**Advances in Bioresearch**
Adv. Biores., Vol 15 (1) January 2024: 340-357

Print ISSN 0976-4585; Online ISSN 2277-1573
Journal's URL:http://www.soeagra.com/abr.html
CODEN: ABRDC3
DOI: 10.15515/abr.0976-4585.15.1.340357

Advances in Bioresearch

## REVIEW ARTICLE

# Biological Activities of Quinazolines: A comprehensive Review

**Muthu Bhupathi G*, Anandakumar K, Selvakumar M, Vinothkumar S**
Vivekanandha Pharmacy College for Women, Veerachipalayam, Sankari West, Salem – 637303. Tamil Nadu, India.
*Corresponding Author's Email: muthubhupathi@gmail.com

**ABSTRACT**
*Quinazolinone moieties are one of the most significant heterocyclic compounds exhibiting outstanding pharmacological properties. In the field of medicinal chemistry, quinazolinone provided enormous scope due to their diverse chemical reactions and abundant available method of synthesis. In this study the latest (2018-2021) reported various biological activities (anticancer activity, antimicrobial activity, antioxidant activity, antitubercular activity, α-glucosidase inhibitor activity, analgesic activity, anti-inflammatory activity, antileishmanial activity, $A_1$ and/or $A_{2a}$ adenosine receptor affinities, anti-HIV activity and anti-angiogenic activity) of quinazolinones are collected and summarized. For the treatment of various diseases huge numbers of drugs are existing, but they are allied with some disadvantages like toxicities, resistance and other adverse effects. To battle with these complications there is need to design and synthesize new-fangled chemical moieties with improved efficacy with different mechanism of action. In modern drug discovery, quinazolinone ring is a significant pharmacophore. The synthesis of new quinazolinone containing compounds were remains a key focus of medicinal research. To find a novel agent in this field, there is still scope for more research work. For further progress of better medicinal compounds, the adaptability of new generation quinazolinone would represent a productive pharmacophore. Consequently, quinazolinone nucleus has an incredible choice for the discovery of more potent, safe, better and new biological agents.*
***Keywords:*** *Quinazoline, Quinazolinone, Anticancer activity, Antitubercular activity, α-Glucosidase inhibitor activity, $A_1$ and/or $A_{2a}$ adenosine receptor affinities, Anti-HIV activity.*

Received 24.12.2023 Revised 01.01.2024 Accepted 30.01.2024

**How to cite this article:**
Muthu B G, Anandakumar K, Selvakumar M, Vinothkumar S. Biological Activities of Quinazolines: A comprehensive Review.. Adv. Biores., Vol 15 [1] January 2024: 340-357.

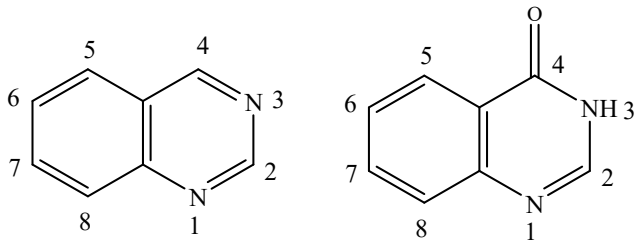
## INTRODUCTION

Heterocyclic chemistry is the branch of organic chemistry dealing with the synthesis, properties, and applications of these heterocycles. A heterocyclic compound or ring structure is a cyclic compound that has atoms of at least two different elements as members of its ring. Heteroatoms constitute a very common fragment of a number of active pharmaceutical ingredients as well as excipients. Many heterocyclic scaffolds can be considered as privilege structures. Most frequently, nitrogen heterocycles or various positional combinations of nitrogen atoms, sulphur, and oxygen in five- or six-membered rings can be found. More than 85% of all biologically-active chemical entities contain a heterocycle. This fact reflects the central role of heterocycles in modern drug design. On the other hand, many heterocyclic lead compounds were isolated from natural resources, and their structures were subsequently simplified and modified by medicinal chemists. Thus, heterocycles have critical importance for medicinal chemists, because using them, it is possible to expand the available drug-like chemical space and drive more effective drug discovery programs[1].

One such important heterocyclic compound is quinazoline. Quinazoline (**I**) is an organic compound with the formula $C_8H_6N_2$(Fig 1). It is an aromatic heterocycle with a bicyclic structure consisting of two fused six-membered aromatic rings, a benzene ring and a pyrimidine ring. It is also known as 1,3-diazanaphthalene. Quinazoline derivatives are one of the most important six-membered nitrogen-containing heterocyclic compounds as many naturally occurring and pharmaceutical compounds contain quinazoline moiety as the core unit. The chemical versatility of quinazolinone derivatives (**II**) has led to

their extensive use as synthons for the preparation of many biologically active compounds. In the field of pharmaceutical and medicinal chemistry, quinazolinone and its derivatives are found to be trendy structures employed for discovery of drugs within the vast range of heterocycles [2, 3].

A review is a survey over a whole subject or division of it, or especially an article making a critical reconsideration and summary of something written.In this study the latest (2018-2021) reported various biological activities (anticancer activity, antimicrobial activity, antioxidant activity, antitubercular activity, *α-glucosidase* inhibitor activity, analgesic activity, anti-inflammatory activity, antileishmanial activity, $A_1$ and/or $A_{2a}$ adenosine receptor affinities**,** anti-HIV activity and antiangiogenic activity) of quinazolinones are collected and summarized.




**Quinazoline (I)** **Quinazolin-4-(3*H*)-one (II)**

**Figure 1: Structure of quinazoline (I) & quinazolin-4-(3*H*)-one (II)**

## BIOLOGICAL ACTIVITIES OF QUINAZOLINES

### Anticancer Activity

According to the global cancer report of 2019, the burden of cancer will exceed more than 18 million becoming one of the major causes of global mortality rate. There is a pressing need to establish novel drug candidates for cancer treatment, though many anticancer agents are available in the market owing to their adverse effects. In recent years, quinazoline and its derivatives have been considered as a novel class of cancer chemotherapeutic agents that show promising activity against different tumors (Fig2).

Abdallah *et al.,* were designed, synthesized and biologically evaluated new nineteen quinazolin-4-one derivatives for their potential anticancer activity based on the pharmacophoric features of VEGFR-2 kinase inhibitors [4]. Out of nineteen tested derivatives, nine quinazolin-4-ones which produced best ***in vitro*** VEGFR-2 tyrosine kinase inhibition activity were further investigated by ***in vitro*** assay against three human cancer cell lines, namely HepG2, PC3 and MCF. The most potent compound of the series was found to be ***N***′-{2-[(3-ethyl-6-nitro-4-oxo-3,4-dihydroquinazoline-2-yl)thio]acetyl}benzohydrazide**1** ($IC_{50}$ = 4.6 ± 0.06 µM, 17.23 ± 1.5, 26.10 ± 2.2 and 30.85 ± 2.3 µg/mL against VEGFR-2 kinase, HepG2, PC3 and MCF, respectively). In addition, against the normal human lung fibroblasts cell line (WI-38) the potent compound of the series showed $IC_{50}$ of 145.93 ± 1.1 µg/mL.They also found that potent compound induced apoptosis in HepG2 cell cycle and arrested cell growth at G2/M phase. Docking studies indicates that this compound bonded correctly in VEGFR-2 by forming three essential hydrogen bonds with the key residues Glu885, Asp1046 and Cys919.

Three series of quinazolinone derivatives possessing hydrazone structures **2** were designed, synthesized and tested for antitumor activity by Shao *et al.*in 2021 [5]. Against human lung cancer cells (A549) and human prostate cancer cells (PC-3) title derivatives exhibited good anti-tumour activities. No apparent toxicity was noted towards those nontumorigenic rat renal tubular epithelial cells (NRK-52E). $IC_{50}$ of potent compound of these series against A549 and PC-3 was found to be 7.36 and 7.73 µmol $L^{-1}$, respectively. They also reported the relationships between the compound structures and numerous biological activities. To direct the future structural units using CoMFA they constructed a good predictive 3-dimensional quantitative structure–activity relationship (3D-QSAR) model.

Nunes *et al.* ,described the synthesis of 4-aminoquinazoline derivatives bearing a 1,2,3-triazole **3** stable core to bridge different aromatic and heterocyclic rings using copper-catalysed azide-alkyne cycloaddition reaction (CuAAC) as a click chemistry strategy based on the 4-aminoquinazoline pharmacophore of kinases [6]. The initial screening of twelve derivatives in tumoral cells (CAL-27, HN13, HGC-27, and BT-20) revealed that the most active in BT-20 cells ($IC_{50}$: 24.6 µM; SI: 3.25) contains a more polar side chain (sulfone). Furthermore, this derivative promoted a significant release of *lactate dehydrogenase (LDH)*, suggesting the induction of cell death by necrosis. In addition, this compound induced G0/G1 stalling in BT-20 cells, which was accompanied by a decrease in the S phase. Western blot analysis of the levels of p-STAT3, p-ERK, PARP, p53 and cleaved caspase-3 revealed p-ERK1/2 and p-

STA3 were drastically decreased in BT-20 cells under this derivative incubation, suggesting the involvement of these two kinases in the mechanisms underlying this compound induced cell cycle arrest, besides loss of proliferation and viability of the breast cancer cell. Molecular docking simulations using the ERK-ulixertinib crystallographic complex showed this derivative could potentially compete with ATP for binding to ERK in a slightly higher affinity than the reference ERK1/2 inhibitor. Further ***in silico*** analyses showed comparable toxicity and pharmacokinetic profiles for this derivative in relation to ulixertinib. Aziz *et al.* designed and synthesized new acetamide **4** and 1,3-thiazolidinone **5** derivatives from their quinazolinone parents and assessed for their cytotoxic activity against MCF-7 and A549 cell lines along with their lead compounds (erlotinib and gefitinib) [7]. Discovery Studio program were used for 3D QSAR pharmacophore and docking molecular modelling studies. Against both MCF-7 and A549 cell lines five of the tested derivatives showed potent cytotoxic activities. Moreover, the molecular modelling studies corroborated to the affinity of the compounds towards EGFR. Hence, these five compounds were then screened for their EGFR inhibition and evaluated as well for their toxicity to normal cells. DNA flow cytometry analysis was conducted for two potent compounds out of five, which indicates that they both induced arrest at G2/M phase of the cell cycle.Jin *et al.,*constructed quinazolines **6** with a benzazepine moiety at the 4-position and based on structural features of several inhibitors of EGFR. Excellent antitumor activities were displayed by most of the compounds [8]. The potent compound displayed excellent antitumor activities against the four tested cell lines with an $IC_{50}$ of 1.06–3.55 μM. Hence, they carried out the enzymatic, signalling pathways and apoptosis assay of this potent compound to study the mechanism of action.

