC value 50 µg/cm^3 [14]. A series of 4"-*O*-benzimidazolyl clarithromycin derivatives were designed and synthesized by C. Cong et al. (2011) and evaluated them for antibacterial activity against

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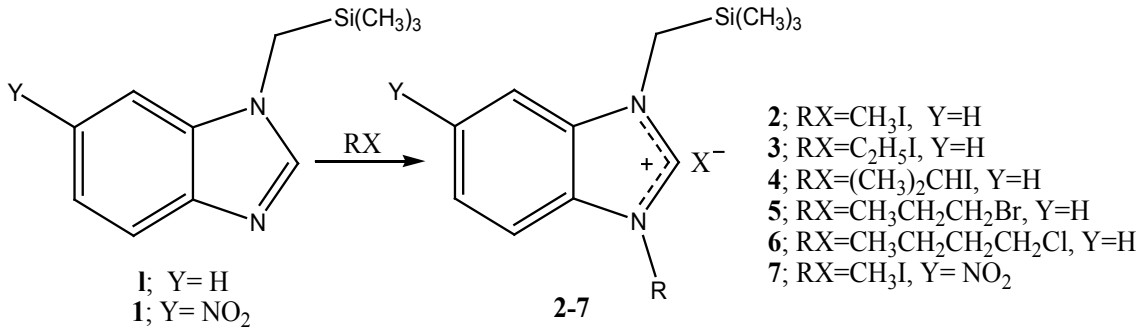
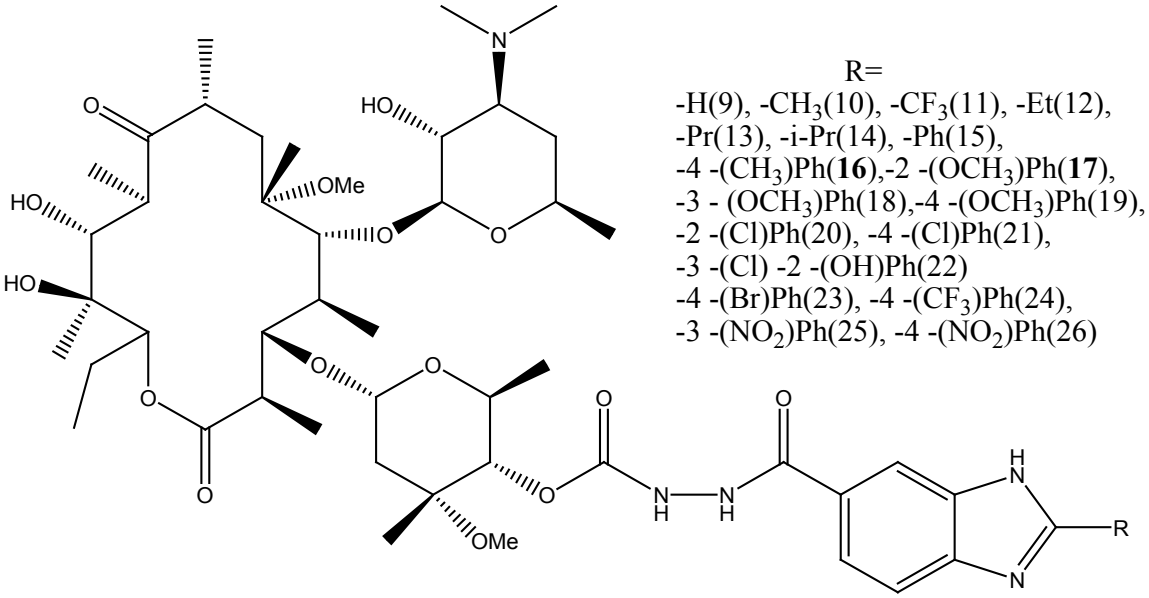
S. pneumoniae ATCC49619, *S. pneumoniae* B1, *S. pneumoniae* A22072, *S. pneumoniae* AB11, and *S. aureus* ATCC25923. Compounds 16 and 17 were the most active against erythromycin-resistant *S. pneumoniae* expressing the erm gene and the mef gene. In addition, 2-methoxypheyl derivative compound 17 exhibited the highest activity against erythromycin-susceptible *S. pneumoniae* ATCC49619 have MIC of 0.03 µg/mL and *S. aureus* ATCC25923 have MIC of 0.03 µg/mL as well. It is also important to notice that the arylbenzimidazolyl derivatives show higher activity against erythromycin-susceptible and erythromycin-resistant strains than the alkyl benzimidazolyl derivatives [15].

