



ANTIMICROBIAL ACTIVITIES OF QUINAZOLINONE AND THEIR DERIVATIVES: A REVIEW

Mahesh Chand, Archana Gupta and Subhash C. Jain

Department of Chemistry, University of Delhi, Delhi-110007
E-mail: mahesh.chand2008@gmail.com

ABSTRACT

Quinazoline and quinazolinone have fused heterocyclic rings have attracted a chemist due to their wide range of applications in the field of medicinal chemistry. There are large number of papers, reports and reviews on quinazoline and quinazolinone for their diversified biological activities such as anti-HIV, anticancer, antifungal, antibacterial, antimutagenic, anticoccidial, anticonvulsant, anti-inflammatory, antidepressant, antimalarial, antioxidant, antileukemic, and antileishmanial activities and other activities. Quinazolinones and their compounds with different substitutions make it as an important chemical for the various biological, physiological and pharmacological significance. Quinazolinone exhibited broad spectrum of biological activities. Infections caused by multi-drug resistant bacteria are of major health concern worldwide due to increasing incidence of infections caused by these microorganisms and their ability of developing antibiotic resistance to multiple antibiotics. Due to some serious side effects in newly introduced antimicrobial agents, the development of a diversified series of antimicrobials still remains a necessity. Quinazolinone and its analogues exhibited wide spectrum of antimicrobial activities. We therefore have made efforts to briefly summarize various quinazolinones possessing antimicrobial activity in this review which continuing improvements have been made for antimicrobial agents containing quinazolinone in various aspects in addition to the antimicrobial spectrum and activity.

KEYWORDS: Quinazoline, Quinazolinone, Antimicrobial Activity,, Antibacterial, Antifungal and Antimalarial

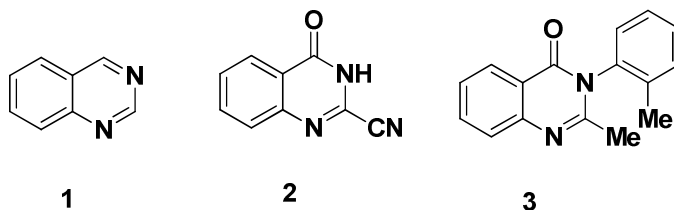
INTRODUCTION

World is facing serious infections caused by multi-drug resistant microorganism caused by the various microorganism as Gram-positive bacteria, Gram-negative bacteria and fungi due to increasing incidence of infections caused by these microorganisms in hospitals and communities, and their ability of developing antibiotic resistance to multiple antibiotics. Due to some serious side effects in newly introduced antibacterial agents such as semi-synthetic streptogramins quinupristin/dalfopristin, daptomycin, the development of a diversified series

of antimicrobials still remains a necessity. Antimicrobial drugs have caused a dramatic change not only of the treatment of infectious diseases but of a fate of mankind.

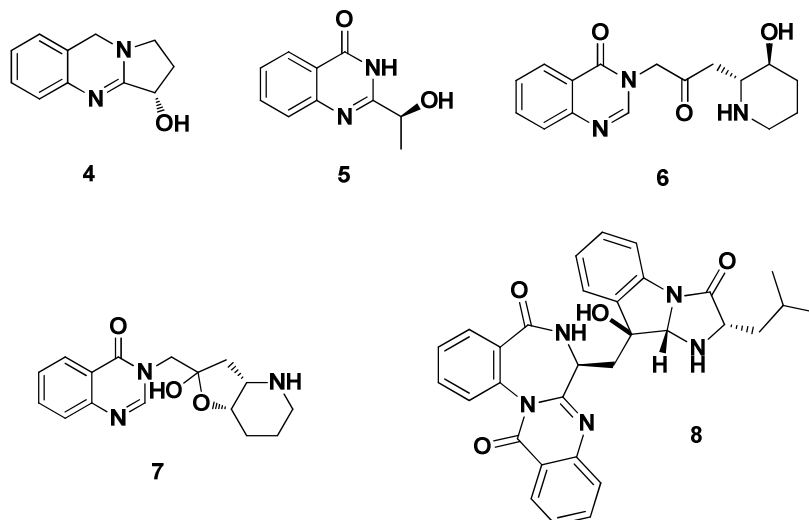
Quinazoline antimicrobials represent an example of drugs with improved pharmacodynamics and safety. Quinazoline antimicrobials developed after norfloxacin have been called new quinolones, and they have still been key drugs. Antimicrobial chemotherapy has conferred huge benefits on human health. Quinazoline deserve special attention because it is also an important tool for the synthesis of new compounds. This unit features in many alkaloids and is also known to show a wide range of biological activity.