Recently, Altamimi *et al.,* reported the synthesis and antitumor activity (against Hela, A549, and MDA cell lines) of novel 8-methoxy-2-trimethoxyphenyl-3-substituted quinazoline-4(3)-ones**7**[9]. Docetaxel was used as reference drug for comparing the antitumor activity of synthesized compounds. They also performed docking and molecular dynamics (MD) simulation was using Autodock Vina program and GROMACS 2018.1 software, respectively. Many of the synthesized compound displayed strong cytotoxic activities against the cancer cell lines tested. The most potent compound of the series was evaluated additionally for VEGFR2 and EGFR inhibitor activity ($IC_{50}$: 98.1 and 106 nM respectively).

Six quinazolines **8** are selected to compare their structures and biological activity by Kaneti *et al.,* Comet Assay and FACS analyses methods were used to study the bioactivity of the tested compounds in breast cancer cells of the MDA cell line [10]. Dispersion corrected density functional theory method, and an electron-correlated molecular orbital theory method was employed for computing interaction energies. Selected compounds significantly change the cell morphology but do not remarkably delay nor change the dynamics of cellular progression through the cell cycle phases. The proposed computational models quantify structural effects on heterocyclic G4-complex stabilization energies, which directly correlate with observed biological activity.

Several quinazolinones **9** were synthesized by Kim *et al.,* to overcome adverse events of idelalisib [11]. They tested ***in vitro*** PI3K enzyme inhibitory activity of synthesized compounds and the viability of cell lines such as MOLT and SUDHL. Among them, two derivatives displayed excellent enzyme activity with **an** $IC_{50}$ of 0.09 nM and 0.39 nM. Among these two, one compound showed an approximately four-fold higher selectivity for PI3Kγ/δ compared with Idelalisib. ***In vivo*** PK experiments of these two compounds revealed that one compound had improved PK compared with Idelalisib.

Hakima *et al.,* evaluated the anti-cancer potential of the novel class of quinazoline tethered acetamide derivatives**10**by employing MTT assay for six cancer cell lines [A 549 (lung), DU 145 (prostate), HT 29 (colon), MCF-7 (breast), SiHA (cervical), B16F10 (mouse skin melanoma)] and one normal human fibroblast cell line [12]. Schotten-Baumann reaction was employed to synthesize quinazoline tethered acetamide derivatives. All the compounds displayed a decent cytotoxicity profile when compared with the standard doxorubicin. Among the fourteen tested derivatives, two compounds, displayed excellent cytotoxicity against SiHA and MCF-7 cancer cell lines.

Das *et al.,*reviewed the outcome of clinical trials of MMPIs **11** for advanced stage solid tumors which can act as a learning experience for future development of successful gelatinase inhibitors for the management of hematological malignancies [13]. There is paucity of data available regarding the role of gelatinases in hematological malignancies. Recent studies have shown that gelatinases activities or functions are correlated with hematological malignancies. Several substrates based non-selective to non-substrate based relatively selective synthetic matrix metalloproteinase inhibitors (MMPIs) had been developed. Few MMPIs had reached in clinical trials during the period of 1990s–2000s. Unfortunately, the anti-tumour and anti-metastatic efficacies of these MMPIs were not justified with patients having several advanced stages solid tumour cancers in any substantial number of clinical trials. Till date not a single MMPI passed phase III clinical trials designed for advanced metastatic cancers due to adverse events as

well as lack of ability to show uniformity in disease prolongation. With the best of our knowledge no clinical trial study has been reported with small molecule synthetic inhibitors against hematological malignancies.

To increase COX-2 selectivity AsmaaSakr *et al.,*designed and synthesized three series of novel quinazolinones 12 & 13 conjugated with indole acetamide, ibuprofen, or thioacetohydrazide [14]. The three synthesised series exhibited superior COX-2 selectivity compared with the previously reported quinazolinones and their NSAID analogue and had equipotent COX-2 selectivity as celecoxib. Compared with celecoxib, three derivatives showed similar anti-inflammatory activity *in vivo*, while two derivatives showed superior inhibition of the inflammatory mediator nitric oxide, and one derivative showed greater antioxidant potential in macrophages cells. Moreover, all selected compounds showed improved analgesic activity and one compound completely abolished the pain response. Additionally, one indole acetamide quinazolinone compound showed anticancer activity in tested cell lines HCT116, HT29, and HCA7. Docking results were consistent with COX-1/2 enzyme assay results. *In silico* studies suggest their high oral bioavailability.

Antioxidant, cytotoxic, and protective effects of a novel 2- trifluoromethylquinazolines **14** and quinazolinones **15** in lipopolysaccharide (LPS)- murine microglia (BV2) and hydrogen peroxide ($H_2O_2$)-mouse neuroblastoma-2a (N2a) cells were investigated by NeeranjiniNallathamby *et al.,* [15]. ABTS and DPPH assays were used for screening the antioxidant activity of synthesized compounds[15]. MTS assay was employed in BV2 and N2a cells for determining the cytotoxic activities. The production of nitric oxide (NO) in LPS-induced BV2 microglia cells was quantified. Out of many tested compounds, highest potential compound displayed 87.7% of ABTS scavenge percentage and 54.2% DPPH inhibition. At 5 and 50 µg/mL concentration, all compounds were noncytotoxic in BV2 and N2a cells. The compounds which showed the highest protective effects in LPS-induced BV2 and $H_2O_2$-induced N2a cells were 5 and 7. Except one compound all tested compounds reduced NO production at concentrations of 50 µg/mL. The quinazolinone series exhibited the highest percentage of NO reduction, ranging from 38 to 60%.

Bathula *et al.,*synthesized evaluated cytotoxic activity (MTT assay using MCF-7 breast cancer and A459 human lung adenocarcinoma cell line) of a series of novel 2-substituted-4-anilinoquinazolines-pyrrole hybrids16 & 17 [16]. The cytotoxic study was conducted using morphological study and MTT assay against adenocarcinoma and human breast cancer cell lines. Some of tested derivatives displayed moderate to promising cytotoxic activity compared with standard doxorubicin (IC50: 41.05 µM at 72 h). Based on the experimental evidences, they also proposed structure activity relationship to provide significant information for the design and development of further potent anticancer agents.

Two novel series of quinazolinone–pyrimidine and benzyl-pyrimidine hybrids18 were designed, synthesized and characterized by Emami*et al*[17]. MAK 203 kit was employed to assess the dipeptidyl peptidase-4 inhibition potencies of synthesized derivatives. The $IC_{50}$ value ofmost potent compound was found to be 34.3 ± 3.3 µM. A kinetic study revealed that it acted as a competitive inhibitor. Molecular modelling of these compounds agreed with the *in vitro* results. They also evaluated the cytotoxic activities of the compounds against three cancerous cell lines (HT-29, SW1116 and A549). Compared to a lung cancer cell line (A549) almost all the compounds exhibited better antiproliferative activity on colon cancer cell lines (HT-29 and SW1116). Sitagliptin and cisplatin was employed as a positive control. Further studies on the hit compounds through cell cycle and apoptosis assays also showed that these compounds could induce cell death by apoptosis or arrest cells in the G2/M phase

Soloaga Ardiles *et al.,*established the relationship between the electronic structure of quinazoline derivatives **19**and the biological activity (expressed as $EC_{50}$) that process in the NTR1 receptor, to propose a 2D pharmacophore using Klopman-Peradejordi-Gomez (KPG) methodology [18]. Calculations are included within the functional density theory (DFT) using the B3LYP / 631G theory level (d, p). The interactions at the orbital-orbital level and by charges are mainly used to derive the biological activity.

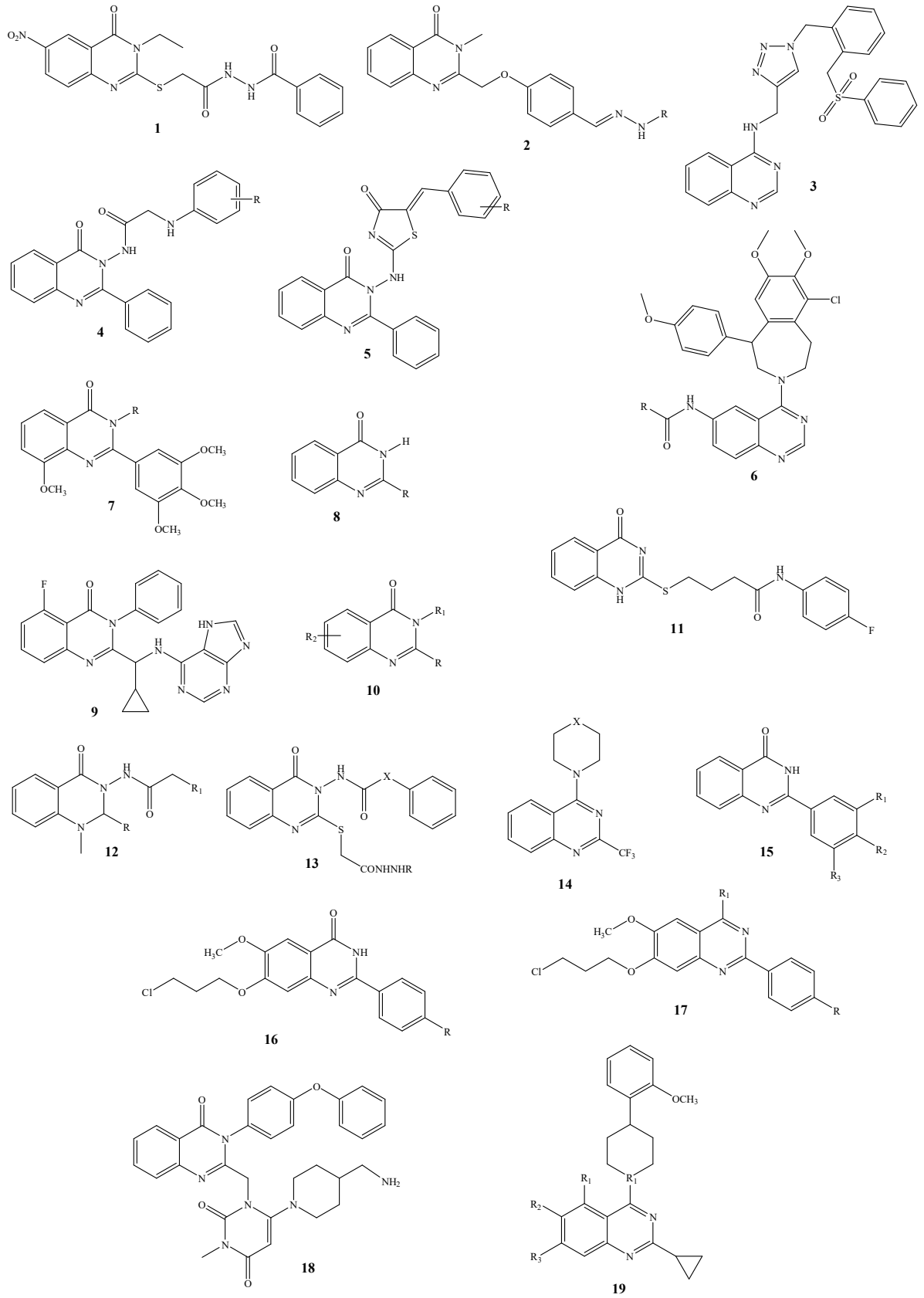


**Figure 2: Anticancer quinazolines**

## Antimicrobial Activity

Owing to the rapid rise in antibiotic resistance, infectious diseases have become serious threat to public health. There is an urgent need to develop new antimicrobial agents with diverse chemical structures and novel mechanisms of action to overcome the resistance. In recent years, Quinazoline-benzimidazole hybrids have emerged as a new class of antimicrobial agents active against S. aureus and M. tuberculosis. With the rapid emergence of antibiotic resistance, efforts are being made to obtain new selective antimicrobial agents. Quinazolinone can provide new antimicrobial candidates (Fig 3).