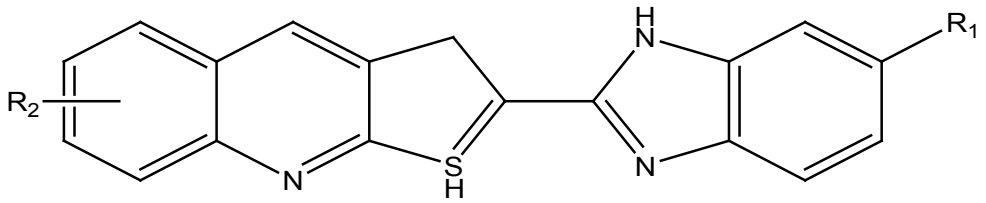


Trimethylsilyl substituted benzimidazole derivatives

Gowda et al. synthesized a new series of 2-(1H-benzimidazol-2-yl)-6-substituted thieno[2,3-b]quinolines and evaluate them for antibacterial activity against *E. coli*, *S. aureus*, *P. aeruginosa*, and *K. pneumonia* strains. Nitro derivatives show antibacterial activity but much less in comparison of taken reference Nitrofurazone [16].



Structure of 4"-O-benzimidazolyl clarithromycin derivatives



4a: R_1=H, R_2=H
4b: R_1=H, R_2= 6 - Me
4c: R_1=H, R_2= 6 -OMe
4d: R_1=H, R_2= 8 - Me
4e: R_1=NO_2, R_2 = H
4f: R_1=NO_2, R_2= 6 - Me
4g: R_1=NO_2, R_2= 6 - OMe
4h: R_1= NO_2, R_2= 8 - Me

2-(1H-benzimidazol-2-yl)-6-substituted thieno[2,3-b]quinolines

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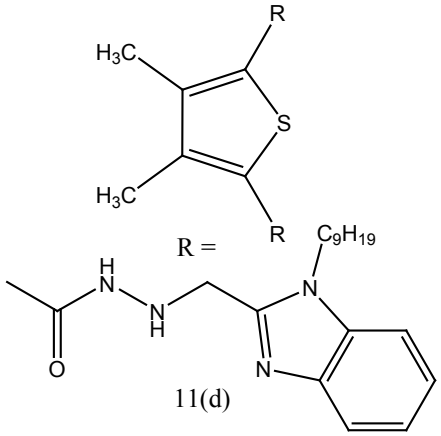
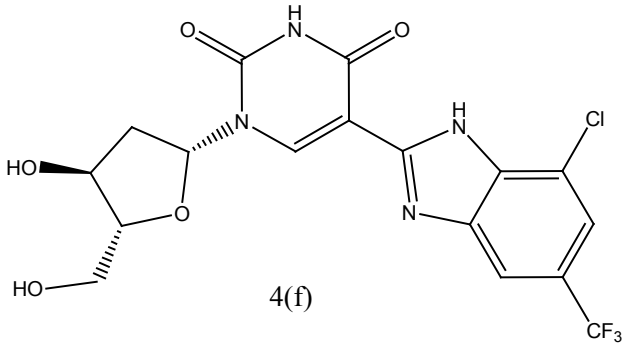
Zhang et al. synthesized a series of benzimidazole derivatives and screened for antibacterial activity against gram (+) and gram (-) bacterial strains. Among of all the compounds 11d and its hydrochloride 13b exhibit remarkable antibacterial activity in comparison of reference drugs Norfloxacin, Chloromycin and Fluconazole. Compound 11d have MIC value of 2 µg/mL, 2 µg/mL, 4 µg/mL, 16 µg/mL, 4 µg/mL, 8 µg/mL, 4 µg/mL, 8 µg/mL, and 4 µg/mL against *S. aureus*, *B. subtilis, M. luteus, E. coli*, *S. dysenteriae*, *P. aeruginosa*, *B. proteus* and *E. typhosa* respectively [17]. A series of novel C-5 benzimidazolyl-20-deoxyuridines was synthesized by Krim et al. in good yields under solvent-free conditions and microwave irradiation from 5-formyl-20-deoxyuridine. All synthesized compounds (4a–h) were evaluated for *in vitro* antibacterial activity against the following bacterial strains; *S. aureus* (ATCC 13709 *in vivo*, ATCC 25923, oxford and MRSA *in vivo*), *E. faecalis* (ATCC 29212 VanS), E. faecium (Van A), *S. pneumoniae* (Van A, ATCC49619, Pen R and Blood effect), *H. influenzae* (ATCC 31517 MMSA), *E. coli* (ATCC 25922) and *P. aeruginosa* (ATCC 27853). Among all the compounds 4e and 4f exhibits good antibacterial activity but 4f exhibit good activity against gram (+) bacteria *S. aureus* (ATCC 13709 *in vivo*, ATCC 25923, oxford and MRSA in vivo) (2 µg/ml), *E. faecalis* (2 µg/ml), *E. faecium* (1 µg/ml) and *S. pneumoniae* (4–16 µg/ml), more potent than the tow reference drugs except in the presence of serum, but in the second test of this compound the activity could not be well reproduced [18].



