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New Generation of Quinazolinone Derivatives as Potent Antimicrobial Agents

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Abstract

Heterocyclic compounds play tremendous roles and wide applications in the field of medicinal chemistry. Among them, quinazoline derivatives have been found to be exhibit various diverse broad pharmacological activities such as antibacterial, antifungal, anti-tuberculosis, anticancer, antivirus, anti-HIV, antimalarial, anti-convulsant, antileishmanial activity, anti-inflammatory, anti-hypertensive, and antidiabetic activity. Due to their vast biological activities, the research and development of Quinazolinone-containing compounds are increasingly active and alluring topics in the field of medicinal chemistry. Quinazolinone and their various derivatives possess wide spectrum of antimicrobial activity. In this work, we have summarized various derivatives of quinazolinone molecule and their substituents exhibits antimicrobial activity.

Keywords: Antimicrobial activity, Heterocyclic compounds, Pharmacological activities, Quinazolinone

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Introduction

The use of antimicrobial agents is critical to successful treatment of infectious diseases. Although there are numerous classes of drugs that are routinely used to treat infections in humans, there are several reasons why the discovery and development of new antimicrobial agents are important. Over the past decade, there has been an increased development of resistance in organisms that are typical pathogens in humans. This increased resistance has limited the selection of antimicrobials that may be used to treat specific organisms. New antimicrobials are also needed for certain groups of organisms. Very limited numbers of antimicrobials are available to treat infections caused by fungi and mycobacteria. In addition, microorganisms are constantly changing, finding new places to live and new ways to survive, and adapting to new situations. With the continuing discovery of new infectious diseases and the development of new disease processes of existing pathogens, it is important to continue to find anti-infective agents that can be used to treat these infections. Development of novel classes of drugs, drugs with fewer side effects, and drugs with shorter lengths of treatment are key in continuing the fight against infectious disease.[1]

Quinazoline was prepared by Gabriel in 1903 although the first derivative was synthesized by Griess. The name was proposed by Widdege, other names such as phenmiazine, benzo-1, 3-diazine and 5; and 6-benzopyrimidine have occasionally been used. The numbering suggested by Paal and Busch is still in use. Quinazoline shows broad variety of biological activity profiles, such as analgesic, anti-inflammatory, antibacterial, diuretic, antihypertensive, antimalarial, sedative, hypoglycemic, antibiotic, and antitumor. These examples clearly demonstrate the potential of quinazoline derivatives as a source of useful pharmacophore for new drug evolution.[2]

Quinazolinone ring system is renown because of its wide spectrum of pharmacological activities due to various substitutions on this ring system. Quinazolinone is one of the most important heterocyclic compound, weak base, having varied biological activities, and still of great scientific interest nowadays. They are widely found in bioorganic and medicinal chemistry with application in drug discovery. This review was focused on the quinazolinones and its different derivatives that possess antimicrobial activities.[3]

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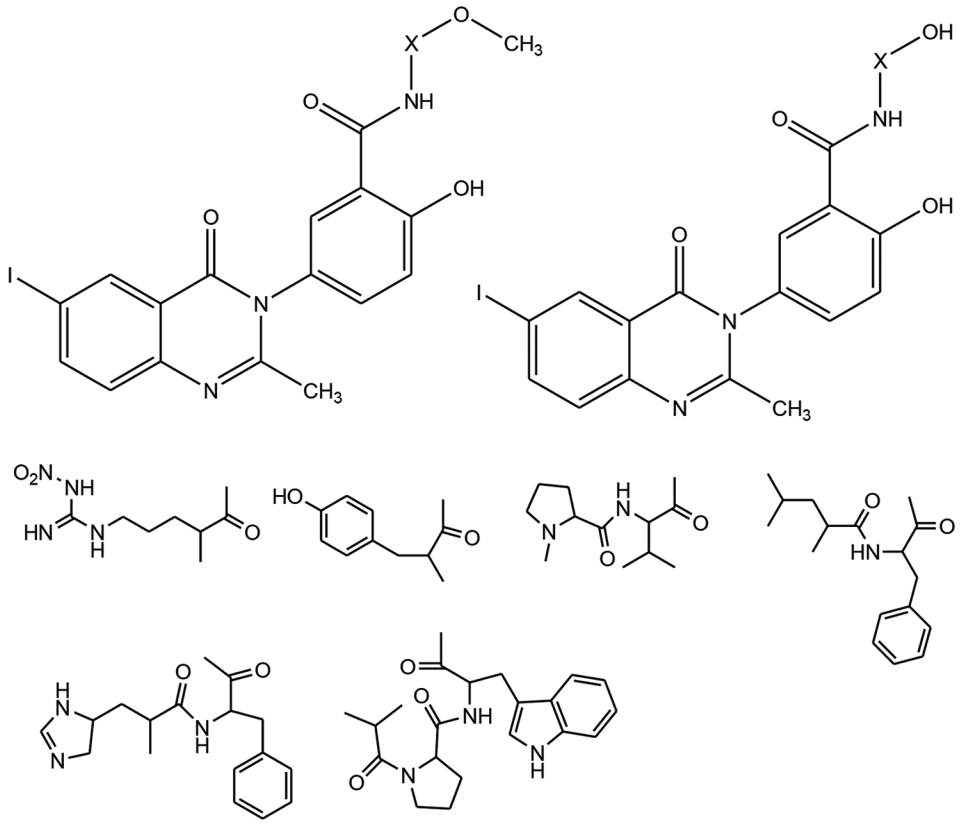
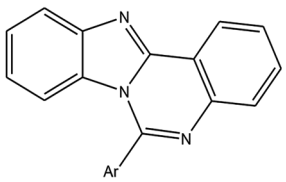
In The Recent Years a Number of Quinazolinone Derivatives have been Synthesized and Found Antimicrobial Activity