Fifteen novel quinazoline-benzimidazole hybrids 20 were synthesized by Malasala *et al.* and evaluated their antimicrobial activity against *S. aureus* ATCC 29213 and *M. tuberculosis* $H_{37}Rv$ [19]. From the study nine potent antibacterial agents with MICs in the range of 4-64 µg/mL were identified. Further, against a panel of drug-resistant clinical isolates which include methicillin and vancomycin-resistant *S. aureus* these potent compounds were found to possess potent antibacterial potential. The selected compounds were found to be less toxic to Vero cells ($CC_{50}$ = 40-≥200 µg/mL) and demonstrated a favourable selectivity index.

2-Pyridyl [3*H*]-quinazolin-4-one derivatives **21 & 22** fused or substituted with different oxygen or nitrogen heterocycle moieties were synthesized by Eweas *et al* as potential anti-tumor and anti-microbial agents [20]. The title compounds were synthesized by two alternative routes from 5-bromo-2-[pyridin4-ylcarbonyl]amino]benzoic acid. Some of the newly synthesized compounds were screened for their antiproliferative and antimicrobial activities against various eukaryotic and prokaryotic cells. The potent compound of the series showed selective antibacterial activity against Gram-positive bacteria *S. aureus* (Zone of inhibition = 26 mm, MIC = 256 µg/ml).

Kavitha *et al.,*synthesized several Schiff bases of quinazolin-4-(3*H*)-one**23** in good yields and screened their antimicrobial potencies by plate hole diffusion method against some pathogenic gram-positive, gram-negative bacteria and fungi [21]. Moderate to significant anti-bacterial and fungal activities was showed by the newly synthesized compounds compared to reference standard drug.

1,3,4-Thiadiazolyl quinazolinones**24** are conveniently synthesized and reported by Abdelmajeid *et al.,*by facile cyclization from anthranilic acid and succinic anhydride [22]. Against selected bacterial and fungal strains, the synthesized compounds were tested for their antimicrobial activity and the obtained results were compared against penicillin. Some of the synthesized derivatives showed promising antimicrobial activity compared tested standard. Geesi *et al.,*reported on efficient process for the synthesis of new 6-bromo-2-chloro-3-butylquinazolin-4(3***H***)-one**25**[23]. The anti-bacterial activity of the synthesized compounds was screened. The intermolecular interactions in the crystal structure was analysed by using Hirshfeld surfaces and their associated two-dimensional fingerprint plots. In addition, density functional theory was employed to generate electrostatic surface potential (ESP).

Ciprofloxacin and sarafloxacin cores were used by hybridization of quinazolinone derivatives **26** by Norouzbahari *et al.,*to design and synthesize a novel series of functionalized fluoroquinolones [24]. A comprehensive set of *in vitro* antibacterial assays (Broth microdilution, well diffusion and disc diffusion assays) in addition to SAR characterisation studies was employed for this purpose. To explore the binding characteristics and interactions, in silico pharmacokinetics prediction assays and molecular docking studies were performed. Antibacterial activities of the synthesized derivatives were evaluated against three gram-positive (Methicillin-resistant *Staphylococcus aureus* (MRSA), *Staphylococcus aureus* and *Enterococcus faecalis*) and three gram-negative bacteria (*Pseudomonas aeruginosa*, *Klebsiella pneumoniae, Escherichia coli*). The compounds exhibited moderate to good activities against gram-positive bacteria and weak to moderate activities against gram-negative bacteria. The potent compound of the ciprofloxacin series showed 60 times more potent activity than reference ciprofloxacin. Molecular docking study results were in accordance with the results of antibacterial activity assays.

Novel quinazolinone-benzenesulfonamides27 were synthesized by Ghorab*et al.,*and screened for their antimicrobial activity against Gram-positive bacteria, Gram-negative bacteria, MRSA and yeast [25]. The most potent compound (Zone of inhibition: 25– 36 mm and MIC: 0.31– 5.0 µg/mL) conjugated with copper oxide nanoparticles CuONPs by gamma irradiation (4.5 KGy). This potent derivative was used to synthesize two nano formulations: CNPs by loading the compound in chitosan nanoparticles and the nanocomposites CuONPs-CNPs. TEM and zeta potential was used to characterize these nano formulations. DNA gyrase was assayed besides the inhibitory profile against *Staphylococcus aureus*(**$IC_{50}$**: 10.57 to 27.32 µM). To determine its relative safety cytotoxic evaluation of potent compound and its two nanoformulations was carried out on normal VERO cell line ($IC_{50}$= 927, 543 and 637 µg/mL, for potent compound, CNPs and CuONPs-CNPs, respectively). Inside the active site of ***S. aureus*** DNA gyrase molecular docking of potent compound was performed and found that inside the active site of ***S.***

***aureus*** DNA gyrase showed that it binds in the same manner as that of the co-crystallized ligand, ciprofloxacin.

Patel *et al.,*synthesized and evaluated antibacterial activity of novel 1,3,4-oxadiazole-fused and piperazine-fused quinazoline derivatives**28**[26]. Potent antibacterial activities were displayed by majority of synthesized derivatives against several different strains of Gram-positive bacteria including multidrug-resistant clinical isolates. At their minimum inhibitory concentrations, the prepared derivatives do not affect cell viability on Human cervical (HeLa) cells.

From anthranilic acid and cinnamoylisothiocyanate Haggam *et al.,*synthesized a novel quinazolinone 29 with 55–99% yields [27]. They studied the antimicrobial potencies of the synthesized derivatives against some bacteria and fungi. Compared to reference cefotaxime, some quinazolin-5-onesdisplayed potential antibacterial activity. In addition, comparing with the reference nystatin some derivatives of quinazolin-5-one can be considered as antifungal agents.

Farooq *et al.,*synthesized a new N-Mannich base of 3, 4-dihydro-3-methyl-2(1***H***)-quinazolinones **30** with substituted amine moieties and substituted aldehyde [28]. Mannich bases were evaluated pharmacologically for their antioxidant, α-amylase enzyme inhibition, antimicrobial, cell cytotoxicity and anti-inflammatory activities. Most of the compounds exhibited potent activities against these bioassays. Two of the synthesized compounds displayed potent antioxidant activity in DPPH free radical ($IC_{50}$: 9.94 ± 0.16 μg/mL and 11.68 ± 0.32 μg/mL). In TAC and TRP antioxidant assays**,** three of the tested compounds displayed significant comparable activity to that of ascorbic acid. Two compounds of this series showed potent activity in inhibiting α-amylase enzyme ($IC_{50}$: 10.17 ± 0.23 μg/mL and 9.48 ± 0.17 μg/mL), when compared with acarbose (13.52 ± 0.19 μg/mL). Among the thirteen synthesized compounds, anti-cancer potential of the four compounds were screened against Hep-G2 cells based on the results of brine shrimp lethality assay ($LD_{50}$) and cell cytotoxicity assay ($IC_{50}$). Compared with cisplatin (2.56 μM) $IC_{50}$ of potent compound was found to be 6.48 μM at 72 h. An ***in vitro*** nitric oxide (NO) assay was performed to shortlist compounds for ***in vivo*** anti-inflammatory assay. One of the derivatives exhibited potent anti-inflammatory activity by decreasing the paw thickness to the maximum compared to reference acetylsalicylic acid.

Various new quinazolinones**31** containing hydrazone structural units were designed and synthesized from isotonic anhydride by Shao *et a l*[29]. The preliminary antibacterial study reveals that the tested derivatives exhibited a certain inhibitory activity against *Xanthomonas oryzae* pv. *Oryzae* (*Xoo*), *Pseudomonas syringae* pv. *actinidiae* (*Psa*) and *Xanthomonas axonopodis* pv. *citri* (*Xac*). Out of several tested compounds, 4-methyl-*N*′-(4-((3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)methoxy) benzylidene) benzenesulfonohydrazide, 2-((4-((2-(2,6-dichlorophenyl)hydrazono)methyl) phenoxy) methyl)-3-methylquinazolin-4(3*H*)-one and *N*′-(4-((3-methyl-4-oxo-3,4-dihydroquinazolin-2 yl)methoxy) benzylidene) benzenesulfonohydrazide displayed better antibacterial activity against *Xoo*, *Xac* and *Psa* than the reference bismerthiazol and thiediazole-copper, respectively. Notably, 2-((4-((2-(3,5-dichlorophenyl) hydrazono)methyl)phenoxy)methyl)-3-methylquinazolin-4(3*H*)-one showed fine broad-spectrum antimicrobial activity against *Xoo*, *Xac* and *Psa*.

Pawar *et al.,*reported the synthesis and antimicrobial evaluation of novel quinazolinones**32** [30]. All the synthesized compounds were screened for antimicrobial activity by Broth dilution method. Most of the derivatives showed good antimicrobial activity against Gram-Positive and Gram-negative bacteria.

A series of six functionally diverse new quinazolinone compounds **33 & 34** were synthesized by a facile one-pot reaction of benzoic acid derivatives, trimethoxymethane and aniline derivatives by Masri*et al*[31]. Three compounds of 3-aryl-8-methylquinazolin-4(3H)-one, and 3-aryl-6,7-dimethoxyquinazolin 4(3H)-one were prepared and tested against multi-drug resistant bacteria. Furthermore, they tested whether conjugation with silver nanoparticles improved the antibacterial efficacy of these quinazolinone derivatives. Cytotoxicity of nanoconjugates on human cells were determined. Among the quinazolinone derivative tested, two compounds conjugated with silver nanoparticles showed enhanced antibacterial activity against *E.coli*, *S. pyogenes*, *K. pneumoniae*, *B. cereus* and *P. aeruginosa* as compared to the compounds.