11(d)



4(f)

Moreira et al. evaluated symmetric bis benzimiazole (sBBZ) conjugates for antibacterial activity against a range of gram (+) and gram (-) bacterial strains. And they found that para-Substituted ethoxy(4), amino(5) and methoxy(9) derivatives displayed potent bacteriostatic activity against MARS, vancomycin-resistant enterococci, streptococci and *Listeria monocytogenes* [19].

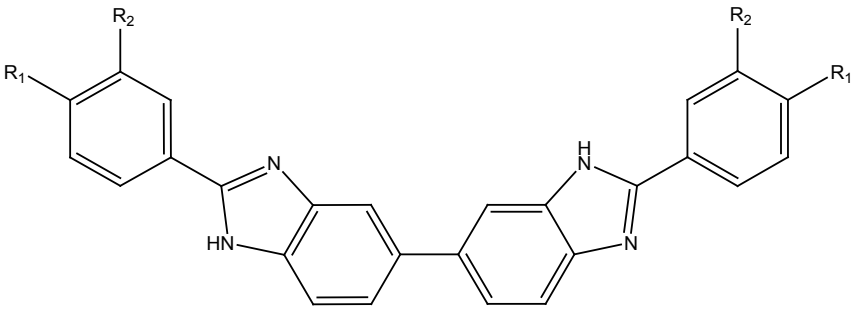


Figure: Structure Of Symmetric Bis Benzimidazole

sBBZ	1	2	3	4	5	6	7	8	9	10
R_1	Me	Et	CF_3	OEt	NH_2	Cl	F	H	OMe	OBn
R_2	H	H	H	H	H	H	H	OMe	H	H

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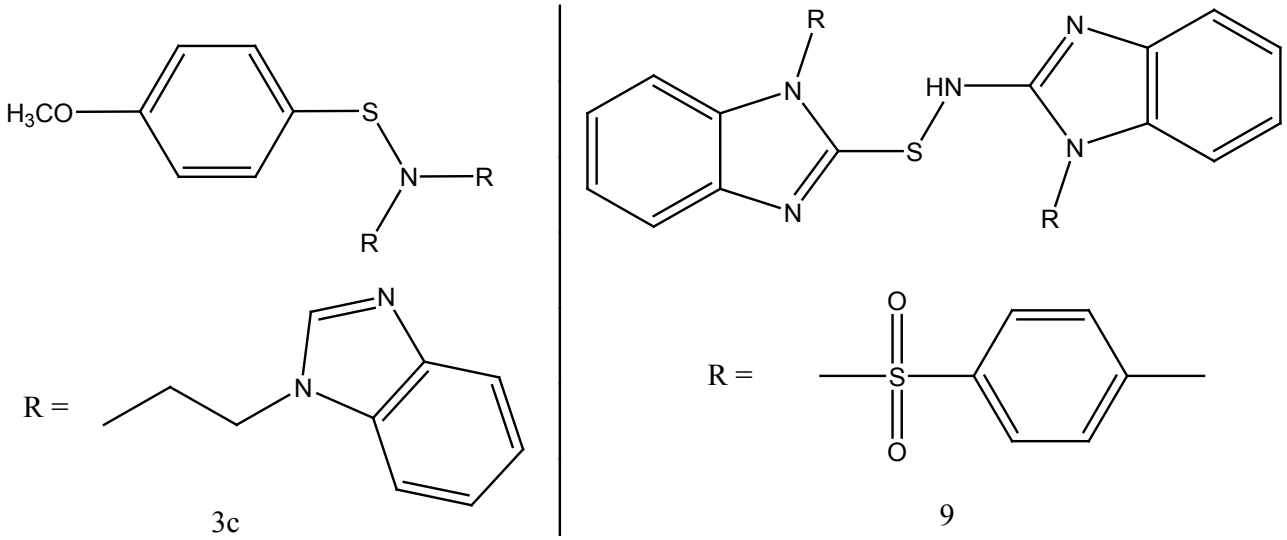
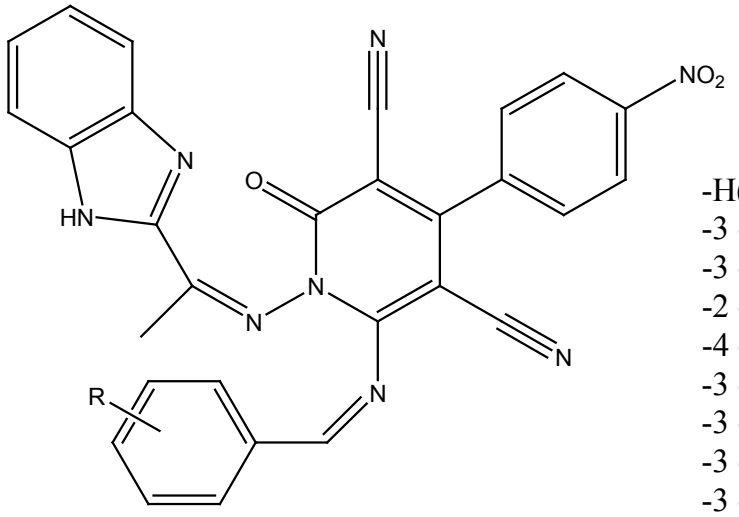
Al-Mohammed et al. synthesized benzimidazole derivatives along with imidazole derivatives. All compounds evaluated for antibacterial activity by using standard gram (+) *S. pyogenes*, *S. aureus*, *B. subtilis, R. ruber*, *E. faecalis*, *S. epidermidis* and gram (-) *E. coli*, *S. typhimurium*, *P. aeruginosa*, *A. calcoacetius* bacterial strains. Compound 3c and 9 exhibit highest antibacterial activities. Used reference drug was Amoxicillin and kanamycin. In case of *A. calcoacetius*, compound 3c have MIC value of 0.05 µg/mL lower than the reference drugs and compound 9 show lower MIC (0.30 µg/mL) in comparison of reference drug kenamycin have MIC of >0.5 µg/mL [20].