Dahiya *et al*., two substituted quinazolinyl/imidazolyl-salicylic acids 5, six were synthesized by the reaction of 6-iodo-2-methylbenzoxazin-4-one/5-nitroimidazole with 5-aminosalicylic acid. Coupling of compounds 5 and 6 with different amino acid ester hydrochlorides, dipeptide, and tripeptide methyl esters yielded novel quinazolino/imidazolopeptide derivatives. All peptide derivatives were assayed for antimicrobial and anthelmintic activities against eight pathogenic microbes and three earthworm species.[4]

Rohini *et al*., a series of 6-arylbenzimidazo [1,2-c] quinazoline compounds were synthesized by the condensation of 2-(o-aminophenyl) benzimidazole with different arylaldehydes, followed by oxidative cyclisation of the resulting 2-o-arylideneaminophenylbenzimidazoles. The antimicrobial



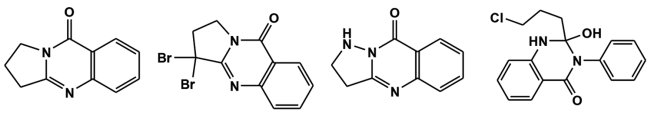
activities of all 6-arylbenzimidazo [1,2-c] quinazolines against three Gram-positive (*Staphylococcus aureus, Bacillus subtilis,* and *Streptococcus pyogenes*), three Gram-negative (*Salmonella typhimurium, Escherichia coli,* and *Klebsiella pneumonia*) bacteria, and three fungal strains (*Aspergillus niger, Candida albicans,* and *Trichoderma viridae*) were evaluated.[5]



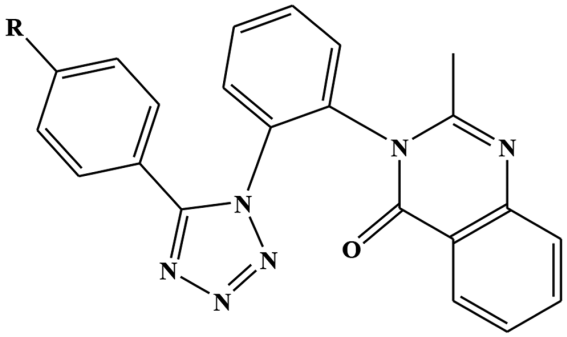
a= 2-hydroxy-benzaldehyde
b= 5-bromo-2-hydroxy-benzaldehyde
c= 2-hydroxy-5-nitro-benzaldehyde
d= 2-hydroxy-5-mrthoxy-benzaldehyde
e= 3-formyl-benzoic acid
f= 3-formyl-4-hydroxy-benzoic acid
g= 4-Hydroxy-3,5-dimethyl-benzaldehyde
h= 3,5-Dimethoxy-benzaldehdye
i= Quinoline-2-carbaldehyde
j= Pyridine-3carbaldehyde

Hassanzadeh F., *et al*., synthesized and evaluated anti-bacterial, anti-fungal and cytotoxic activity of some new quinazolinone derivatives. Quinazolinone ring system is renown because of its wide spectrum of pharmacological activities due to various substitutions on this ring system.[6]