Mehta *et al.,*synthesized several new 2-(4-(2-chloroacetyl)piperazin-1-yl)-*N*-(2-(4-chlorophenyl)-4-oxoquinazolin-3(4*H*)-yl)acetamide derivatives**35**[32]. Tube dilution technique AND MTT assay was employed to evaluate in vitro antimicrobial and anticancer activities of the synthesized compounds. Schrodinger 2018-1, maestro *v11.5* software was employed to study molecular docking. Four of the tested derivatives displayed significant antimicrobial activity which is comparable to the standards ciprofloxacin and fluconazole. Among the synthesized compounds, one of the tested derivatives displayed good anticancer activity but lower than the standard 5-fluorouracil and tomudex. Good docking score was

generated for two tested derivatives in molecular docking study with better anticancer potency within the binding pocket.

Türk *et al.,* synthesized a series of novel 2-methyl-3-[4-(substituted aminosulfonyl) phenyl]-4(3*H*)-quinazolinones **36** and tested for their biofilm formation and swarming motility inhibitory activities in *P. aeruginosa*[33]. The synthesized derivatives at a concentration of 12.5 µM reduced the biofilm formation by 20-32% and swarming motility by 51-62% in *P. aeruginosa*. In addition, to elucidate the possible key interactions of the synthesized derivatives with the active site of the *P. aeruginosa* QS receptor LasR, molecular docking studies were also performed. Furthermore, some molecular properties related to drug likeness and ADME were predicted.

Antibacterial activity of series of 1-substituted-3-(4-oxo-2-phenylquinazolin3(4H)-yl) urea and thiourea analogues**37** are reported by Sandhya *et al*[34]. Antibacterial activity of six synthesized quinazolinone was screened against *S. aureus* and *E. coli* using ciprofloxacin as standard. The synthesized analogues have shown good yield and comparable antibacterial with reference ciprofloxacin.

The in vitro activities of five quinazolinone **38** antibacterial, were tested by Ceballos et al., against 210 strains of methicillin-resistant Staphylococcus aureus (MRSA) [35]. The MIC50/MIC90 values (in Î¼g/ml) were as follows: Q1, 0.5/2; Q2, 1/4; Q3, 2/4; Q4, 0.06/0.25; and Q5, 0.125/0.5. Several strains with high MIC values (from 8 â‰¥ 32â€‰Î¼g/ml) for some of these compounds exhibited amino acid changes in the penicillin-binding proteins, which are targeted by these antibacterial.

Three-dimensional quantitative structure activity analysis (3D QSAR) has been carried out by Bhattacharya *et al.,*on some already reported 4(3*H*)-quinazolinone derivatives **39** to explore the structural requirements for antifungal and antibacterial activities [36]. Partial least square (PLS) method was used in comparative molecular field analysis (CoMFA) to generate QSAR models. To understand the steric and electrostatic field contribution on the biological activity CoMFA descriptors were calculated on aligned structures. The generated CoMFA models for antifungal activity showed a cross-validation coefficient ($q^2$) of 0.578, non-cross validation coefficient ($r^2$) of 0.923 and standard error of 0.0177. The predictive ability of the model was validated using external validation with predictive factor ($r^2_{pred}$) of 0.94 for antifungal activity. The significant statistical parameters indicated the reliability and good predictive power of the developed model. The 3D contour maps generated from CoMFA models were analysed for key structural requirements for improved activity.

New class of fused quinazolines **40** has been designed and synthesized by Nandwana *et al.,* via copper-catalysed Ullmann type C–N coupling followed by intramolecular cross-dehydrogenative coupling reaction in moderate to good yields [37]. The synthesized compounds were tested for in vitro antibacterial activity against three Gram negative (*Escherichia coli, Pseudomonas putida, and Salmonella typhi*) and two Gram positive (*Bacillus subtilis, and Staphylococcus aureus*) bacteria. Among all tested compounds, three compounds exhibited promising minimum inhibitory concentration (MIC) values (4–8 µg/mL) for all bacterial strains tested compared to reference ciprofloxacin. The synthesized compounds were also evaluated for their in vitro antifungal activity against *Aspergillus niger* and *Candida albicans*. The potent antibacterial compounds also showed pronounced antifungal activity (MIC: 8–16 µg/mL) against both strains. The bactericidal assay by propidium iodide and live–dead bacterial cell screening using a mixture of acridine orange/ethidium bromide (AO/Et·Br) showed considerable changes in the bacterial cell membrane, which might be the cause or consequence of cell death. Moreover, the hemolytic activity for most potent compounds showed their safety profile toward human blood cells.

A novel 2-substitued-(3-pyridyl)-quinazolinone derivatives **41** were synthesized, characterized, and evaluated for bacteriostatic activity by Zhang *et al.* ,against three species of phytopathogenic bacteria (*Xanthomonas oryzaepv. oryzae*, *Xoo*, *Ralstonia solanacearum*, and *Xanthomonas axonopodispv. citri*, *Xac)*[38]. Biological evaluation showed that five of the tested compounds exhibited higher antibacterial activity than standard bismerthiazol. Particularly two compounds showed significant bacteriostatic activity against Xac.

Palladium-catalyzed reactions was used by Shaikha S-Al-Neyadi*et al.,*for the design and synthesis of a novel quinazoline derivatives**42**[39]. Against four pathogenic bacteria synthesized compounds were screened for their antibacterial activities. Potent compounds of the series showed higher sensitivity to *S. aureus* (gram-positive) with an MIC ≤ 0.25-0.5 µg/ml.

Chaitanya*et al.,*synthesized and evaluated antimicrobial activity of novel substituted 8-bromo-2-(dimethylamino)-3-(3-(dimethylamino)propyl)quinazoline-4(3*H*)-ones **43** with excellent yields [40]. The in vitro antibacterial activity of test compounds was assessed against three Gram-positive bacteria (*Bacillus subtilis, Bacillus sphaericus* and *Staphylococcus aureus*), and three Gram-negative bacteria (*Pseudomonas aeruginosa, Klebsiella aerogenes* and *Chromobacteriumviolaceum*), and antifungal activity against four fungi (*Candida albicans, Aspergillus fumigates, Trichophyton rubrum* and *Trichophyton*

*mentagrophytes)*. Most of the compounds of this series were exhibited more potent anti-bacterial and anti-fungal activity against standard drugs.

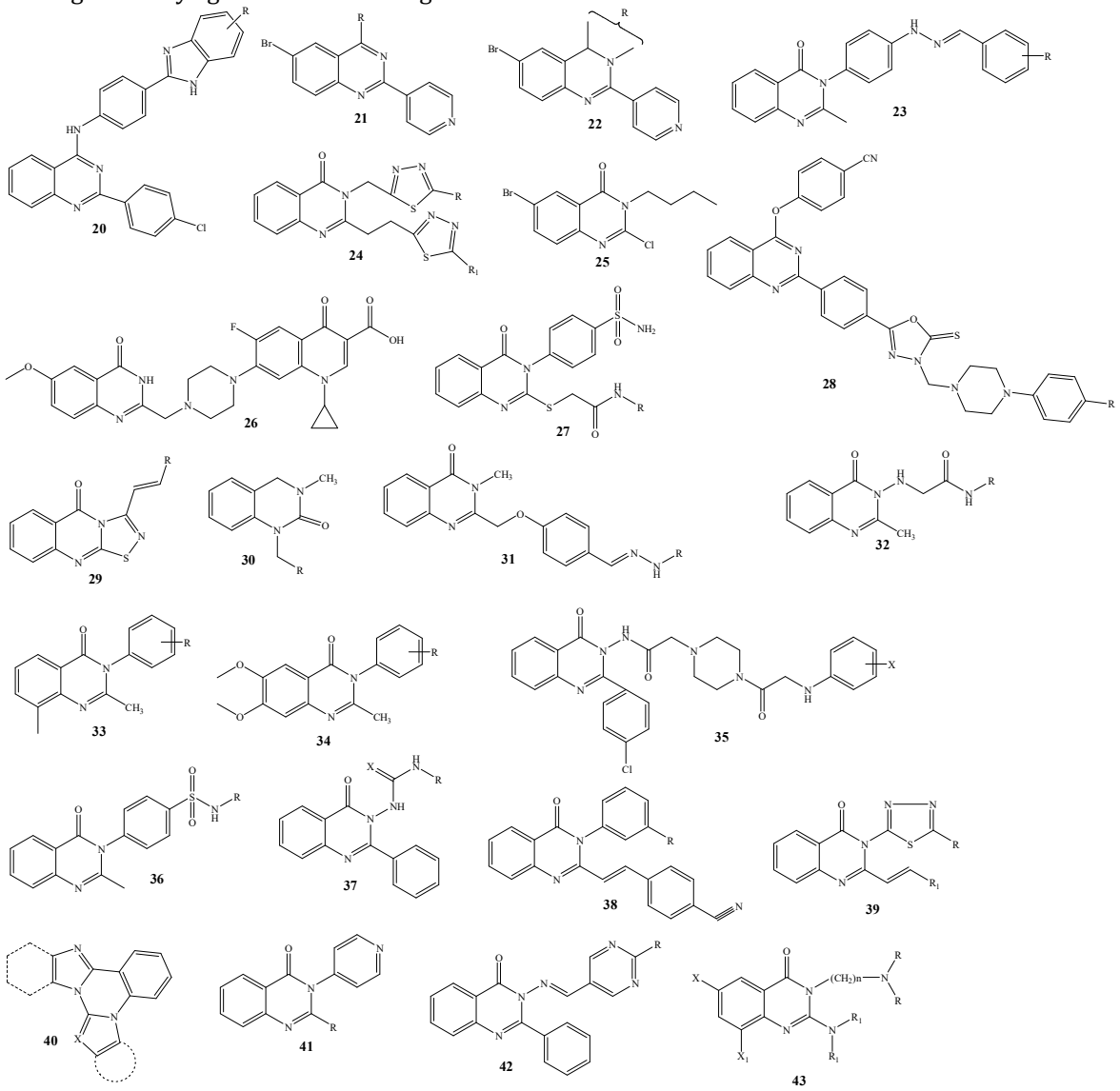


**Figure 3: Antimicrobial quinazolines**

## Antioxidant Activity

The evaluation of antioxidant compounds that counteract the mutagenic effects caused by the direct action of reactive oxygen species on DNA molecule is of considerable interest. The newly derived antioxidant activity of quinazolinone derivatives were illustrated in Figure 4.