Structure Of 3c and 9

Desai et al. synthesized a series of benzimidazole bearing 2-pyridones and evaluated for their *in vitro* antibacterial activity. They used two gram (-) bacterial strain, i.e., *E. coli* (MTCC-443), *P. aeruginosa* (MTCC-1688) and two gram (-) bacterial strain *S. aureus* (MTCC-96), S. pyogenes (MTCC-442). Benzimidazole derivatives 5q and 5r exhibit equivalent or sometimes more potent antibacterial activity in compare of reference drug. Compound 5q have MIC value 12.5 µg/mL more which is more than reference drugs Ciprofloxacin (50 µg/mL) and Chloramphenicol (50 µg/mL) in case of *P. aeruginosa* [21].



R =

-H(a), -2 -OH(b),
-3 -OH(c), -4 -OH(d),
-3 -F(e), -4 -F(f),
-2 -Cl(g), -3 -Cl(h),
-4 -Cl(i), -2 -CH_3(j),
-3 -CH_3(k), -4 -CH_3(l),
-3 -OCH_3(m), -4 -OCH_3(n),
-3 -NO_2(o), -4 -NO_2(p)
-3 -Br(q), -4 -Br(r)

Structure of benzimidazole derivatives 5(a-r)

Noolvi et al. synthesized a series of 1-methyl-N-[(substituted-phenylmethylidene)-1H-benzimidazol-2-amines (4a–4g) and novel azetidine-2-one derivatives of 1H-benzimidazole (5a-5g) compounds and screened all synthesized compound for antibacterial activity along with cytotoxic activity. Used bacterial strain were of *S. aureus*, *B. pumillus*, *E. coli* and *P. aeruginosa* bacteria. Unfortunately, no one synthesized compound shown good antibacterial activity (in term of MIC value) in compare of reference drug ampicillin [22].

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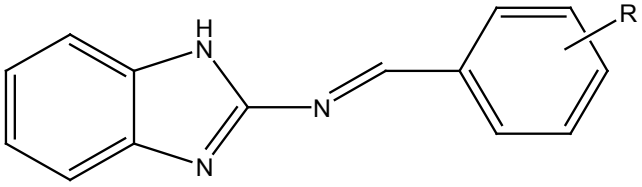
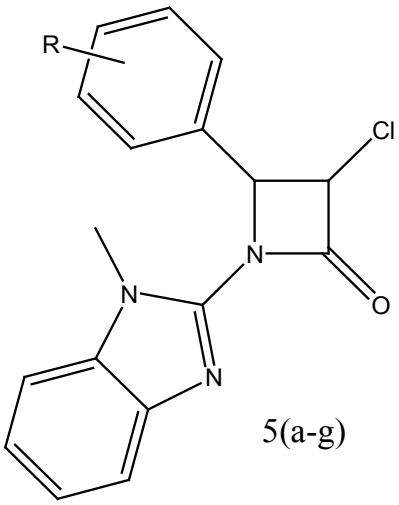


