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REVIEW ARTICLE OPEN ACCESS

Recent Developments in the Antimicrobial Activity of Quinazoline

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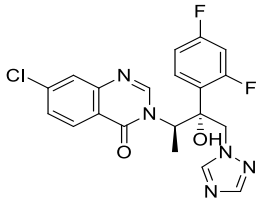
Abstract

Quinazoline derivatives have gained increasing attention in the synthesis and bioactivities study due to their substantial biological activities. To develop antibacterial agents that are more effective, Quinazoline is frequently tested for studies. Lead compounds containing Quinazoline with significant antimicrobial activity have been identified in the recent years. The emergence of drug-resistant microbial pathogens has spurred intensive research on novel antimicrobial agents. Quinazoline derivatives have shown promising potential as antimicrobial agents due to their diverse chemical structures and pharmacological activities. This review critically examines the recent developments in the antimicrobial activity of quinazoline compounds. Additionally, the potential challenges and future directions in the development of quinazoline-based antimicrobials are explored. The comprehensive analysis of recent advancements in the field of quinazoline antimicrobial research presented in this review will aid in the design of more effective and targeted therapeutic strategies against drug-resistant pathogens.

KEY WORDS: quinazoline, antimicrobials, anticancer, quinazolin-3,4-dione, quinazolinone, antibiotic resistance.

1. INTRODUCTION

The increasing cases of antibiotic-resistant pathogens that can cause serious infections have become a matter of concern. It is predicted that an extensive epidemic of resistant bacterial infections could potentially harm millions of people. For that, there is an urgent need to introduce new antibiotic molecules. As it takes a considerable time to introduce a new drug molecule into the market, necessity for screening a lot of compounds thus arises[1]. Importance of Quinazolinone ring system is well established to its wide spectrum of pharmacological activities. It is considered as one of the most important structures in medicinal chemistry. Quinazolinone derivatives have been known to have antibacterial, antifungal, anti-tuberculosis, anticancer and anti-inflammatory agents[2].



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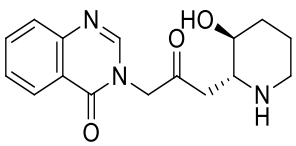

b

Figure 1. (a). Albaconazole **(b).** Febrifugine

Two marketed antimicrobial drugs containing quinazoline structure are Albaconazole and Febrifugine **(Fig. 1)**[3]. This review mainly focuses on recent update on the studies regarding quinazoline based scaffolds with antimicrobial activity. Consideration has been taken to cover the most recent references.

New quinazoline derivatives having both sulfonate ester and piperidine-4-carboxamide groups were synthesized and studied for their antimicrobial effects against *Xanthomonas oryzae* which is responsible for bacterial blight and bacterial leaf streak of rice.

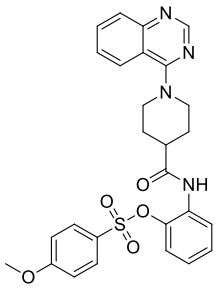

Figure 2. Compound III-17[4]

In a view to fight against bacterial resistance, 18 novel 5, 6-dihydrotetrazolo[1,5-c]quinazolines were synthesized and tested through *in-vitro* serial dilution method for antimicrobial activity against *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella aerogenes*, *Pseudomonas aeruginosa*, and *Candida albicans*. Study revealed that compound b3 **(Fig. 3)** demonstrated antibacterial activity along with high affinity toward all studied proteins: 50S ribosomal protein L19 (PDB ID: 6WQN), sterol 14-alpha demethylase (PDB ID: 5TZ1), and ras-related protein Rab-9A (PDB ID: 1WMS[5].