A series of 2,3-substituted quinazolinone derivatives**44** were investigated by different assays, and the relationship between their biological properties and chemical structure was examined by Hricovíniova *et al*[41]. Comet assay and DNA topology assay was employed to evaluate genotoxicity and the potential DNA-protective effects of tested compounds. DPPH-radical-scavenging, reducing power, and total antioxidant status (TAS) assays was used for studying antioxidant activity of test compounds. MTT assay was performed in human renal epithelial cells (TH-1) and renal carcinoma cells (Caki-1) to assess the cytotoxic effect of compounds. Compounds having electron-donating moieties, were the most potent members of this series. Compounds were not genotoxic and considerably decreased the levels of DNA lesions induced by oxidants ($H_2O_2$, $Fe^{2+}$ ions). Furthermore, compounds exhibited higher cytotoxicity in Caki-1 compared to that in TH-1 cells.

Fifteen novel quinazolinone derivatives**45** bearing benzenesulfonamide moiety with variable heterocyclic tail, were synthesized by Soliman *et al*[42]. DPPH assay was used to screen the antioxidant potential of the prepared derivatives and the obtained results were compared with ascorbic acid. The N-(pyrazin-2-

yl)-2-[(4-oxo-3-(4-sulfamoylphenyl)-3,4-dihydroquinazolin-2-yl)thio]acetamide was the most active scaffold in this series with greater scavenging activity than that of ascorbic acid. In vivo acute toxicity study of the above mentioned compound indicates its relative safety with a median lethal dose of 200 mg/kg. The possible antioxidant and hepatoprotective activities of this derivative was evaluated in irradiated mice. This derivative displayed mitigation of gamma radiation-induced oxidative stress verified by the decline in MDA, ROS and NF-κB levels. Moreover, SOD and PON1 activities, as well as $Zn^{2+}$ levels, were improved in liver tissues.

New quinazolinone derivatives **46** comprising pyridine, Schiff base, 2-azetidinone, 4-thiazolidinoneand moieties are synthesized and screened for antimicrobial and in vitro antioxidant properties by Abdalgane *et al* [43]. The tested derivatives exhibited potent antimicrobial and antioxidant properties.

Priya *et al.,* synthesized a series of five Mannich bases of quinazolinone **47** by treating quinazolinones with various aromatic amines [44]. All the synthesized compounds were screened for antioxidant activity by DPPH radicals scavenging method and antimicrobial activity by cup plate method. Varying degree of antioxidant and antimicrobial activity was exhibited by test compounds.

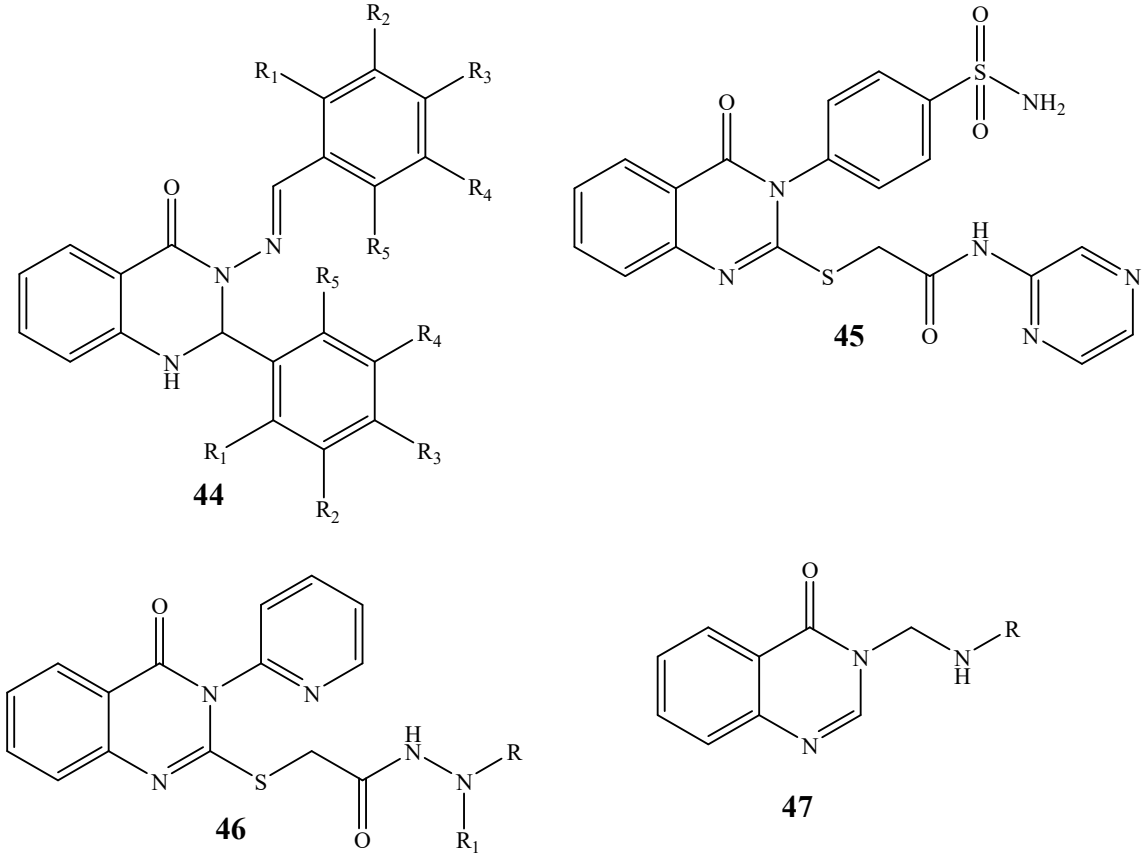



**Figure 4: Antioxidant quinazolines**

**Anti-Tubercular Activity**

At a global level, tuberculosis (TB) is the disease of human values. It suffers from major health, social and economic burden in many countries. There is an inability of an effective vaccine or the use of vaccine were too long and expensive, have increased risk of spread of this disease.

Krishnarth *et al.,*synthesized a series of quinazolinones **48** from 2-amino-3,4,5-trimethoxy benzoic acid and Vilsmeir reagent [45]. Synthesized compounds were screened for their antimicrobial activity. All the synthesized compounds shown varying degree of antimicrobial activity. In addition, the most potent four derivatives of the series were further screened for antitubercular activity against bacteria *Mycobacterium H37Rv*. Significant antitubercular activity was displayed by these four derivatives.

Three different novel series of quinazolinone hybrids, namely triazepino-quinazolinones, thiazolo-triazolo-quinazolinones and triazolo-quinazolinones **49** have been synthesized by Pandey *et al*(Fig 5) [46]. ***In vitro*** antitubercular and antimicrobial activities of the synthesized compounds were biologically screened against various pathogenic strain. Pronounced antimicrobial activity was exhibited by some of

the compounds which are comparable to that of standard drugs. Four of the tested derivatives exhibited relatively very good antibacterial and antifungal activity against selected pathogenic bacteria and fungi. The potent compounds of the series showed 5.2 µg/mL as MIC against *M. tuberculosis* ($H_{37}Rv$) in antitubercular activity screening. Molecular docking studies revealed that these compounds have good binding energy and better binding affinity within the active pocket on selective targets.

Sonogashira cross-coupling and dechloroamination reactions was employed by Dilebo*et al.,*for the synthesis of a series of 4-(pyridylamino)- and 4-(ethynylpyridine)quinazolines50[47]. Title derivatives were screened for their in vitro antitubercular activity using rifampicin as a reference drug by Alamar Blue assay (***Mtb*** H37Rv strain) method. Results revealed promising $MIC_{90}$ ranging from < 0.7 to > 125 µM. At a maximum concentration of 50 µM the cytotoxicity of the prepared derivatives was tested against the Raw 264.7 microphage cell line. They theoretically explained the possible mode of interaction against the *Mycobacterium tuberculosis* using molecular 3ZXR protein.

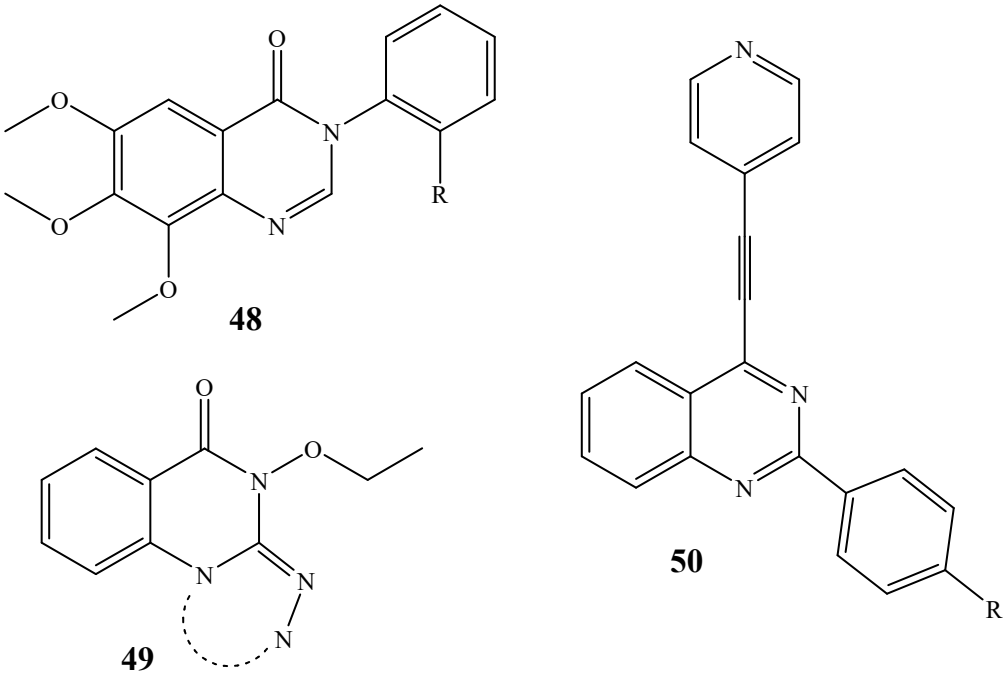



**Figure 5: Antitubercular quinazolines**

***α-Glucosidase*** **Inhibitor Activity**

Azimi*et al.,*designed, synthesized and screened novel quinazolinone-pyrazole hybrids **51** for their *α-glucosidase* inhibitory activity (Fig 6) [48]. Compared to standard acarbose ($IC_{50}$: 750.0 ± 10.0 µM), all the molecular hybrids exhibited in vitro *α-glucosidase* inhibitory activity ($IC_{50}$: 60.5 ± 0.3 µM - 186.6 ± 20 µM). Different substitutions on phenyl rings of diphenyl pyrazole moiety affected the inhibitory activities. The enzyme kinetic studies of the most potent compound revealed that it inhibited *α-glucosidase* in a competitive mode with a Ki of 56 µM. Molecular docking and molecular dynamic study was also reported.