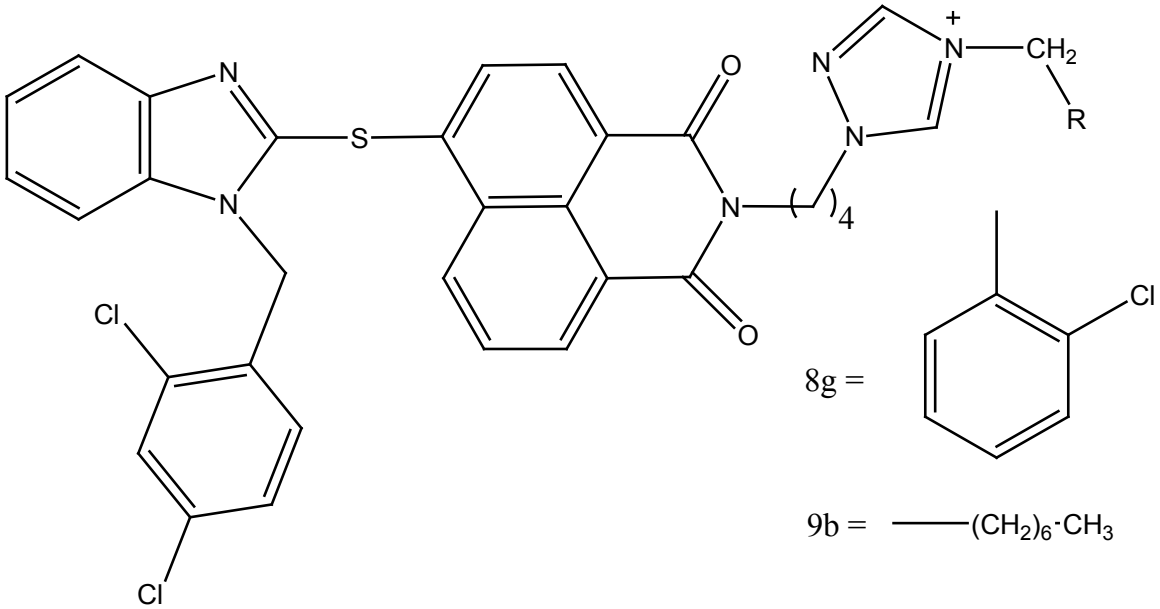
4(a-g)

R= 4-Chloro, 4-Nitro, 2-Nitro, 3-Nitro, N, N-dimethyl amino, 2,5-dimethoxy, 2-Chloro



5(a-g)

Zhou et al. synthesized benzimidazole derived naphthalimide triazole derivatives. All of the new compounds were screened for their antibacterial activity. All newly compounds were effective growth inhibitor for bacterial strain. But most effective compounds are the following according to their MIC value: 8g and 9b (2 ± 0.9 µg/mL) for *S. aureus*; 8b, 8g and 9b have 14 ± 3.5 µg/mL, 14 ± 3.5 µg/mL and 29.71 µg/mL respectively for MRSA; 6e (4 ± 0.9 µg/mL), 8b (14 ± 3.5 µg/mL), 8g (4 ± 0.9 µg/mL), 8h (7 ± 1.8 µg/mL), 9b (4 ± 0.9 µg/mL) and 9c (14 ± 7.1 µg/mL) for B. subtilis; 8b (29 ± 7.1 µg/mL), 8g (14 ± 3.5 µg/mL), 9b (29 ± 7.1 µg/mL) for M. luteus; 6g (4 ± 0.9 µg/mL), 6i (14 ± 3.5 µg/mL), 8a (14 ± 3.5 µg/mL), 8b (19 ± 7.1 µg/mL) 8g(7 ± 1.8 µg/mL), 9b (19 ± 7.1 µg/mL) for B. proteus; 8g (7 ± 1.8 µg/mL) for *E. coli*; 8b (14 ± 3.5 µg/mL), 8g (14 ± 3.5 µg/mL) for *P. aeruginosa*; 8g (9 ± 3.5 µg/mL), 9a (19 ± 7.1 µg/mL) for B. typhi. All the taken values are more than taken references Chloromycine and Norfloxacin. Acoording to study, 8g and 9b derivatives are more promising for antibacterial activity [23].