Quinazoline is a heterocyclic moiety containing benzene ring fused to pyrimidine. The quinazoline **1** is a frequently encountered unit in organic chemistry as well as in medicinal chemistry. The first quinazoline was synthesised in the late 1860s from anthranilic acid and cyanogen to obtain 2-cyanoquinazolinone **2**.^{I,II} Since then, a remarkable number of quinazoline synthesis have been carried out, and the details are included in a number of reviews and monographs on quinazoline chemistry and synthesis.^{III,IV} Methaqualone (**3**) is perhaps the most well known synthetic quinazoline drug, which has been examined extensively due to its sedative-hypnotic effects.^{V,VI} It was first synthesized in 1951 from 2-methylaniline and 2-(acetylamino)benzoic acid using phosphorus trichloride.^{VII} There are many other quinazoline drugs which also belong to the group of quinazolin-3H-4-ones and exhibit anticonvulsant, antibacterial, antidiabetic properties.^{VII-XII}



Quinazoline in Nature: Distribution and Sources

Quinazoline alkaloids are continuously updated in Natural Product Reports,^{XIII} and comprehensive reviews.^{XIV-XVI} These have been isolated from several families in the plant kingdom, as well as from bacteria and animal species, and many are bio-genetically derived from anthranilic acid. The first quinazoline alkaloid isolated was Vasicine (peganine, **4**) in 1888, produced by *Adhatoda vasica*, and was also later isolated from other species. Some other quinazoline alkaloids that have been isolated, characterized, and synthesised are Chrysogine (**5**),^{XVII,XVIII} Febrifugine (**6**) and Isofebrifugine (**7**).^{XIX-XXII} The latter two compounds are potential antimalarial drugs, but unfortunately are toxic to man. This has led to extensive synthesis and biological screening of many quinazoline derivatives and a number of interesting new alkaloids have been isolated. The structural diversity of fungal quinazolines has been broadened with the discovery of Asperlicin (**8**), produced by *Aspergillus alliaceus*, which is a potent cholecystokinin (CCK) antagonist.^{XXIII-XXV}



In 1968, mainly only two derivatives of quinazoline were used, soporific & anticonvulsant-methaqualone and diuretic quinathazone. By 1980, about 50 different derivatives of this class were included possessing different biological actions like 'soporific, sedative, tranquilizing, analgesic, anticonvulsant, antitussive, myorelexant, antirheumatic, hypotensive, antiallergic, bronchodilating, antidiabetic, cholagogue, diuretic, cystatic, antimalarial, spermicidal.

The increasing incidence of infection caused by the rapid development of bacterial resistance to most of the known antibiotics is a serious health problem. Consequently, there is an urgent need for the development of novel types of antimicrobial agents targeting unique mechanisms and pathways. Bacteria and fungi generally develop drug resistance in three ways: producing metabolizing enzymes for the degradation of the drugs, modifying their targets to render the drugs ineffective and expressing a high level of efflux proteins that 'pump' the drug out in order to lower its concentration. As multidrug resistant bacterial strains proliferate, the necessity for effective therapy has stimulated research into the design and synthesis of novel antimicrobial molecules.

Quinazoline moiety is of great importance to chemists as well as biologists as it is found in a large variety of naturally occurring compounds possessing diverse biological activities. Quinazoline derivatives have been used as antimalarial, anti-inflammatory, anticancer, antibiotic, antihypertensive, anti HIV and as tyrosine kinase PDGF-RTK inhibiting agents.