A series of new quinazolinone-dihydropyrano[3,2-***b***]pyran derivatives **52** were synthesized and investigated for *α-glucosidase* and *α-amylase* inhibitory activities by Sherafati*et al*[49]. Compared to the standard acarbose tested derivatives displayed high *α-glucosidase* inhibition effects but an inactive against *α-amylase*. The most potent compound ($IC_{50}$: 40.1 ± 0.6 µM) of the series displayed 18.75 times more inhibitory activity than reference acarboase ($IC_{50}$: 750.0 ± 12.5 µM). Docking studies confirmed obtained experimental results. Against normal fibroblast cells, the cytotoxicity of the most potent compounds was determined. In addition, they also predicted *in silico* drug-likeness, ADME, and toxicity of these compounds.

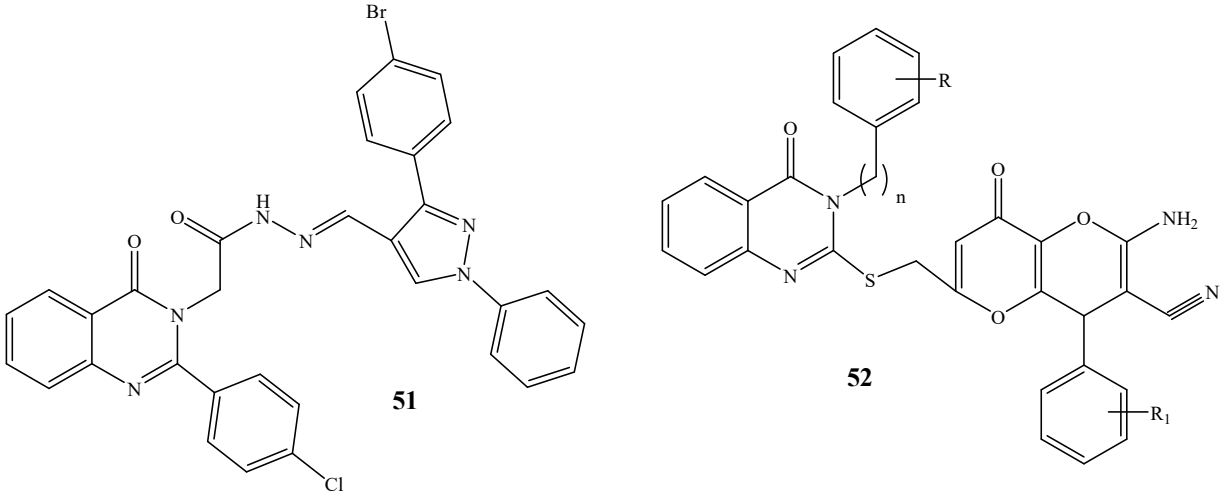
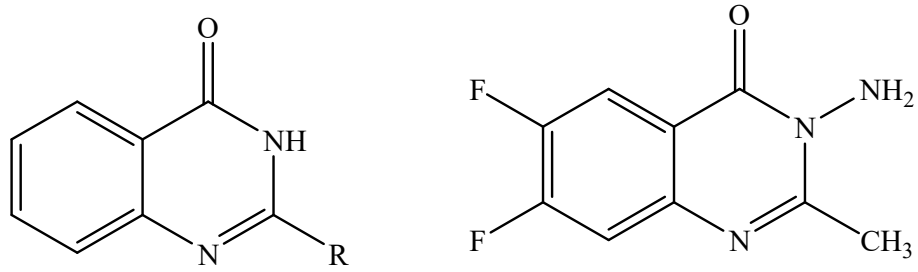



**Figure 6: α-Glucosidase inhibitor quinazolines**

**Analgesic Activity**

Osarumwense *et al.*synthesized and evaluated analgesic activity of quinazolin-4(3*H*)-one, 2-methyl-4(3*H*)-quinazolinone and 2–phenyl-4(3H)-quinazolin-4(3*H*)–one**53**(Fig 7) [50]. Acetic acid induced writhing method was employed in mice for screening analgesic activity of synthesized compounds. Synthesized compounds showed significant analgesic activity compared to standard aspirin and indomethacin. Phenyl derivative exhibited higher analgesic activity followed by methyl and unsubstituted derivative.

Osarumwense *et al.,*reported the synthesis and antibacterial evaluation of 5, 6-difluoro-2-methyl-4H-benzo(d)(1, 3)-oxazin-4-one and 3-amino-5, 6-difluoro-2-mehtyl-quinzolin-4(3*H*)-one**54**[51]. The synthesized compounds were screened against various strains of microorganism such as *Staphylococcus aureus, Bacillus species, Escherichia coli, Klebsiella pneumonia, Serratia Marcensces,* and *Candida albicans*.

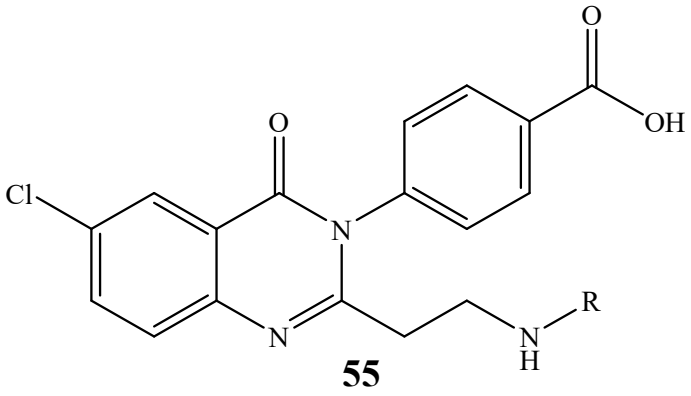



# Figure 7: Analgesic quinazolines

**Anti-Inflammatory Activity**

Patel *et al.,* synthesized and screened anti-inflammatory activity of a series of sixteen different quinazolinones **55** from 5-chloro anthranilic acid (Fig 8) [52]. Most of the prepared derivatives had shown good consequence to moderate anti-inflammatory activity. Among the synthesized compounds three derivatives showed high anti-inflammatory activity compared to reference diclofenac sodium.




**55**

**Figure 8: Antiinflammatory quinazolines**

**Antileishmanial Activity**

Currently available drugs being used to treat leishmaniasis have several shortcomings, including high toxicity, drug administration that requires hospitalization, and the emergence of parasite resistance against clinically used drugs. As a result, there is a dire need for the development of new antileishmanial drugs that are safe, affordable, and efficient.

Two new series of quinazolinone derivatives **56-58** were synthesized by Prinsloo *et al.* ,investigated as potential antileishmanial agents against the *Leishmania* (*L.*) *donovani* and *L. major* species (Fig 9) [53]. Vero cells was used to know in vitro cytotoxicity profiles of these synthesized compounds. Compared to the reference halofuginone and febrifugine tested derivatives were found to be safer and without any toxic activities against mammalian cells. However, they had demonstrated poor antileishmanial growth inhibition efficacies. Potent compounds of this series displayed 35% and 29% growth inhibitory efficacies for the *L. major* and *L. donovani*, respectively.

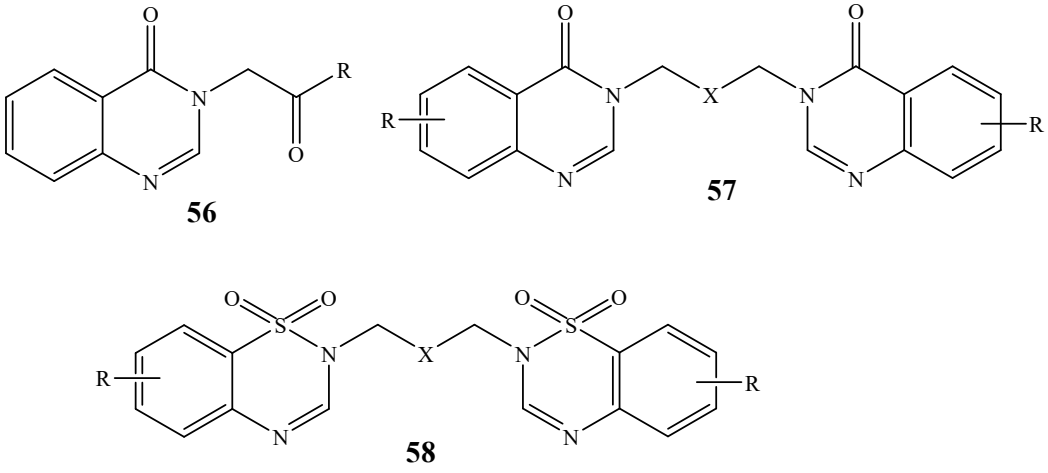


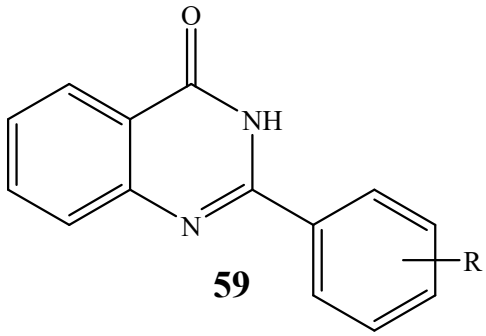

**Figure 9: Antiilesmanial quinazolines**

**A1 and/or A2A Adenosine Receptor Affinities**

Antagonists of the adenosine receptors ($A_1$ and $A_{2A}$ subtypes) are widely researched as potential drug candidates for their role in Parkinson's disease-related cognitive deficits ($A_1$ subtype), motor dysfunction ($A_{2A}$ subtype) and to exhibit neuroprotective properties ($A_{2A}$ subtype).

Pieterse *et al.,* structurally modified the α-pyrone core to explore related benzoxazinone and quinazolinone homologues**59** previously unknown as adenosine receptor antagonists (Fig 10) [54]. Overall, the C2-substituted quinazolinone analogues displayed superior $A_1$ and $A_{2A}$ adenosine receptor affinity over their C2-substituted benzoxazinone homologues. The quinazolinones displayed varying degrees of affinity (low micromolar range) towards the $A_1$ and $A_{2A}$ adenosine receptor subtypes. The highest $A_1$ adenosine receptor affinity and selectivity were favoured by methyl ***para***-substitution of phenyl ring B ($A_1\boldsymbol{K}_i$ = 2.50 μM). On the other hand, 3,4-dimethoxy substitution of phenyl ring B afforded the best $A_{2A}$ adenosine receptor binding ($A_{2A}\boldsymbol{K}_i$ = 2.81 μM) among the quinazolinones investigated.



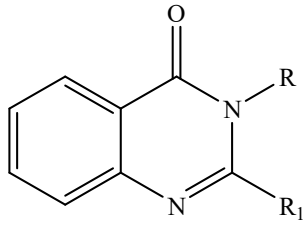

**59**

**Figure 10: Adenosine receptor antagonist quinazolines**

**Anti-HIV Activity**

Although major efforts have been devoted to the effective treatment of HIV-1 infection, it has remained one of the leading causes of deaths around the world. So, development of anti-HIV-1 agents featuring novel structure is essential.