8g =

9b = $-(CH_2)_6\cdot CH_3$

Geeta et al. synthesized 26 novel benaimidazole derivatives bearing an alkyl chain at N^{-1} position of benzimidazole. All of the synthesized compounds were screened for antimicrobial activity of gram (+) bacterial strain of *S. aureus* and *B. subtilis* and gram (-) bacterial strain of *E. coli*, *S. typhi*, *K. pneumoniae* and *P. aeruginosa* bacteria, along with anti-HIV activity. Compound 37, 43 (a methyl substituted), 44 (an ethyl substituted), 45, 50 and 51 exhibits higher antibacterial activity but less than the standard [24]. Zhou et al. designed and synthesized a series of 5-fluorouracil benzimidazoles. They found that all the synthesized compounds shown moderate to excellent antibacterial activity against all tested bacterial strains. Among all the compounds, 5c exhibits remarkable antibacterial activity compared with chloromycine and norfloxacin. Compound 5c have MIC of (2 ± 0.21 µg/mL) against MRSA, (4 ± 0.59 µg/mL) against *S. aureus*, (16 ± 1.75 µg/mL) against *B. subtilis*, (64 ± 6.34 µg/mL) against *M. luteus*, (2 ± 0.21 µg/mL) against *E. coli* DH52, (8 ± 1.16 µg/mL) against *E. coli* JM109, (4 ± 0.59 µg/mL) against *B. proteus* and (8 ± 1.16 µg/mL) against *B. typhi* [25].

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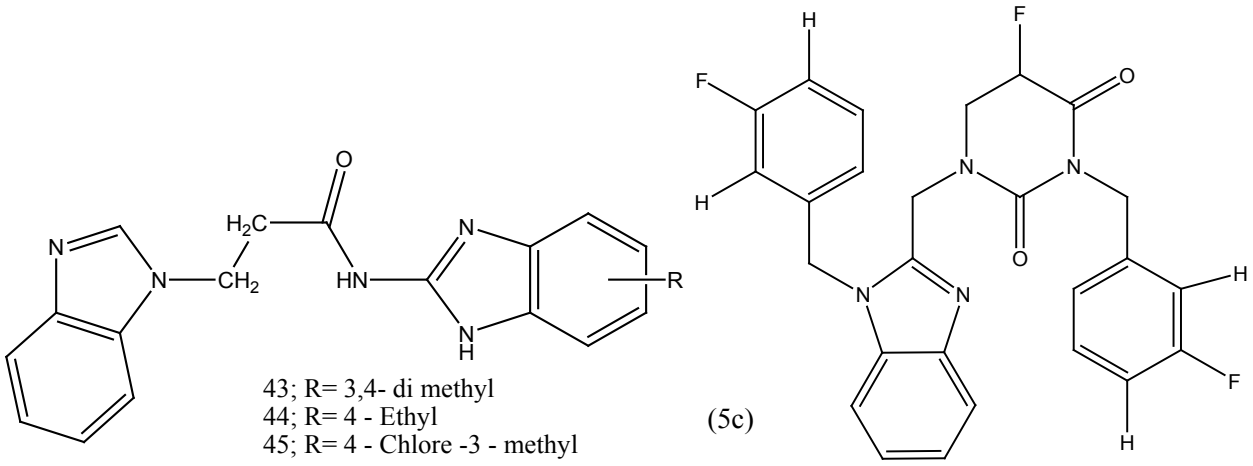
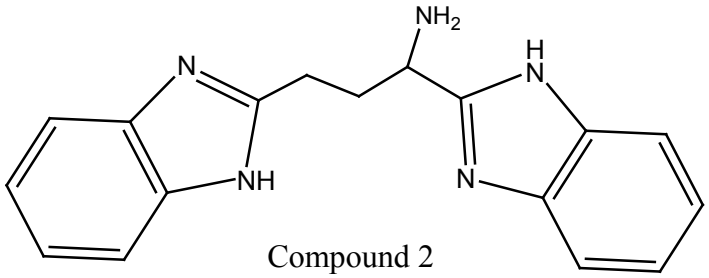


43; R= 3,4- di methyl
44; R= 4 - Ethyl
45; R= 4 - Chlore -3 - methyl

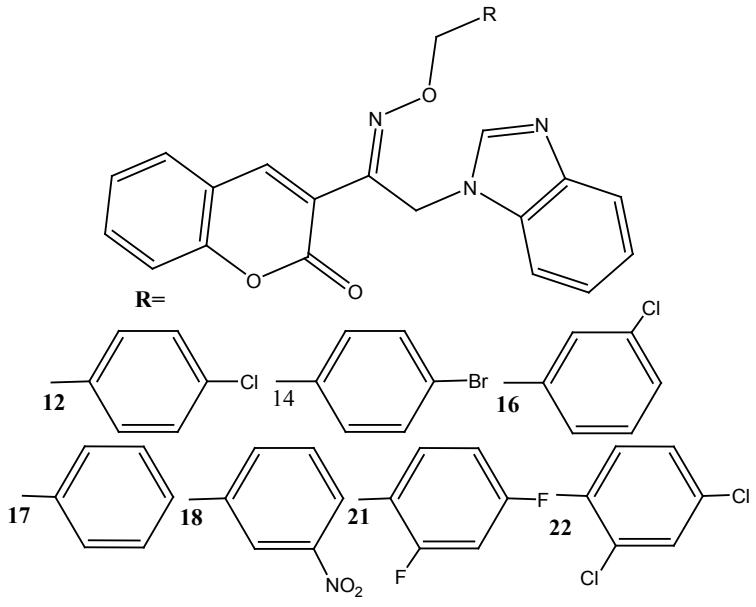
(5c)