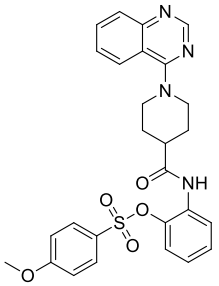

Figure 2. Compound III-17[6]

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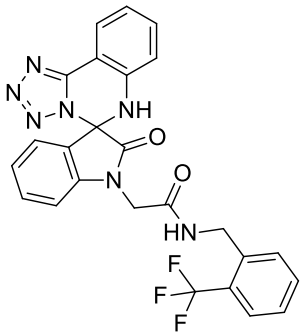

Figure 3. Compound b3[5]

Methicillin-resistant *S. aureus* strains are often resistant to other classes of antibiotics, thus making treatment options limited. This major problem has led to the search for new compounds active against these strains[6]**.** Sulfonamides have shown anti-methicillin-resistant *Staphylococcus aureus* (MRSA) activity and could be developed for producing potential dug candidates. The initial screening of a series of quinazolinone benzenesulfonamide derivatives 5–18 against multidrug-resistant bacterial and fungal strains was done. The potential compounds were conjugated with Zinc oxide nanoparticles (ZnONPs) to study the effect of nanoparticle formation on the antimicrobial, cytotoxic and immunomodulatory activity. Compounds 5, 11, 16 and 18 **(Fig. 4)** revealed promising antimicrobial and cytotoxic activities. The safety profiles improved and antimicrobial activity was increased through nanoformulation. Compounds 5 and 11 demonstrated an increase in spleen and thymus weight and boosted the activation of CD4+ and CD8+ T lymphocytes[7].

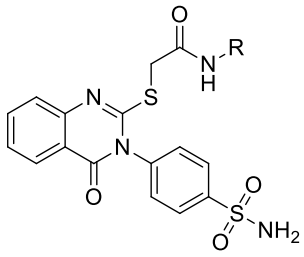

Figure 4. Compounds 5, 11, 16, 18[7]

A Series of 7-chloro-3-[substituted (amino/phenyl amino)]-2-phenyl quinazolin-4(3H)-one/thione (Fig. 5) derivatives and 1-(7-chloro-4-oxo/-2-phenylquinazoline-3(4H-yl))substituted urea derivatives were synthesized and characterized. The antibacterial, analgesic, and anti-inflammatory efficacy was examined by using the agar diffusion cup plate method, tail immersion method, and carrageenan-induced paw oedema method, respectively. Among the tested compounds, five compounds were found to be effective with antimicrobial, analgesic and anti-inflammatory activity[8].

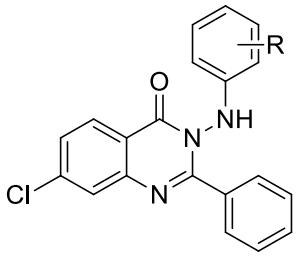

Figure 5. -chloro-3-[substituted (amino/phenyl amino)]- 2-phenyl quinazolin-4(3H)-one/thione[8]

In an organic synthesis study, the reaction of 2-furylvinyl- and 2-thienylvinyl-2,3-dihydroquinazolin-4(1H)-ones with maleic anhydride gave isoindolo[2,1-a]quinazoline-11(13)-carboxylic acids (Fig. 06) via the tandem acylation/ intramolecular Diels-Alder reaction of vinylarenes (IMDAV). The target isoindoloquinazolines were evaluated in vitro against common bacterial pathogens strains (Escherichia coli, Staphylococcus aureus, etc.). It was revealed that some of thienoisoindolequinazoline derivatives exibited a potent antibacterial activity at the level of MIC values of 16–32 μg mL−1. Selected 2,3-dihydroquinazolin-4(1H)-ones and isoindolo[2,1-a]quinazolinecarboxylic acids displayed antiviral activity (against the influenza virus A/Puerto Rico/8/34 – H1N1)[9].

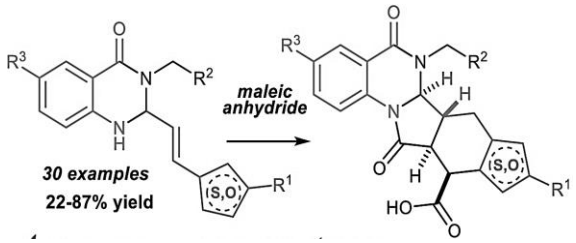

Figure 6. Isoindolo[2,1-*a*]quinazoline-11(13)-carboxylic acids[9]

A series of mono-and dibromo of 3′-(oxiranyl, hydrazide, oxadiazolo and pyrazolo)-methylene-spiro[isobenzofuran-1,2′-quinazoline]-3,4′(3′H)-dione derivatives **(Fig. 7)** were synthesized. The synthesized compounds were evaluated in vitro for their antibacterial and antifungal activity. The 6-bromo or 6,8-dibromo quinazolin-3,4-dione nucleus bearing oxirane hydrazino acetyl, hydrazide, oxadiazole and pyrazole groups at position (3) were found to be most potent against the gram-positive bacteria, gram-negative bacteria, and fungi *w.r.t* Chloramphenicol and Fluconazole[10].