Hajimahdi *et al.,*designed and synthesized several 2,3-diaryl-4-quinazolinones **60** using a one-pot multicomponent reaction (Fig 11). Hela cell-based single-cycle replication assay was employed to study the anti-HIV-1 activity of test compounds [55]. Most of the compounds showed efficacy against HIV-1 replication. The $EC_{50}$ value of potent compound of the series was found to be 37 μM. Docking studies indicated that synthesized compounds can interact with the key residues of the HIV-1 integrase active site.



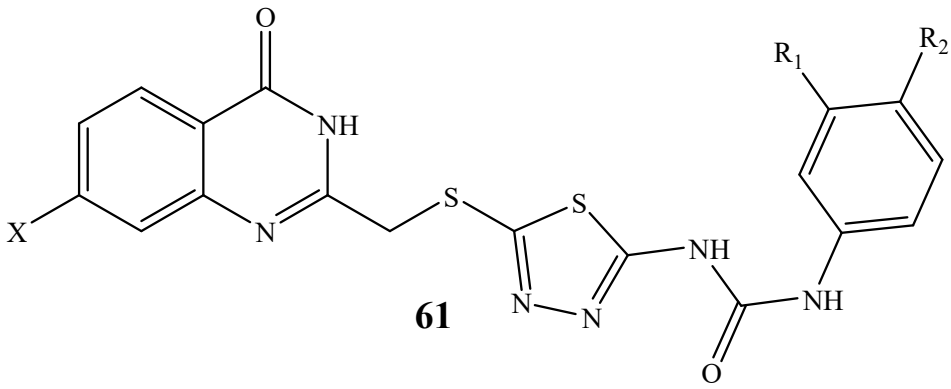

**60**

**Figure 11: Anti-HIV quinazolines**

**Anti-angiogenic Activity**

A series of quinazolin-4(3***H***)-one **61** based agents containing thiadiazole-urea were designed, synthesized, and biologically evaluated by Faraji *et al*(Fig 12). Compared to reference sorafenib ($IC_{50}$: 17.3 μM) one of the test compound ($IC_{50}$: 17.7 μM) moderately reduced the proliferation rate of PC3 cells [56]. When they were exposed to another derivative ($IC_{50}$ = 6.1 μM), there was also a significant reduction in the number of HUVEC cells. Annexin V-FITC/propidium iodide double staining assay was employed to examine the potential of compounds in inducing apoptosis. A substantial effort was dedicated to gathering comprehensive data across CAM assay. These data showed that **the potent compound** moderately inhibits the growth of corresponding blood vessels. Finally, the outcomes of Western blotting proposed a mechanism of action, by which the phosphorylation of VEGFR-2 is inhibited by the potent derivative of this series.




61

**Figure 12: Antiangiogenic quinazolines**

## CONCLUSION

In modern drug discovery, quinazoline nucleus is an important pharmacophore. As a source of novel biological agents, gradually more attention has been given for the synthesis of quinazoline compounds. For further medicinal research these quinazoline compounds are a resource. The information gained by many investigates has suggested that substituted quinazolines and heterocycles, which are the structural isosteres of nucleotides, allow them to interact easily with the biopolymers, possess pharmacological activity with lower toxicities. Changes in the quinazoline derivatives have offered better biological properties that have established beneficial for the evolution of novel medicinal agents with enhanced potency and reduced toxicity. The present review highlights the various recently reported (2018-2021) biological activities (anticancer activity, antimicrobial activity, antioxidant activity, antitubercular activity, *α-glucosidase* inhibitor activity, analgesic activity, anti-inflammatory activity, antileishmanial activity, $A_1$ and/or $A_{2a}$ adenosine receptor affinities**,** anti-HIV activity and antiangiogenic activity) of several prepared quinazolines and their derivatives.

## Conflict of interest

The author does not declare any conflict of interest.

## REFERENCES


1. Jampilek, J.(2019). Heterocycles in medicinal chemistry. Molecules, 24(21): 3839.doi:10.3390/molecules24213839
2. Mass, E.B., Duarte, G.V.,Russowsky, D.(2021). The Quinazoline-Chalcone and Quinazolinone-Chalcone Hybrids: A Promising Combination for Biological Activity. Mini Reviews in Medicinal Chemistry,21(2): 186-203.doi: 10.2174/1389557520666200730160325
3. Pantola, P.,Agarwal, P.(2021). An Illustrated Review on Chemical Properties, Synthetic Methods and Biological Activities of Quinazolines. Future Journal of Pharmaceuticalsand Health Sciences, 1(2): 12-20.
4. Abdallah, A.E., Eissa, S.I., Al Ward, M.M.S., Mabrouk, R.R., Mehany, A.B., El-Zahabi, M.A.(2021). Design, synthesis and molecular modelling of new quinazolin-4 (3H)-one based VEGFR-2 kinase inhibitors for potential anticancer evaluation. Bioorganic Chemistry,109: 104695.
5. Shao, L.H., Fan, S.L., Meng, Y.F., Gan, Y.Y., Shao, W.B., Wang, Z.C., Chen, D.P., Ouyang, G.P. (2021). Design, ssynthesis, biological activities and 3D-QSAR studies of quinazolinone derivatives containing hydrazone structural units. New Journal of Chemistry, 45(10): 4626-4631.doi: 10.1039/D0NJ05450J
6. Nunes, P.S.G., da Silva, G., Nascimento, S., Mantoani, S.P., de Andrade, P., Bernardes, E.S., Kawano, D.F., Leopoldino, A.M., Carvalho, I.(2021). Synthesis, biological evaluation and molecular docking studies of novel 1, 2, 3-triazole-quinazolines as antiproliferative agents displaying ERK inhibitory activity. Bioorganic chemistry, 113: 104982.doi: 10.1016/j.bioorg.2021.104982
7. Aziz, M.W., Kamal, A.M., Mohamed, K.O., Elgendy, A.A.(2021). Design, synthesis and assessment of new series of quinazolinone derivatives as EGFR inhibitors along with their cytotoxic evaluation against MCF7 and A549 cancer cell lines. Bioorganic andMedicinal Chemistry Letters, 41: 127987.doi: 10.1016/j.bmcl.2021.127987
8. Jin, H., Wu, B.X., Zheng, Q., Hu, C.H., Tang, X.Z., Zhang, W., Rao, G.W. (2021). Design, synthesis, biological evaluation and docking study of novel quinazoline derivatives as EGFR-TK inhibitors. Future Medicinal Chemistry, 13(7):601-612. doi: 10.4155/fmc-2020-0015
9. Altamimi, A.S., El-Azab, A.S., Abdelhamid, S.G., Alamri, M.A., Bayoumi, A.H., Alqahtani, S.M., Alabbas, A.B., Altharawi, A.I., Alossaimi, M.A., Mohamed, M.A., (2021). Synthesis, Anticancer Screening of Some Novel Trimethoxy Quinazolines and VEGFR2, EGFR Tyrosine Kinase Inhibitors Assay; Molecular Docking Studies. Molecules, 26(10): 2992.doi: 10.3390/molecules26102992

**10.** Kaneti, J., Georgieva, M., Rangelov, M., Philipova, I., Vasileva, B., Angelov, I., Staneva, D., Miloshev, G., Bakalova, S. (2021). Biological activity of quinazoline analogues and molecular modeling of their interactions with G-quadruplexes. Biochimica et Biophysica Acta (BBA)-General Subjects, 1865(1): 129773.doi:10.1016/j.bbagen.2020.129773

**11.** Kim, Y.S., Cheon, M.G., Boggu, P.R., Koh, S.Y., Park, G.M., Kim, G., Park, S.H., Park, S.L., Lee, C.W., Kim, J.W., Jung, Y.H.(2021). Synthesis and biological evaluation of novel purinyl quinazolinone derivatives as PI3Kδ-specific inhibitors for the treatment of hematologic malignancies. Bioorganic and Medicinal Chemistry,116312.doi: 10.1016/j.bmc.2021.116312

**12.** Hakima, F., Salfi, R., Bhikshapathi, D., Khan, A.(2022). Anticancer Evaluation of Novel Quinazolinone Acetamides: Synthesis and Characterization. Anti-cancer Agents in Medicinal Chemistry.22(5): 926-932. doi:10.2174/1871520621666210524164351

**13.** Das, S., Amin, S.A., Jha, T. (2021). Inhibitors of gelatinases (MMP-2 and MMP-9) for the management of hematological malignancies. European Journal of Medicinal Chemistry, 113623.doi: 10.1016/j.ejmech.2021.113623

**14.** Sakr, A.,Rezq, S., Ibrahim, S.M., Soliman, E., Baraka, M.M.,Romero, D.G.,Kothayer, H. (2021). Design and synthesis of novel quinazolinones conjugated ibuprofen, indole acetamide, or thioacetohydrazide as selective COX-2 inhibitors: anti-inflammatory, analgesic and anticancer activities, Journal of Enzyme Inhibition and Medicinal Chemistry, 36(1): 1810-1828. doi: 10.1080/14756366.2021.1956912

**15.** Nallathamby, N., Phan, C., Sova, M.,Saso, L., Sabaratnam, V. (2021).Synthesized 2-Trifluoromethylquinazolines and Quinazolinones Protect BV2 and N2a Cells against LPS- and H<sub>2</sub>O<sub>2</sub>-induced Cytotoxicity". Medicinal Chemistry, 17(6). doi: 10.2174/1573406416666191218095635

**16.** Bathula, R., Mondal, P., Raparla, R.,Satla, S.R., (2020). Evaluation of antitumor potential of synthesized novel 2-substituted 4-anilinoquinazolines as quinazoline-pyrrole hybrids in MCF-7 human breast cancer cell line and A-549 human lung adenocarcinoma cell lines. Future Journal of Pharmaceutical Sciences, 6(1): 1-11.doi: 10.1186/s43094-020-00059-5

**17.** Emami, L., Faghih, Z., Sakhteman, A., Rezaei, Z., Faghih, Z., Salehi, F., Khabnadideh, S. (2020). Design, synthesis, molecular simulation, and biological activities of novel quinazolinone-pyrimidine hybrid derivatives as dipeptidyl peptidase-4 inhibitors and anticancer agents. New Journal of Chemistry, 44(45): 19515-19531.doi: 10.1039/D0NJ03774E

**18.** SoloagaArdiles, C., Castro Rodriguez, C., SurcoLuque, J.(2020). Correlation between the electronic structure of quinazoline derivatives and the activity of the NTR1 receptor. Journal of the Chilean Chemical Society, 65(1): 4686-4691.