Negi et al. synthesized and screened amino acids derived benzimidazole derivatives for antibacterial activity against standard bacterial strain of *S. aureus* MTCC 1144, *S. pneumonia* MTCC 655, *S. pyogenes* MTCC 442, *P. aeruginosa* MTCC 2474, *K. pneumoniae* MTCC 4030. Compound 2 (derived from glutamic acid) exhibits excellent antibacterial activity against all bacterial strain in compare of other synthesized compounds. Compound 1 and 2 show higher antibacterial activities than reference drug erythromycin in case of *P. aeruginosa*. Antibacterial activity was shown in term of minimum inhibition zone (MIZ) [26].



Compound 2

Singh et al. synthesized a new series of 11 novel coumarin-benzimidazole hybrid compounds and screened for their antibacterial activity against 9 bacterial strains of gram (+) (*B. subtilis* MTCC 1789, *B. cereus* MTCC 1305, *S. aureus* ATCC 9144, *S. aureus* ATCC 6538P, *4* ATCC 155) and gram (-) bacteria (*P. aeruginosa* ATCC 25668, *P. vulgaris* ATCC 29905, *K. pneumoniae* ATCC 29665, *E. coli* MTCC 739). Compound 12 exhibit significant activity against *B. subtilis, S. aureus* ATCC 6538P, *P. aeruginosa* and *E. coli* having MIC value of 0.95 µg/mL, 1.56 µg/mL, 3.12 µg/mL, and 3.12 µg/mL respectively. Compound 14 exhibit significant activity against *B. subtilis* and *P. vulgaris* having MIC value of 6.25 µg/mL and 1.56 µg/mL respectively. Compound 16, 17, 18, 21, and 22 exhibits significant activity against *P. vulgaris with* MIC value of 12.25 µg/mL, 3.12 µg/mL, 12.25 µg/mL, 1.56 µg/mL and 1.56 µg/mL respectively [27].



Coumarin-Benzimidazole Hybrid

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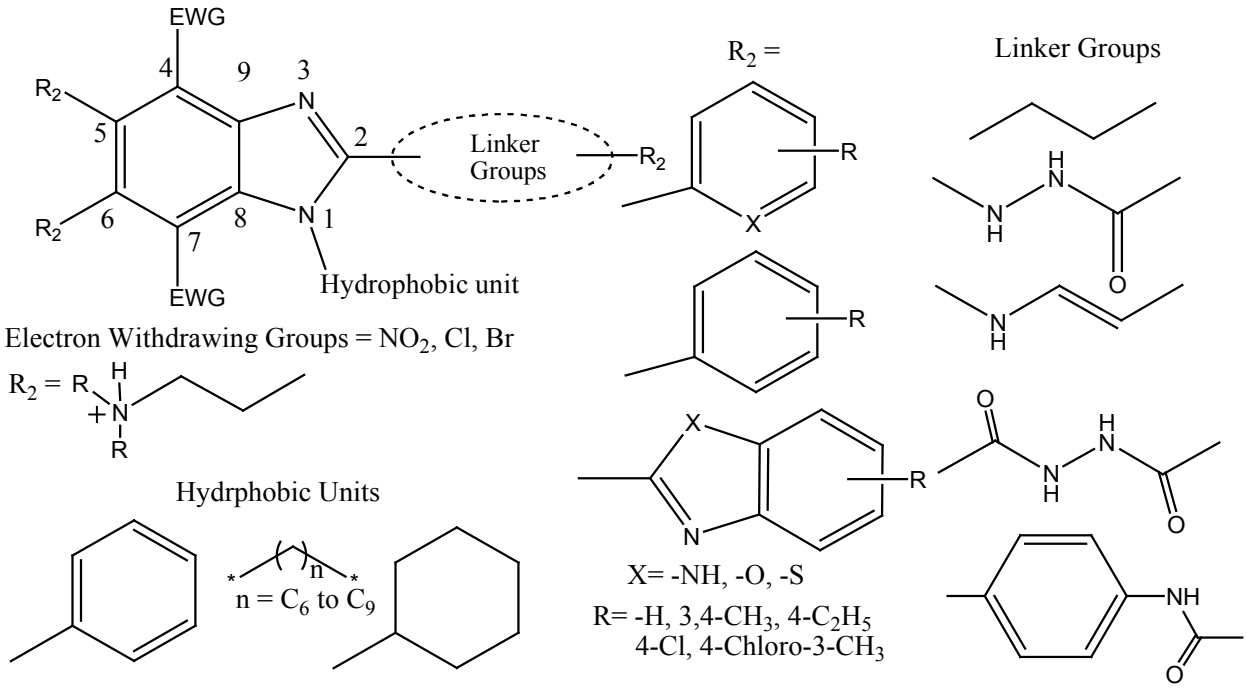
CONCLUDING DISCUSSION