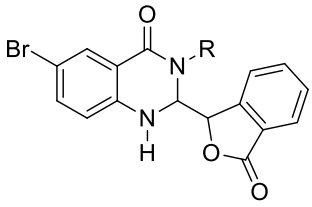

Figure 7. 6-bromo-2-(3-oxo-1,3-dihydroisobenzofuran -1-yl)-2,3-dihydroquinazolin-4(1H)-one[10]

Topoisomerases (topo) inhibitors are clinically implied as antimicrobials and anticancer agents. Quinazoline-2,4-diones (diones) **(Fig. 8)** are structural mimics of fluoroquinolones and can show the same topo inhibiting activity, thus can act as promising candidates for antibiotic-resistant bacteria or as anticancer chemotherapy agents. A major problem in this theory is the lesser amount of accumulation of diones inside the cell. So, an explorative study was done to work on two strategies for increasing the cellular accumulation of diones. Taking a hypothesis that the cell penetration difference between fluoroquinolone and diones was related to the charge and physical properties of the molecules, a panel of N1-biphenyl diones with altered charged groups at C7 and N3 were synthesized to evaluate whether changes in the charged groups at these locations could alter the ability of diones to enter cells, evade efflux, and inhibit topo I. Topo I DNA relaxation, cell viability, and DNA binding were evaluated for these compounds. It was determined that DNA binding, enzyme inhibition, and cell viability inhibition track well together, which suggests that, at least in the cell types studied, cell penetration does not appear to be a major issue. The DNA binding assays also confirm that DNA binding is an important factor in topo I inhibition for these compounds[11].

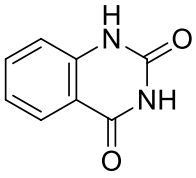

Figure 8. Quinazoline-2,4-diones[11]

Globally, rotavirus (RV) is the most common cause of acute gastroenteritis in infants and toddlers. Unfortunately, there are currently no agents available to treat rotavirus infection in specific. Despite the availability of certain immunizations, there are no licensed antivirals that can attack rotavirus in hosts specifically. In this study, an in vitro investigation of the effectiveness of benzoquinazoline derivatives 1–16 against human rotavirus Wa strains was done. All compounds exhibited antiviral activity; however, compounds 1–3, 9 and 16 showed the greatest activity (reduction percentages ranged from 50 to 66%). *In-silico* molecular docking of highly active compounds, was done. Results showed that the compounds 1, 3, 9, and 16 **(Fig. 9)** were promising anti-rotavirus candidates[12].

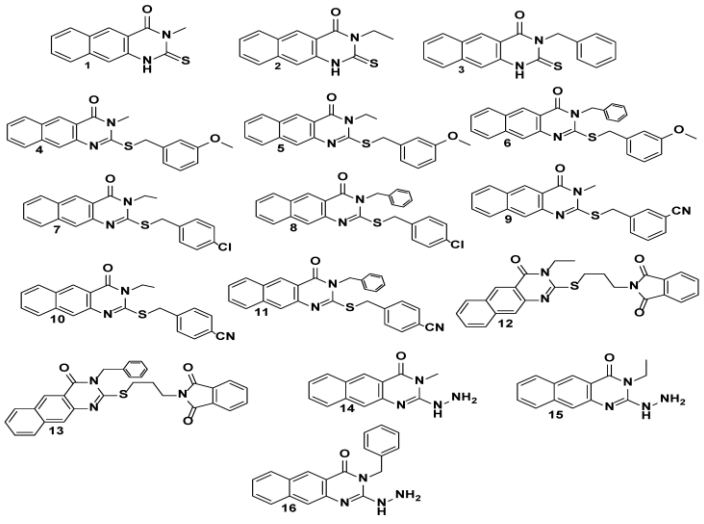

Figure 9. Compounds 1, 3, 9, 16[12]