Inspired by the recent literature study and also as a part of our search programme for generating novel biologically active compounds, we have now taken up the synthesis of novel 1,2,3-triazole analogues containing biologically active moieties. The search for new, effective and safe nuclei has led to an improvement by increasing their potency. This was achieved by creating new biologically active agents by molecular modifications. Several nitrogen containing heterocyclic systems find a wide variety of therapeutic activities, therefore we choose quinazoline as our basic nucleus.

BIOLOGICAL IMPORTANCE

The quinazoline and quinazolinone skeleton is frequently encountered in medicinal chemistry. The various substituted quinazolines and quinazolinones are having significant antihypertensive, antineoplastic, antidepressant, and antipsychotic activities whereas some derivatives of quinazoline and quinazolinones are found to be effective agents such as analgesic, antipsychotic, antiarrhythmic, sedative hypnotics, antibacterial, anti-inflammatory,

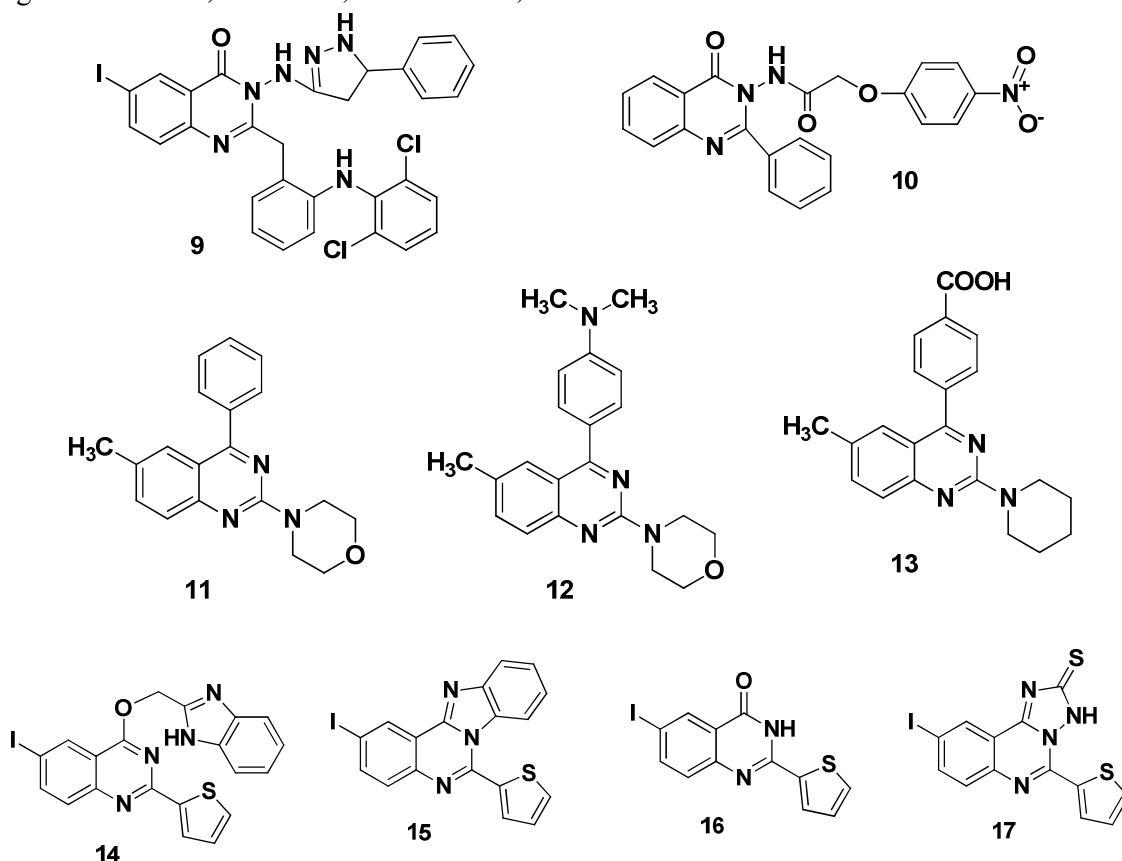
antifungal, antimalarial, anticonvulsant, anticoccidial, anti-Parkinsonism, cancer and other activities.^{XXVI-XXVIII}