Khodarahmi *et al*., synthesis of some new quinazolinone derivatives and evaluation of their antimicrobial activities. The synthesized compounds were evaluated against six strains of bacteria (three Gram-positive and three Gram-negative) and three strains of fungi. Overall results of antimicrobial tests showed that the compounds had better bacteriostatic activity against Gram-negative bacteria. The obtained results of MBC revealed that these compounds had more significant bacteriostatic than bactericidal activities. Almost all of the screened compounds showed good activity against *C. albicans* and *A. niger*. The obtained results of MFC indicated that these compounds had more significant fungistatic than fungicidal activities.[7]



Kumar *et al*. synthesized compounds of quinazoline-1 derivatives and to test their antimicrobial and anti-HIV1 activities. A quick-witted method was developed for the synthesis of novel substituted quinazolinone derivatives by summarizing diverse diamines with benzoxazine reactions, and it demonstrated the benefits of typical reactions, handy operation, and outstanding product yields. It was found that compounds possessed a wide range of antimicrobial and anti-HIV1 activity.[8]

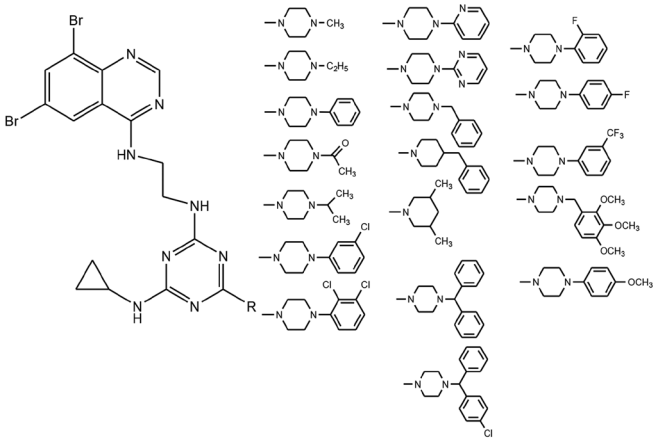


R= -H -F, -CN, -Cl, NO_2,

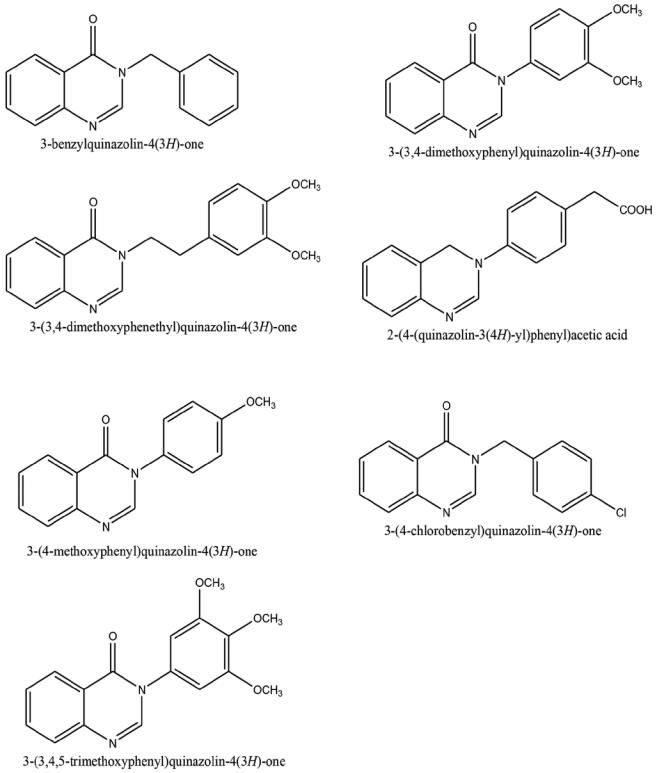
Zein *et al*. synthesis of 2-Acetyl-1, 3-diarylidene-2, 3-dihydro-1H-pyrazino [2, 1-b] quinazoline-4, 6-dione derivatives. The prepared compounds also exhibited antimicrobial activity.[9]