Transcription regulator protein receptor PqsR (MvfR) inhibition could be a promising strategy to inhibit Quorum Sensing in *P.aeruginosa* to overcome antimicrobial resistance. A series of novel quinazolinone disulfide-containing competitive inhibitor of PqsR were synthesized. The most potent analogue 8q (Fig. 10) efficiently inhibited the Pseudomonas Quinolone Signal system with an IC50 value of 4.5 µM. It also showed complete suppression of pyocyanin production and a significant reduction in biofilm formation by *P.aeruginosa* (PAO1) with low cytotoxicity. Additionally, 8q produced synergy in combination with known antibiotics such as ciprofloxacin and tobramycin. Finally, molecular docking analysis suggested that compound 8q could bind with the ligand-binding domain of PqsR in a similar fashion to the native ligand[13].

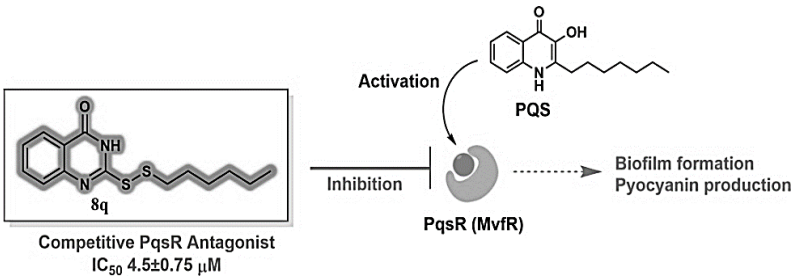

Figure 10. Compound 8q and mechanism of inhibition[13]

Tuberculosis (TB) is still a major health problem, as one-third of the world's people are infected with Mycobacterium tuberculosis, and two million dies from it per annum worldwide. In the present article, an *in*-silico study on some novel quinazoline derivatives (A and B series) as potential antitubercular was done. Computational docking studies of the A and B series ligands were executed against tuberculosis (PDB id - 1P44), aiming the enoyl reductase with Auto dock Vina (Pyrx). Molecular docking studies were performed with Autodock Vina (Pyrx) and the binding energy of these was compound calculated using the Lamarck's Genetic Algorithm (LGA) method. The results showed that many compounds were significantly active against the enoyl reductase enzyme compared to at present used drug Bedaquiline (-9.4 kcal/mol). The outcome of the in silico studies provided brawny evidence for the reflection of valuable ligands in quinazoline derivatives as potential enoyl reductase inhibitors, and compounds A1c, A2b, A2c, A3c, B1c, B2c, B3a, B3b, B3c, B3d, and B3e with significant binding energy can generate significant antitubercular activity for additional development, which can prove their therapeutic potential[14].

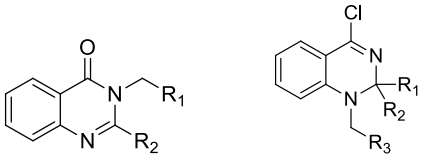

Figure 11. Series A and B[14]

Fungal diseases remain a major problem in the agriculture sector causing huge loss in economy. It is vital to create effective fungicides with novel chemotypes due to resistance to the current selective agents. A series of novel quinazolin-6-ylcarboxylates were synthesized and evaluated for their fungicidal activity on different phytopathogenic fungi. Most of these compounds showed excellent fungicidal activities against *Botrytis cinerea* and *Exserohilum rostratum*, especially compound F17 (Fig. 12) displayed the highest activity with EC50 values as 3.79 µg/mL against *B. cinerea* and 2.90 µg/mL against *E. rostratum*, which was similar to or even better than those of the commercial fungicides, such as pyraclostrobin (EC50, 3.68, 17.38 µg/mL) and hymexazol (EC_{50}, 4.56, 2.13 µg/mL). Moreover, compound F17 significantly arrested the lesion expansion of *B. cinerea* infection on tomato detached leaves and strongly suppressed grey mold disease on tomato seedlings in greenhouse. The abilities of compound F17 to induce cell apoptosis of the non-germinated spores, to limit oxalic acid production, to reduce malate dehydrogenase (MDH) expression, and to block the active pocket of MDH protein were demonstrated in *B. cinerea*. The novel quinazolin-6-ylcarboxylates containing ATP-binding site-directed moiety, especially compound F17, could be developed as a potential fungicidal candidate for further study[15].