Antibacterial Activity

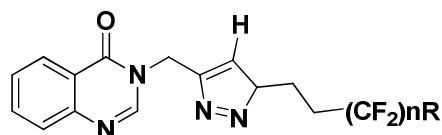
The *in vitro* antibacterial evaluation against different strains of bacteria at two different concentrations 100 $\mu\text{g/mL}$ and 50 $\mu\text{g/mL}$ of the series of new 2-[2-(2,6-dichlorophenyl)amino]phenylmethyl-3-[(5-substitutedphenyl)-1,5-dihydro-1*H*-pyrazol-3-yl-amino]-6-iodoquinazolin-4(3*H*)ones compounds (**9**) possessed impressive antibacterial activities.^{XXIX} Quinazolinone derivatives were synthesized and evaluated for antibacterial activity and from them, compounds (**10**) showed more potent antibacterial activity than the standard drug ampicillin.^{XXX}

Quinazolines derivatives were evaluated for their biological activity on various bacterial cultures^{XXXI} and the results showed comparative activity of the compounds **12** and **13** against *K. pneumoniae* as compared to ciprofloxacin but compound **11** showed greater activity against *S. sonnei*, *E. faecalis*, and *P. aeruginosa* as compared to ciprofloxacin.

Screened a series of some novel substituted iodoquinazoline derivatives for their antimicrobial activity^{XXXII} had showed remarkable activity of compounds **15** and **16** towards the gramnegative bacteria *E. coli*, whereas compounds **14**, **15**, and **17** showed potent activity against *S. aureus*, *B. subtilis*, *S. Cerevisiae*, and *C. albicans*.

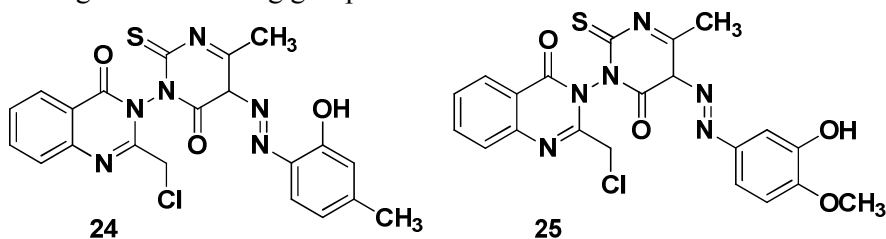


The antibacterial and antifungal activity of the 3-[5-(4-substituted phenyl)-1,3,4-thiadiazole-2-yl]-2-styryl quinazolin-4(3*H*)-ones (**18**) had reported.^{XXXII} The 6,7,8,9-tetrahydro-5(*H*)-5-nitrophenylthiazolo[2,3-*b*]-quinazolin-3(2*H*)-one derivatives and The 3-[(2-hydroxy-quinolin-3-ylmethylene)-amino]-2-phenyl-3*H*-quinazolin-4-one (**19**) and its metal (II) complexes showed antimicrobial activity^{XXXIII, XXXIV} along with some quinazolinone derivatives (**20**).^{XXXV}



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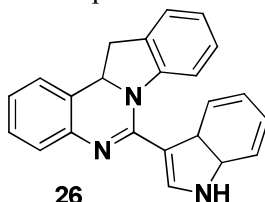
The potential antibacterial effects of the synthesized 2, 3-disubstituted quinazolin-4(3H)-ones derivatives were screened against Gram-positive and Gram-negative bacteria. Compound (24) with methyl and compound (25) with methoxy-substituted ring are found to be more active molecules in the respective series compared to the compounds bearing other electron donating or withdrawing groups.^{XLII}