A series of novel compounds containing benzimidazole nucleus were designed, synthesized and screened for antibacterial activity along with others biological activities. But unfortunately, none compound becomes an antibiotic for the clinical use. On the basis of above discussion it's possible to design a hypothetical model to reduce bacterial infection. Researcher suggests so many facts about structural optimization on benzimidazole nucleus, and to simplify we tabulate all synthesized compound with bacterial strains in the **Table 1.**



Hypothetical model for bacterial inhibition

After examination of all the facts, we prepare a possible hypothetical model for bacterial growth inhibition. Various substitutions required on benzimidazole nucleus such as a hydrophobic unit at N^{-1} (benzene, cyclohexane, or aliphatic chain) for better antibacterial activity as shown in the research work of Zhang et al. Compound 11a-f with alkyl chain of different length exhibits better antimicrobial efficiency. A benzenoid group at C-2 attached with a linker group containing nitrogen preferentially, but N-3 is must be unsubstituted because of possible interaction with different groups of lone pair electron present at nitrogen. At C-4 or C-7 an electron withdrawing group will be suitable due to electron density factor. Electron density is very important factor to reach optimum value of activity and it's also a well-known fact that high electron density causes difficulties in diffusion through bacterial or microorganism cell wall or substantial activity loss may occurs. A substituted ammonium group must be at C-5 or C-7 position. It increases the cell membrane permeability.

Table 1. Effective synthesized compound against bacterial strains.

S. No.	Bacterial strain	Synthesized compound
1	*S. aureus*	Comp I [14]; Comp 17 [15]; Comp 11d, 13b [17]; Comp 4f [18]; Comp 3c, 9 [20]; Comp 8g, 9b [23]; Comp 5c [25]; Comp 12 [27];
2	*K. pneumoniae*	Comp 43, 44, 45 [24]
3	*B. subtilis*	Comp 13b [17]; Comp 3c, 9 [20]; Comp 8g, 9b [23]; Comp 5c [25]; Comp 12 [27]
4	*S. epidermis*	Comp 3c, 9 [20]
5	*P. aeruginosa*	Comp I [14]; Comp 11d, 13b [17]; Comp 5q [21]; Comp 3c, 9 [20]; Comp 8g [23]; Comp 1, 2 [26]; Comp 12 [27]
6	*P. vulgaris*	Comp 5b, 5c, 5f, 5h, 5i [13]; Comp 14, 17, 21, 22 [27]
7	*S. typhimurium*	Comp 3c, 9 [20]
8	*E. coli*	Comp I [14]; Comp 5b [13]; Comp 11d [17]; Comp 3c, 9 [20]; Comp 8g [23]; Comp 43, 44, 45 [24]; Comp 5c [25]; Comp 12 [27]
9	*S. pneumonia*	Comp 17 [15]; Comp 4f [18]
10	*R. ruber*	Comp 3c, 9 [20]
11	*B. proteus*	Comp 13b [17]; Comp 8g, 9b [23]; Comp 5c [25]
12	*B. typhi*	Comp 8g [23]; Comp 5c [25]

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13	*M. luteus*	Comp 13b [17]; Comp 8g, 9b [23]; Comp 5c [25]
14	*E. faecalis*	Comp I [14]; Comp 4f [18]
15	*A. calcoacetius*	Comp 3c, 9 [20]
16	*E. typhosa*	Comp 13b [17]
17	*S. dysenteriae*	Comp 11d 13b [17]
18	*E. faecium*	Comp 4f [18]
19	*Enterococci*	Comp sSBZ [19]
20	*Streptococci*	Comp sSBZ [19]
21	*L. monocytogenes*	Comp sSBZ [19]
22	*S. pyogenes*	Comp 3c, 9 [20]
23	*E. faecalis*	Comp 3c, 9 [20]
24	*S. typhi*	Comp 43, 44, 45 [24]
25	*MARS*	Comp 11d [17]; Comp 8g, 9b [23]; Comp 5c [25]

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