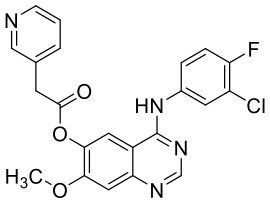

Figure 12. Compound F17[15]

In a study, synthesis of 1-mercapto-4-phenethyl-4*H*-spiro[benzo[*h*][1,2,4]triazolo[4,3-*a*]quinazoline-6,1′-cyclohe-ptane]-5(7*H*)-one **(Fig. 13)** and related derivatives was performed. A study of the antitumor properties of the synthesized compounds showed that some of them were active (37–66%) against sarcoma 180. The synthesized compounds possessed weak bacteriostatic activity against Gram-positive (*St. aureus* 209 P and 1) and Gram-negative microorganisms (*Sh. flexneri* 6858 and *E. coli* 0 – 55)[16].

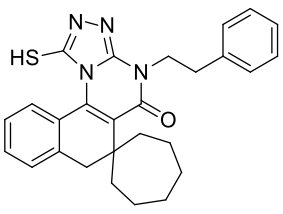

Figure 13.1-mercapto-4-phenethyl-4*H*-spiro[benzo[*h*][1,2,4] triazolo[4,3-*a*]quinazoline-6,1′-cycloheptane]- 5(7*H*)-one[16]

Plant bacterial illnesses cause dramatic damage to agricultural products globally, yet there are few efficient antibacterial available at present. Two series of novel quinazolinone derivatives were synthesized and tested against plant bacteria. Compound D32 **(Fig. 14)** was identified as a potent antibacterial inhibitor against Xanthomonas oryzae pv. Oryzae (Xoo), with an EC50 value of 1.5 μg/mL, much better in inhibitory capacity compared to bismerthiazol (BT) and thiodiazole copper (TC) (31.9 and 74.2 μg/mL). The study supports compound D32 as a potential antibacterial which further requires in depth study[17].

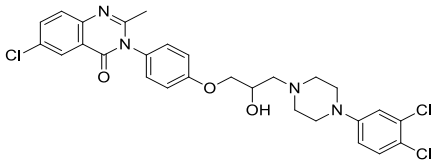

Figure 14. Compound D32[17]

Chorismate mutase (MtbCM), is a known target for the identification of anti-tubercular agents. A series of 4(3H)-quinazolinone derivatives were prepared through sonochemical approach (Fig. 15). Other analogues of quinazolinone such as pteridin-4(3H)-one and pyrido[2,3-d]pyrimidin-4(3H)-one derivatives were also prepared using this approach. The in silico docking studies indicated 3d, 3n and 3u as possible inhibitors that showed H-bonding with the residues ASP69 and GLU106 and a common pi-alkyl interaction with the critical dimer interface residue ARG103 of MtbCM. In vitro testing against MtbCM revealed that these compounds exhibited good activities (> 50% inhibition). Structure-Activity-Relationship (SAR) study revealed beneficial effects of the C-2 substituent in the order benzene > pyridine > indole ring[18].

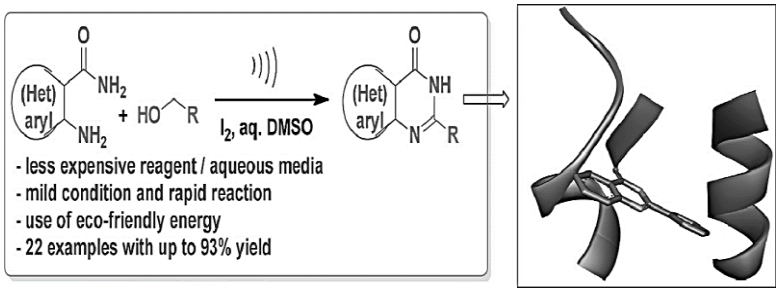

Figure 15. Preparation of 4(3*H*)-quinazolinone derivatives through sonochemical approach[18]