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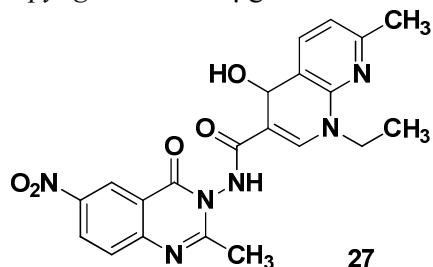
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The analogues of 6-substituted indolo [1, 2-c]quinazolines were prepared and investigated for antibacterial activity against various strains of Gram positive bacteria, Gram-negative bacteria and pathogenic Fungi (*Aspergillus niger*, *Candida albicans* and *Trichoderma viridae*). Ampicillin and ketoconazole were used as reference compounds compound (26) proved to be one of the most active broad spectrum antimicrobial agents.^{XLIII}



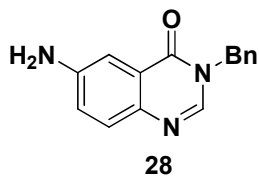
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New quinazolone compounds were performed their *in vitro* antimicrobial screening on randomly collected microbial strains. The derivatives showed marked inhibitory activity against enteric pathogen like *Aeromonas hydrophila* and to be active against *Streptococcus pyogenes*. Among the respiratory pathogens included in their study, compound (27) is found to have high activity against *S. pyogenes* at 300 µg ml.^{XLIV}

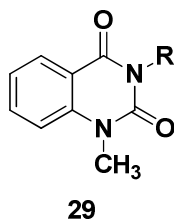


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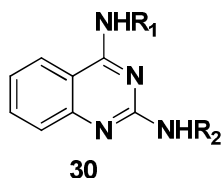
The synthesis of 2, 6-substitutedquinazolin-4-ones and screened those *in vitro* antimicrobial activity against a panel of standard strains of Gram-positive bacteria, Gram-negative bacteria, and yeast-like pathogenic fungus have reported. Compound (28) showed broad-spectrum antimicrobial activity comparable to the known antibiotic gentamicin.^{XLV}



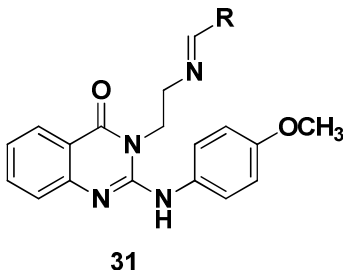
The evaluation for their *in vitro* antimicrobial activity against six strains of bacteria and five strains of fungi of the synthesized novel 1-methyl-3-substituted quinazoline-2, 4-dione derivatives (**29**) was studied. Most of the compounds exhibited moderate antimicrobial activities against the tested strains.^{XLVI}



The antibacterial evaluation of the synthesized new series of N2, N4-disubstituted quinazoline-2,4-diamines (**30**) were reported against multidrug resistant *Staphylococcus aureus*. This study led to the identification of N2, N4-disubstituted quinazoline-2, 4-diamines with minimum inhibitory concentrations (MICs) in the low micromolar range in addition to favourable physicochemical properties.^{XLVII}

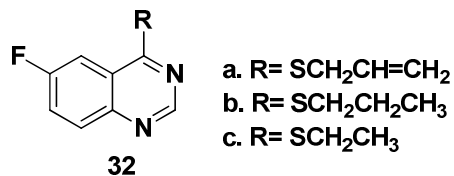


Twenty-seven novel (*E*)-3-[2-arylideneaminoethyl]-2-[4-(trifluoromethoxy) anilino]-4(3*H*)-quinazolinone derivatives (**31**) were evaluated for their activity against six fungi (*Gibberella zeae*, *Fusarium oxysporum*, *Clematis mandshurica*, *Paralepetopsis sasakii*, *Phytophthora infestans*, and *Sclerotinia sclerotiorum*) and three bacterial strains (*Xanthomonas oryzae*, tomato bacterial wilt, and tobacco bacterial wilt). Notably, these compounds exhibited the highest activity against tomato bacterial wilt and *X. oryzae*, with 50% effective concentration (EC₅₀) values ranging from 45.96 to 93.31 μg/mL and from 20.09 to 21.33 μg/mL respectively.^{XLVIII}