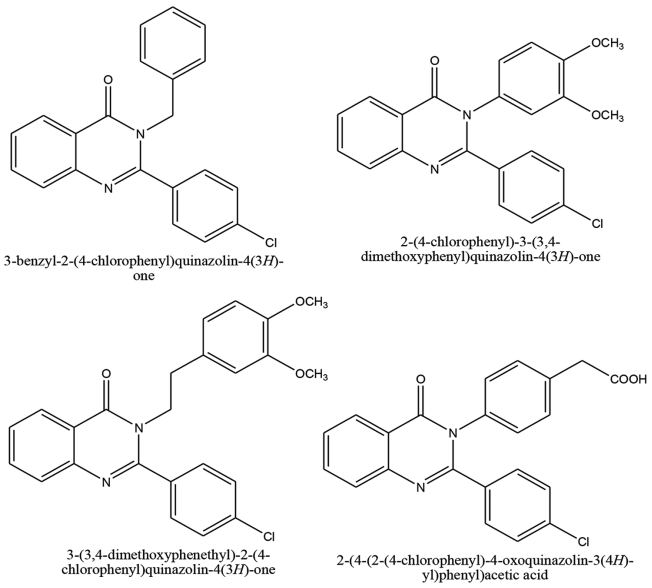
Tran *et al*. synthesized a series of quinazoline derivatives and evaluated against *Mycobacterium tuberculosis* as GlmU uridyltransferase inhibitors.[10]

Modh *et al*. design, synthesis, antimicrobial activity, and anti-HIV activity evaluation of novel hybrid quinazoline–triazine derivatives. Further, evaluated the *in vitro* anti-HIV activity of the newly synthesized compounds against HIV-1 (IIIB) and HIV-2 (ROD) viral strains and as well as *in vitro* antimicrobial activity against four bacteria (*S. aureus*, *Bacillus cereus*, *Pseudomonas aeruginosa*, and *K. pneumoniae*) and two fungi (*Aspergillus clavatus* and *C. albicans*) using the paper agar streak dilution method.[11]

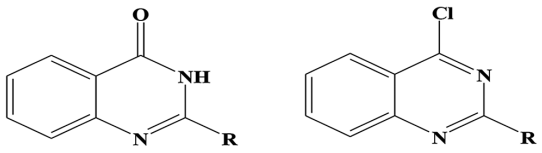


Mabkhot YN., *et al*, reported synthesis, anti-microbial and molecular docking studies of Quinazolin-4(3H)-one derivative.. In this work, synthesis, antimicrobial activities, and molecular docking studies of some new series of substituted quinazolinone. Among the prepared products, 3-benzyl-2-(4-chlorophenyl) quinazolin-4(3H)-one was found to exhibits the most potent *in vitro* antimicrobial activity against *S. aureus*, *B. subtilis*, *P. aeruginosa*, and *E. coli*, respectively.[12]



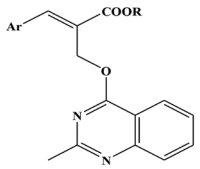


Chavan *et al*., synthesis and evaluation of some new 4, 6-disubstituted quinazoline derivatives for antimicrobial and antifungal activities. The newly synthesized derivatives were evaluated for their antimicrobial activity against *E. coli* and *S. aureus* and for antifungal activities against *C. albicans* and found promising antimicrobial and antifungal activities.[13]



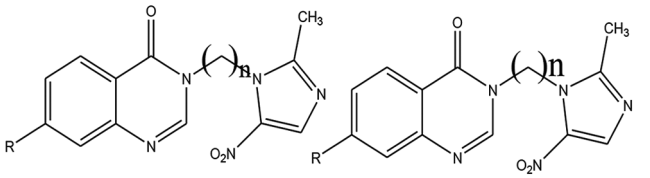
R = CH_3, Br, I, OCH_3

Chebrolu *et al*., synthesis, characterization and antimicrobial activity of some new Baylis-Hillman derived Cinnamyl substituted quinazolinone derivatives. The compounds without any substitution at the aryl group exhibited good antibacterial activity especially on *Staphylococcus epidermidis*, replacement of hydrogen atom of the aryl group by CF_3 or by fluorine exhibited significant antibacterial activity on both Gram-positive (*S. epidermidis*) and Gram-negative (*K. pneumonia*) organisms compared to other compounds. All the compounds exhibited interesting antifungal activity on *C. albicans* microorganism exclusively and inactive on the remaining organisms.[14]

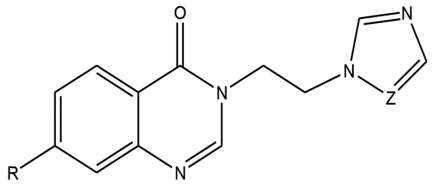


Ar	R
C_6H_5	CH_3
4-$OMeC_6H_4$	CH_3
2-$CF_3C_6H_4$	CH_3
4-$NO_2C_6H_4$	CH_3
C_8H_7 Naphthalen 1-yl	CH_3
4-BrC_6H_4	CH_2CH_3