Due to rise in antibiotic resistance, infectious diseases have become major problem worldwide. Quinazoline-benzimidazole hybrids have emerged as a new class of antimicrobial agents active against *S. aureus* and *M. tuberculosis*. In the current study, fifteen new Quinazoline-benzimidazole hybrids were synthesized and evaluated for antimicrobial activity against *S. aureus* ATCC 29213 and M. tuberculosis H37Rv. Nine effective antibacterial agents, 8a, 8b, 8c, 8d, 8f, 8g, 8h, 8i, and 10c (Fig 16-17) were found to have MICs of 4-64 g/mL. With regard to a panel of vancomycin- and methicillin-resistant clinical isolates, the compounds were discovered to have strong antibacterial activity. The chosen compounds showed a good selectivity index and were shown to be less hazardous to Vero cells (CC50 = 40-200 g/mL). These novel benzimidazol-2-yl quinazoline derivatives have shown excellent results, and they now hold promise as antimicrobial treatments for MDR-S. aureus and Mycobacterial infections[19].

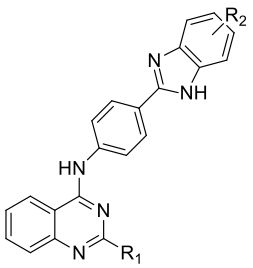

Figure 16. Compound 8a-j[19]

Compound	R_1	R_2
8a	Phenyl	4-nitro
8b	Phenyl	4-chloro
8c	Phenyl	H
8d	Phenyl	4-fluoro
8e	Phenyl	4-bromo
8f	3,4 dimethoxyphenyl	4-nitro
8g	3,4 dimethoxyphenylphenyl	4-chloro
8h	4 chlorophenyl	H
8i	4 chlorophenyl	4-fluoro
8j	4 chlorophenyl	4-chloro

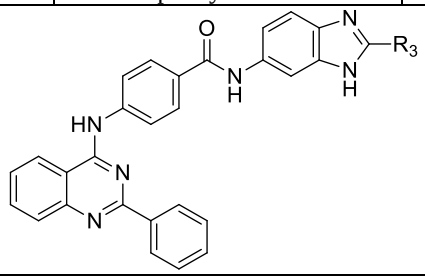

Figure 17. Compound 10a-d[19]

Compound	R3
10a	Trifluoromethyl
10b	4-bromo-2-fluorophenyl
10c	8-chloroquinolin-3-yl
10d	Naphthalin-2-yl

Novel 4-(substituted aniline) quinazolines **(Fig. 18)** were synthesised, and their potential antibacterial, antifungal, and

anticancer effects as well as acute toxicity were studied. On the basis of their spectrum data and elemental analyses, the structures of the produced compounds were verified. Its antifungal properties were assessed by the poison plate method, antibacterial activity by the agar cup method, and *in vitro* anticancer activity by employing the HeLa & MCF-7 cell line. Quinazoline derivatives only have marginal antibacterial efficacy against gram positive pathogens, whereas they have no effect on gram negative strains. Contrarily, 2(S24-bromo)'s and 3-nitro substitution on the 4-aniloquinazoline ring demonstrated high antifungal activity (90%) against *Fusarium moniliforme*, making it comparable to griseofulvin[20].

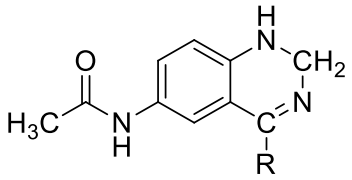

Figure 18. 4-(substituted aniline) quinazolines[20]

In a study, the thiourea group and phenyl ring were substituted at the N-3 and C-2 positions of the quinazoline ring, respectively, to create a new quinazolinone analogue. The prepared analog's antibacterial, antitubercular, and anti-HIV potencies were evaluated. The antibacterial effectiveness of fully produced derivatives was evaluated against a variety of gram-positive and gram-negative microorganism strains using the agar dilution method. The most effective activity against *Klebsiella pneumoniae*, *Proteus vulgaris*, and *Staphylococcus epidermidis* was demonstrated by compound 1-(3-chlorophenyl)-2-methyl-3-(4-oxo-2-methylquinazolin-3(4H)-yl)isothioureas (Xi) at 1.6 g/mL. The substance (Xi) demonstrated antitubercular activity against HIV-1 and HIV-2 at a minimum microgram concentration of 6.25 g/mL and anti-HIV activity at a concentration of 1.17 g/mL. The substance (Xi) is a possible starting point for further development and optimisation of novel antitubercular and anti-HIV drugs. The results obtained from this investigation reveal that the synthesized and biologically analyzed Quinazolines showed promise antibacterial, antitubercular, and anti-HIV capabilities and new scaffolds for antimicrobial action[21].