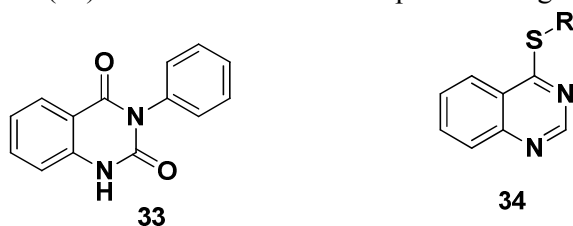
Antifungal Activity

The antifungal activities had shown by a series of few novel S-substituted-6-fluoro-4-alkyl (aryl)thioquinazoline derivatives (**32**). From all, especially compound **c**, having a wide spectrum of bioactivity; it shows potent inhibitory activity on the growth of most of the fungi with EC₅₀ values ranging from 8.3 to 64.2 μg/mL.^{XLIX}



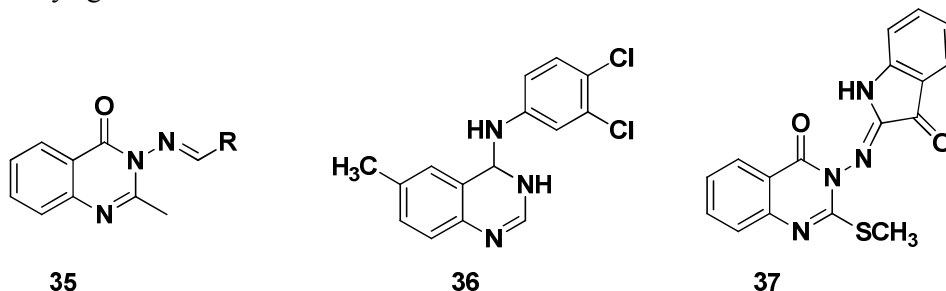
Antitubercular Activity

3-Arylquinazoline-2,4(1*H*,3*H*)-diones (**33**) were found as anti-TB agents along with a series of quinazoline derivatives (**34**) were exhibited for their pharmacological activity as anti-TB.^L



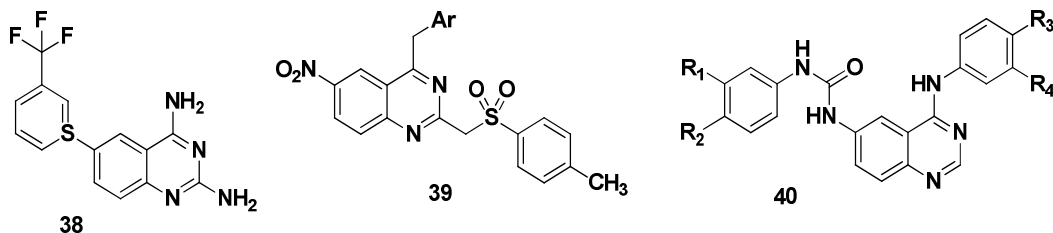
Antiviral Agents

A series of Schiff bases of some 2-phenyl quinazoline-4(3*H*)-one derivatives are evaluated for their activity as antiviral agents.^{LII} Compound **35** exhibited antiviral activity against herpes simplex virus-1 (KOS), herpes simplex virus-2(G), herpes simplex virus-1 (TK- KOS ACV), and vaccinia virus in HEL cell culture at selectivity index of 100, 100, 100, and 125, respectively, whereas cytotoxicity was observed at 100 µg/mL and demonstrated good activity against herpes simplex virus-1 (KOS), herpes simplex virus-2 (G), and vaccinia virus. The protein kinase inhibitory activity and anticytomegaloviral activity showed few quinazoline (**36**) compounds.^{LII} Quinazolinones act as anti-HIV activity whereas compounds 3-amino-2-methyl mercaptoquinazolin-4(3*H*)-one (**37**) were synthesized by condensing the acidic imino group of isatin with formaldehyde and secondary amines and evaluated for anti-HIV activity against HIV-1 III B in MT-4 cells.^{LIII}