Peng L., *et al*, discussed synthesis and biological evaluation of a new class of quinazolinone azoles as potential antimicrobial agents and their interactions with calf thymus DNA and human serum albumin. Bioactive assay showed that some target compounds exhibited significant antimicrobial potency. The hydrogen bonds and Van der Waals forces played important roles in the association of compound human serum albumin.[15]

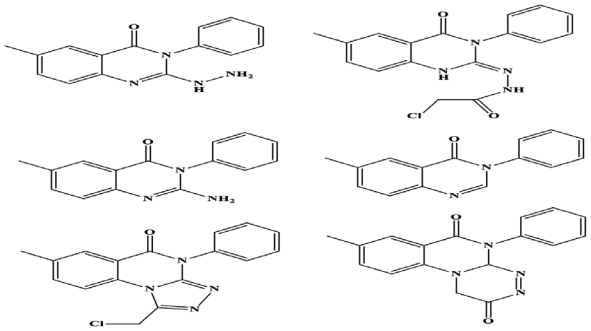


	a	b	c	d	e	f	g	h	i	j
R	F	F	F	F	F	Cl	Cl	Cl	Cl	Cl
n	2	4	5	6	10	2	4	5	6	10

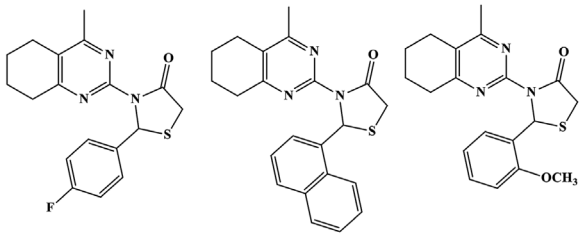


	a	b	c	d
R	F	Cl	F	Cl
Z	C	C	N	N

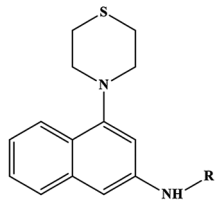
Alanazi *et al*., some new derivatives of substituted-4(3H)-quinazolinones were synthesized and evaluated for their *in vitro* antitumor and antimicrobial activities.[16]



Gupta *et al*., a series of new 4-thiazolidinone derivatives was synthesized, characterized by spectral techniques, and screened for antimicrobial activity. All the compounds showed moderate-to-good antimicrobial activity. Compounds (2-[4-fluoro-phenyl]-3-[4-methyl-5,6,7,8-tetrahydro-quinazolin-2-yl]-thiazolidin-4-one) and (3-[4,6-dimethyl-pyrimidin-2-yl]-2-[2-methoxy-phenyl]-thiazolidin-4-one) were the most potent compounds of the series, exhibiting marked antimicrobial activity against *Pseudomonas fluorescens*, *S. aureus*, and the fungal strains.[17]

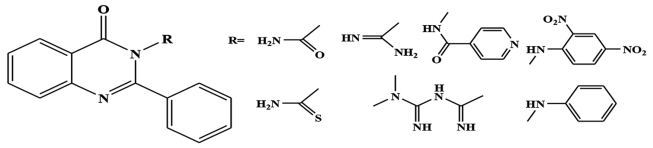


Prabhakar V., *et al*, a novel series of Quinazolines were synthesised. Anti-bacterial and anti-fungal activities were evaluated and compared with the standard drugs such as Amoxicillin and Fluconazole.[18]



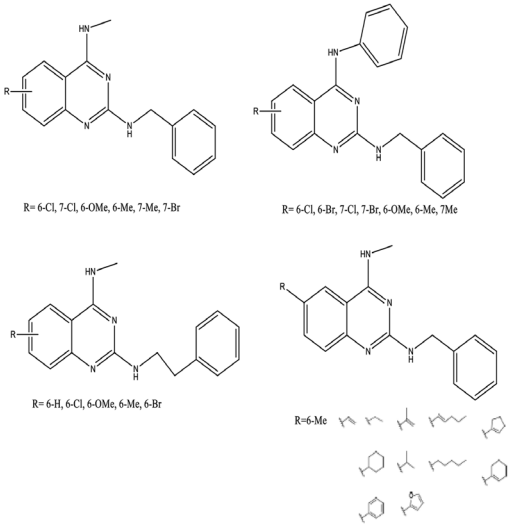
R= Phenyl, 4-Methyl phenyl, 4-Methoxy phenyl, 4-Tri fluoro phenyl, 4-Chloro phenyl, 4-Bromo phenyl, 4-Nitro phenyl, pyridin-4-yl boronic acid, thiophen-2- yl boronic acid, furan-2-yl boronic acid