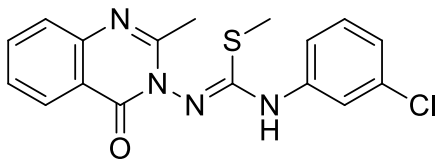

Figure 19. Compound Xi[21]

This study involved the three-step synthesis of novel 3-aryl, 2-substituted quinazoline-4 (3H) - one derivatives. By using several chemical reactions, such as cyclization and condensation process, compounds were produced with a good yield (59.5–85%). The chemical structures of the resulting compounds were additionally confirmed by elemental microanalysis and spectroscopic techniques (IR, 1HNMR). Compounds (IVa, IVb, IVc, IVd, IVe and IVf) were screened for their in vitro anti-leishmanial activity against *L. aethiopica* isolate (CL/039/09). All tested compounds (IVa (0.03766 µg/ml), IVb (0.00538 µg/ml, IVc (0.00412 µg/ml, IVd (0.00110 µg/ml), IVe (0.03017 µg/ml) and IVf (0.03894 µg/ml)) showed excellent potency that was much better than the standard drug, amphotericin B (IC50 = 0.04359 ug/ml). The results of acute toxicity indicated that all the test compounds (IVa, IVb, IVc, IVd, IVe and IVf) proved to be non-toxic and well tolerated by the experimental animals up to 300 mg/kg in oral and 140 mg/kg in parental studies[22].

In a study, schiff base was obtained from the reaction between 2-amino benzohydrazide and 2-Hydroxy-4-methoxy benzaldehyde using the reflux method in HPLC grade methanol for 2 hours producing 71% yield. The structures characterized by ESI-mass, Mass, 1H NMR, IR, 13C NMR, the metal complex of quinazolinone schiff base derivative were tested for antibiotics such as Streptomycin, Ampicillin and Nystatin. Metal complexes of Ni, Zn, Cu, and Pd were prepared in which Ni metal complex and Pd metal complex were highly potent drug that inhibit only gram-negative bacteria. All the metal complexes are able to inhibit gram negative bacteria. Zn and Cu metal complexes are effective broad-spectrum drug which can inhibit the growth of both gram-positive and gram-negative bacteria. All the metal complexes exhibited antifungal activity. Among them, Pd metal complex was most potent antifungal drug[23].

In search of effective antibacterial agents, a series of novel quinazolines, having thiazole and 1,3,4-oxadiazole heterocycles were synthesized and characterized by spectroscopic techniques. Their antibacterial potential was evaluated against MTCC strains, wherein compounds 6d (*Escherichia coli*, MIC = 100 µg mL−1) and 6e (E. coli, MIC = 62.5 µg mL−1) were most active against Gram-negative bacteria while compound 6f (*Staphylococcus aureus*, MIC = 50 µg mL−1) was most active against Gram-positive bacteria. Additionally, molecular docking was against bacterial DNA gyrase which showed good antibacterial potential[24].

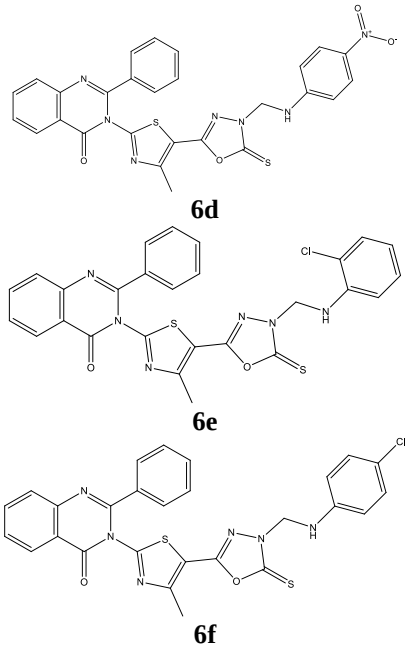

Figure 20. Compounds 6d, 6e, and 6f[24]

Thirteen 5-phenyl-5,6-dihydrotetrazolo[1,5-c]quinazolines were synthesized and tested against reference Tedizolid to

check penicillin-binding protein 2X (PBP 2X) (PDB ID: 2ZC4)binding affinity. Among the synthesized compounds, substance 12 showed good preliminary antifungal results towards *C. albicans*[5].