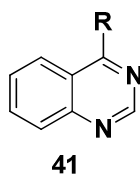


Antimalarial Agents

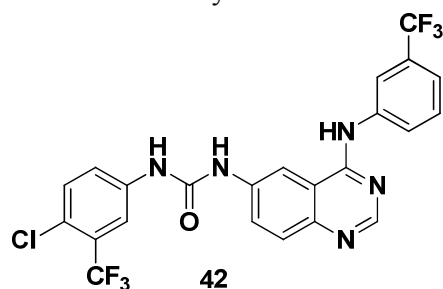
The 2,4-diamino-6-[(aryl)thio]quinazoline compounds were known to their antimalarial properties wherein the 4-amino group was replaced by hydrazine and hydroxyamino moieties and they found that such changes reduce markedly the antimalarial properties of this series. The compound (**38**) was tested against a normal drug-sensitive strain of *Plasmodium berghei* in mice by the parenteral route.^{LIV} A series of quinazoline derivatives (**39**) were evaluated for their antiplasmodial activity^{LV} and showed a high potential activity in comparison with chloroquine and doxycycline. A series of new 6-ureido-4-anilinoquinazolines (**40**) were evaluated for their potent activity as antimalarial agents.^{LVI}



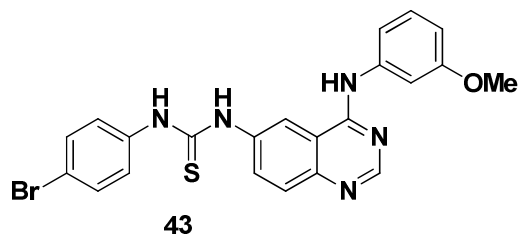
Quantitative structure activity relationship (QSAR) model for antimalarial activity, developed from a set of 51 substituted quinazolines (**41**) that exhibited remarkable *in vitro* activity against sensitive and multidrug-resistant *Plasmodium falciparum* malaria. 2D-QSAR was done using partial least squares method coupled with stepwise variable selection; subsequently, 3D-QSAR was carried out using stepwise variable selection k-nearest neighbor molecular field analysis (kNNMF) approach. The results helped to understand the nature of substituents around quinazoline nucleus, thereby providing new guidelines for the design of novel antimalarials.^{LVII}



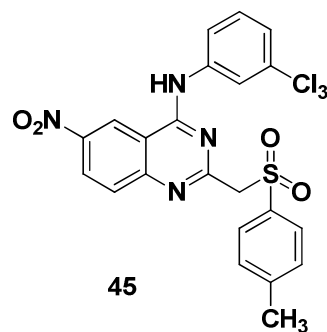
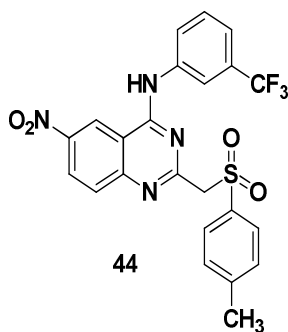
The synthesis and *in vitro* antimalarial evaluation of the series of new 6-ureido-4-anilinoquinazolines derivatives were reported activity against chloroquine-sensitive *P. falciparum*. Compound (**42**) had IC₅₀ value of 2.27 ng/mL which was equipotent to the standard drug chloroquine used in the bioassay.^{LVIII}



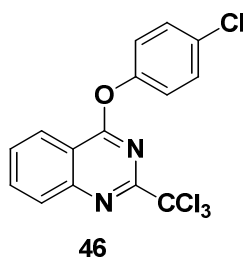
New series of 6-thioureido-4-anilinoquinazolines derivatives were synthesized and investigated those *in vitro* against multidrug resistant *Plasmodium yoelii nigeriensis*. Compound (**43**) shows 50% curative effect in the mouse model at an oral dose of 100 mg/kg× 4 days.^{LIX}