Rajasekhar KK., *et al*, a series of 2, 3-disubstituted quinazolinone derivatives were synthesized. The structures of new compounds were confirmed by IR, ^{1}H NMR and Mass Spectroscopy. They have been reported to show significant antibacterial and antitubercular activities. A binding affinity prediction by AutoDock Vina was higher for the 2-phenyl series, which may be due to increased hydrophobic interactions within the binding site of enoyl-acyl carrier protein reductase.[19]



Antypenko LM., *et al*., series of 1-R-2-([1,2,4] triazolo[1,5-c] quinazoline-2-ylthio) etanon(ol)s were synthesized, evaluated by spectral data and studied against *S. aureus, M. luteum, E. faecalis, E. aerogenes, P. aeruginosa, C. sakazakii, E. coli, K. pneumonia, hospital Streptococcus spp., C. albicans* and *A. niger*. Molecular docking showed their good affinity into the active sites of EcPanK-AMPPNP and hDHFR. Hence, reported results will be used for subsequent QSAR model creation and purposeful antimicrobial modification of the strongest compounds.[20]

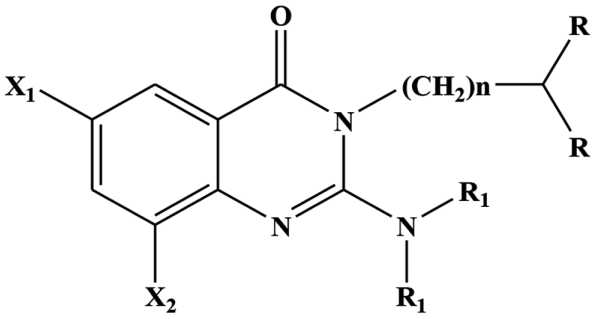
Fleeman R., *et al*, studied characterizing the antimicrobial activity of N^2, N^4-Disubstituted Quinazoline-2, 4-Diamines toward multidrug-resistant Acinetobacter baumannii. N^2, N^4-disubstituted quinazoline-2, 4-diamines have strong antimicrobial and antibiofilm activities against both Gram-positive organisms and Gram-negative pathogens, suggesting strong potential for their development as antibacterial agents.[21]



Kapoor B., *et al*., synthesized and evaluated anti-microbial activity of Quinazolinone peptide derivatives. All the synthesized derivatives exhibited moderate to significant antibacterial activity against both Gram-positive and Gram-negative bacteria. Peptide derivatives of quinazolinone are promising antimicrobial agent and can be used for the synthesis of other novel compounds.[22]

Nandwana *et al*. design and synthesis of Imidazo/Benzimidazo [1,2-c] quinazoline derivatives and evaluation of their antimicrobial activity. A new class of fused quinazolines has been designed and synthesized through copper-catalyzed Ullmann type C–N coupling followed by intramolecular cross-dehydrogenative coupling reaction in moderate to good yields. The synthesized compounds were tested for *in vitro* antibacterial activity and antifungal activity.[23]

Chaitanya *et al*., a series of novel substituted 8-bromo-2-(dimethylamino)-3-(3-[dimethylamino] propyl) quinazoline-4(3H)-one derivatives were prepared with excellent yields and evaluate their antimicrobial activity.[24]



Comp.	X1	X2	n	R	R1
A	H	Br	2	CH_3	CH_3
B	H	Br	2	CH_3	C_2H_5
C	H	Br	3	CH_3	CH_3
D	H	Br	3	CH_3	C_2H_5
E	H	Br	2	C_2H_5	CH_3
F	H	Br	2	C_2H_5	C_2H_5
G	H	Br	3	C_2H_5	CH_3
H	H	Br	3	C_2H_5	C_2H_5

Conclusion

Several developed quinazolinone derivatives possessed good to superior antimicrobial activities. This review provides important information for the upcoming design of new antimicrobial agents based quinazolinone skeleton. This review has complied significant information about antimicrobial activities of various derivatives based on quinazolinone heterocyclic nucleus as per the recent most literature survey. It may be concluded by this present review article that quinazolinone nucleus is a versatile and medicinally important nuclei having promising antimicrobial potential which may provide lead compounds for drug design and development of potent antimicrobial agents.

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