In this study novel quinazolinones were designed and synthesized from anthranilic acid by a multistep synthesis and synthesized compounds were characterized by FT-IR, 1H-NMR, Mass spectroscopy. Compounds were screened for their antibacterial and antifungal activities by agar streak dilution test against various pathogenic strains of bacteria and fungi. Antimicrobial studies revealed that all compounds exhibited mild to good antibacterial activity and mild to moderate antifungal activity. Out of thirteen tested compounds, the most active compound was found to be Compound VIIg **(Fig. 21)**[26].

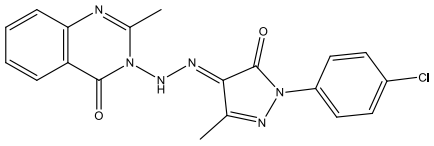

Figure 21. Compound VIIg

In this study, novel quinazolinone derivatives were synthesized and evaluated against metabolic enzymes viz. α-glycosidase, acetylcholinesterase, butyrylcholinesterase, human carbonic anhydrase I, and II. These compounds exhibited high inhibitory activities in comparison to used standard inhibitors with Ki values in the range of 19.28–135.88 nM for α-glycosidase (Ki value for standard inhibitor = 187.71 nM), 0.68–23.01 nM for acetylcholinesterase (Ki value for standard inhibitor = 53.31 nM), 1.01–29.56 nM for butyrylcholinesterase (Ki value for standard inhibitor = 58.16 nM), 10.25–126.05 nM for human carbonic anhydrase I (Ki value for standard inhibitor = 248.18 nM), and 13.46–178.35 nM for human carbonic anhydrase II (Ki value for standard inhibitor = 323.72). Cytotoxicity assay of the title compounds 7a-n against cancer cell lines MCF-7 and LNCaP demonstrated that these compounds do not show significant cytotoxic effects[27].

A new series of quinazolin-4(3H)-one compounds (4a–f, 5a–d) were synthesized as antimicrobial agents. The starting compound, 2-hydrazinylquinazolin-4(3H)-one (Fig. 22) (2), was synthesized and treated with different carbonyl compounds to afford the hydrazone derivatives 4a–f. In addition, the hydrazone derivatives 4a–d was treated with a DMF/POCl3 mixture to give the formyl-pyrazole derivatives 5a–d. All the target compounds were evaluated as antimicrobial agents against four bacterial and four fungal strains. The most potent antimicrobial activity was shown by 5a with MIC values in the range (1–16) µg/mL. In addition, the most potent compounds against E. coli were evaluated for their inhibitory activity against *E. coli* DNA gyrase, whereas the target compounds 4a, 5a, 5c, and 5d showed the most potent inhibition to the target enzyme with IC50 values ranging from 3.19 to 4.17 µM. Molecular docking studies were performed for the most active compounds against the target *E. coli* DNA gyrase to determine their binding affinity within the enzyme's active site. Moreover, ADME evaluations of these compounds predicted their high oral bioavailability and good GI absorption[28]

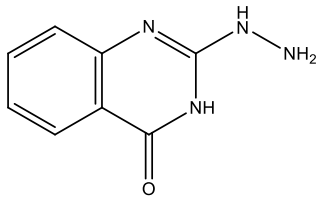

Figure 22. 2-hydrazinylquinazolin-4(3*H*)-one[28]

2. CONCLUSION

From the present review, it is revealed that a significant amount of work has been done in the past three years on the antimicrobial activity of quinazoline and related derivatives. Promising results have been obtained from the studies and further work is required to improve the existing drug candidates. Resistance to the traditional agents though cause a concerning issue yet it is noteworthy to have a pipeline of potential quinazoline based structures.

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