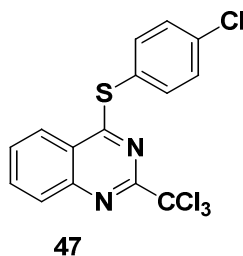
The quinazoline derivatives were synthesized and screened for *in vitro* antiplasmodial activity on the W2 chloroquino-resistant *Plasmodium falciparum* strain. The compounds (**44**) & (**45**) have found both significant antiplasmodial activities and low toxicity, compared with two reference drugs: chloroquine and doxycycline.^{LX}



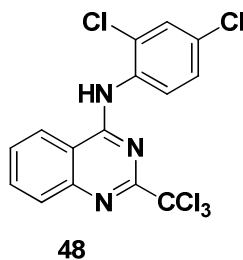
The investigation of new series 4-phenoxy-2-trichloromethylquinazoline was done and evaluation those *in vitro* antiplasmodial activity against multi resistant W2 *Plasmodium falciparum* strain. Compound (46) shown significant specific activity against the Plasmodium genus in comparison with Toxoplasma.^{LXI}



In vitro antiplasmodial activity against the human malaria parasite *Plasmodium falciparum* was studies of the series of new 4-thiophenoxy-2-trichloromethylquinazolines derivatives and compound (47) in comparison with chloroquine and doxycycline chosen as reference-drugs.^{LXII}

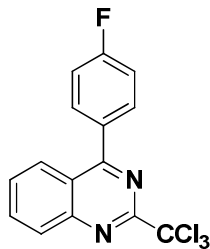


In vitro antiplasmodial activity evaluated of the synthesized some new 4-anilino-2-trichloromethylquinazolines derivatives. The molecules substituted by a bromine, chlorine or CF₃ group on the *meta* position of the aniline moiety were the most promising. Despite a non negligible toxicity, compound (48), maintains good selectivity index because of its high antiplasmodial activity.^{LXIII}



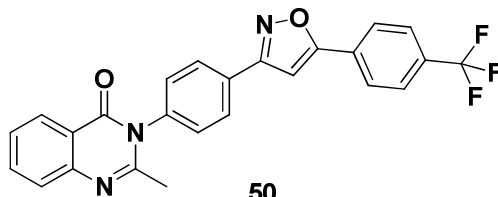
New 4-aryl-2-trichloromethylquinazolines derivatives were synthesized and they were evaluated for anti-plasmodial activity on both chloroquino-resistant and sensitive *Plasmodium falciparum* strains and the selectivity indexes for THP1 and HepG2 human cells

were also calculated, revealing their anti-plasmodial potential. Compound (49), was found quite good selectivity index, similar to those of chloroquine, and so, despite superior IC₅₀ values because of its safer profile toward human cells.^{LXIV}



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The antimicrobial evaluation of the synthesized series of novel isoxazole coupled quinazolin-4(3H)-one derivatives were done and all compounds shown mild to good antimicrobial activity. From all, compounds, 2-methyl-3-(4-(5-(4-(trifluoromethyl) phenyl) isoxazol-3-yl)phenyl)quinazolin-4(3H)-one (50) was found to be the most active compound.^{LXV}



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CONCLUSION

Heterocyclic pharmacophores containing quinazoline and quinazolinone nucleus plays most important role in the field of medicinal chemistry. The potential pharmacological profiles of quinazoline and quinazolinone have led the interest of many researchers to explore the utility of this moiety for better and varied pharmacological activities. A large number of quinazolinone based pharmaceuticals are becoming very important class of therapeutic agents and are likely to replace many obtainable organic based pharmaceuticals in the very near future. The quinazolinone compounds represent much progress with regard to the older compounds.

The review reports synthetic approaches to some of the quinazolinone derivatives and it highlights the use of quinazolinone derivatives having antimicrobial activity. The quinazolinone derivatives show significant antimicrobial activity against a variety of microorganisms such as fungi, Gram +ve and Gram -ve bacteria.

This review will help to gets an efficient way of understanding about antimicrobial quinazolinone pharmacophores which can further aid the process of drug design developments. This study may also accelerate the designing processes to generate a larger number of therapeutically active molecules.

CONFLICT OF INTERESTS

The author declares that there is no conflict of interests regarding the publication of this paper.

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