**19.** Malasala, S., Ahmad, M.N., Akunuri, R., Shukla, M., Kaul, G., Dasgupta, A., Madhavi, Y.V., Chopra, S., Nanduri, S. (2021). Synthesis and evaluation of new quinazoline-benzimidazole hybrids as potent anti-microbial agents against multidrug resistant Staphylococcus aureus and Mycobacterium tuberculosis. European Journal of Medicinal Chemistry, 212: 112996.doi: 10.1016/j.ejmech.2020.112996

**20.** Eweas, A., Abdallah, Q., Elbadawy, M.(2021). Synthesis and biological evaluation of some new 2-pyridylquinazoline derivatives. Current Chemistry Letters, 10(4): 459-470.doi: 10.5267/j. ccl. 2021.4.005

**21.** Kavitha, K., Mohan, S., Srinivasan, N., Suresh, R.(2021). Design, Synthesis, Characterization of Antimicrobial activity of Schiff bases of novel Quinazolin-4-one Derivatives. Research Journal of Pharmacy and Technology, 14(1): 466-470.doi: 10.5958/0974-360X.2021.00085.8

**22.** Abdelmajeid, A., Ashour, M.T.(2021). Synthesis and evaluation of in vitro biological activity of new series of quinazolinone and benzoxazinone derivatives. Egyptian Journal of Chemistry, 64(5): 2653-2661.doi: 10.21608/EJCHEM.2021.61385.3319

**23.** Geesi, M.H., Kaiba, A., Al-Tamimi, A.M.S., Guionneau, P., Ibnouf, E.O., Azzallou, R., Bakht, M.A., Riadi, Y.(2021). Synthesis, antibacterial evaluation, crystal structure and molecular interactions analysis of new 6-Bromo-2-chloro-3-butylquinazolin-4 (3H)-one. Journal of Molecular Structure, 1225: 129166.

**24.** Norouzbahari, M., Salarinejad, S., Güran, M., Şanlıtürk, G., Emamgholipour, Z., Bijanzadeh, H.R., Toolabi, M., Foroumadi, A.(2020). Design, synthesis, molecular docking study, and antibacterial evaluation of some new fluoroquinolone analogues bearing a quinazolinone moiety. *DARU* Journal of Pharmaceutical Sciences, 28(2): 661-672.doi: 10.1007/s40199-020-00373-6

**25.** Ghorab, M.M.,Alqahtani, A.S., Soliman, A.M., Askar, A.A. (2020). Novel N-(substituted) thioacetamide quinazolinone benzenesulfonamides as antimicrobial agents. International Journal of Nanomedicine, 15: 3161p.

**26.** Patel, A.B.(2020). Investigation of the antibacterial activity of new quinazoline derivatives against methicillin and quinolone resistant Staphylococcus aureus. Journal of Chemical Research, 44(5-6): 315-321.doi: 10.1177/1747519819895887

**27.** Haggam, R.A., Soylem, E.A., Assy, M.G., Arastiedy, M.F.(2020). Synthesis and antimicrobial evaluation of new series of quinazolin-5-one derivatives. Journal of the Iranian Chemical Society, 17(7): 1715-1723.

**28.** Farooq, S., Mazhar, A., Ullah, N.(2020). One-pot multicomponent synthesis of novel 3, 4-dihydro-3-methyl-2 (1H)-quinazolinone derivatives and their biological evaluation as potential antioxidants, enzyme inhibitors, antimicrobials, cytotoxic and anti-inflammatory agents. Arabian Journal of Chemistry, 13(12): 9145-9165.doi: 10.1016/j.arabjc.2020.10.039

**29.** Shao, L., Gan, Y., Zhang, L.Q., Wang, Z.C., Ouyang, G.P.(2020). Design, Synthesis and Biological Activity of Quinazolinone Derivatives Containing Hydrazone Structural Units. Chinese Journal of Organic Chemistry, 40(7): 1975-1982.doi: 10.6023/cjoc202003013

**30.** Pawar, P. Y., M., W. S. (2020).Synthesis and evaluation of antimicrobial activity of quinazolinone derivatives. International Journal of Current Pharmaceutical Research, 12(3): 114-116.doi: 10.22159/ijcpr.2020v12i3.38318

**31.** Masri, A., Anwar, A., Khan, N.A., Shahbaz, M.S., Khan, K.M., Shahabuddin, S., Siddiqui, R.(2019). Antibacterial effects of quinazolin-4 (3H)-one functionalized-conjugated silver nanoparticles. Antibiotics, 8(4): 179.doi: 10.3390/antibiotics8040179

**32.** Mehta, S., Kumar, S., Marwaha, R.K., Narasimhan, B., Ramasamy, K., Lim, S.M., Shah, S.A.A., Mani, V.(2019). Synthesis, molecular docking and biological potentials of new 2-(4-(2-chloroacetyl) piperazin-1-yl)-N-(2-(4-chlorophenyl)-4-oxoquinazolin-3 (4 H)-yl) acetamide derivatives. BMC chemistry, 13(1): 1-21.doi: 10.1186/s13065-019-0629-0

**33.** Turk, S., Karakuş, S., Ece, A., Ulusoy, S., Bosgelmez-Tınaz, G.(2019). Synthesis, Structure Elucidation and Biological Activities of Some Novel 4 (3H)-Quinazolinones as Anti-Biofilm Agents. Letters in Drug Design & Discovery, 16(3): 313-321.doi: 10.2174/1570180815666180621101123

**34.** Dhokale, S.R., Thakar, S.R.,Bansode, D.A., Mahadik, K.R. (2019).Synthesis, screening of novel 1-substituted-3-(4-oxo-2-phenylquinazolin3(4H)-yl) urea and thiourea analogues as potent antibacterials. International Journal of Pharmacy and Pharmaceutical Sciences, 11(11) 38-42. doi: 10.22159/ijpps.2019v11i11.35461

**35.** Ceballos, S., Kim, C., Qian, Y., Mobashery, S., Chang, M., Torres, C.(2019). Susceptibility of methicillin-resistant Staphylococcus aureus to five quinazolinone antibacterial. Antimicrobial agents and chemotherapy, 64(1): e01344-19.doi: 10.1128/AAC.01344-19

**36.** Bhattacharya, S., Rajoriya, V., Jana, P., Kashaw, V. (2019). Comparative Molecular Field Analysis on 4 (3H) Quinazolinone derivatives for the Development of Potential Antimicrobial Agents. Journal of Drug Delivery and Therapeutics, 9(2): 603-611.doi: org/10.22270/jddt.v9i2.2706

**37.** Nandwana, N.K., Singh, R.P., Patel, O.P., Dhiman, S., Saini, H.K., Jha, P.N., Kumar, A. (2018). Design and synthesis of imidazo/benzimidazo [1, 2-c] quinazoline derivatives and evaluation of their antimicrobial activity. *ACS* omega, 3(11): 16338-16346.doi: org/10.1021/acsomega.8b01592

**38.** Zhang, L., Chen, Q., Li, X.Q., Wu, S.Q., Wan, J.L., Ouyang, G.P. (2018). Synthesis and Antibacterial Activity of 2-substitued-(3-pyridyl)-quinazolinone Derivatives. Journal of Heterocyclic Chemistry, 55(3): 743-749.doi: org/10.5772/intechopen.89203

**39.** S-Al-Neyadi, S., Salem, A.A., Ghazawi, A., Pal, T., Abdou, I.M. (2018). Synthesis and Functionalization of Novel Quinazoline Scaffolds as Antibacterial Agents, Research and Reviews: Journal of Chemistry, 7(3): 14-31.

**40.** Chaitanya, P., Ravi, G., Damodhar, S., RavinderNath, A.(2018). Synthesis, characterization and evaluation of anti-microbial activity of novel substituted quinazoline derivatives. Rasayan Journal of Chemistry, 11, 1357-1365.

**41.** Hricoviniova, J., Hricoviniova, Z., Kozics, K. (2021). Antioxidant, Cytotoxic, Genotoxic, and DNA-Protective Potential of 2, 3-Substituted Quinazolinones: Structure—Activity Relationship Study. International Journal of Molecular Sciences, 22(2): 610.doi: 10.3390/ijms22020610

**42.** Soliman, A.M., Karam, H.M., Mekkawy, M.H., Ghorab, M.M. (2020). Antioxidant activity of novel quinazolinones bearing sulfonamide: potential radiomodulatory effects on liver tissues via NF-κB/PON1 pathway. European journal of medicinal chemistry, 197: 112333.doi: 10.1016/j.bmcl.2021.128002

**43.** Abdalgane, H.A., Mohammed, H.H., Askar, F.W.(2019). Synthesis and biological evaluation studies of some quinazolinone derivatives as antimicrobial and antioxidant agents. Journal of Pharmaceutical Sciences and Research, 11(1): 54-57.doi:10.5155/eurjchem.5.4.628-634.1120

**44.** Priya, D., Srimathi, R., Anjana, G.V. (2018). Synthesis and evaluation of some mannich bases of Quinazolinone nucleus. Asian Journal of Pharmaceutical and clinical research, 11(2): 407-409.doi: 10.22159/ajpcr.2018.v11i2.22644

**45.** Krishnarth, N., Verma, S.K., Chaudhary, A.(2020). Synthesis and Anti-Inflammatory Activity of Some Novel Quinazolinone Derivatives. FABAD Journal of Pharmaceutical Sciences, 45(3): 205-210.

**46.** Pandey, S.K., Yadava, U., Upadhyay, A., Sharma, M.L.(2021). Synthesis, biological evaluation and molecular docking studies of novel quinazolinones as antitubercular and antimicrobial agents. Bioorganic Chemistry, 108: 104611.doi: 10.1016/j.bioorg.2020.104611

**47.** Dilebo, K.B., Gumede, N.J., Nxumalo, W., Matsebatlela, T.M., Mangokoana, D., Moraone, N.R., Omondi, B., Mampa, R.M.(2021). Synthesis, In Vitro Cytotoxic, Anti-Mycobacterium tuberculosis and Molecular Docking Studies of 4-Pyridylamino-and 4-(Ethynylpyridine) quinazolines. Journal of Molecular Structure, 130824.

**48.** Azimi, F., Azizian, H., Najafi, M., Hassanzadeh, F., Sadeghi-Aliabadi, H., Ghasemi, J.B., Faramarzi, M.A., Mojtabavi, S., Larijani, B., Saghaei, L., Mahdavi, M.(2021). Design and synthesis of novel quinazolinone-pyrazole derivatives as potential α-glucosidase inhibitors: Structure-activity relationship, molecular modeling and kinetic study. Bioorganic Chemistry, 114: 105127.doi: 10.1007/s11030-021-10310-7

**49.** Sherafati, M., Mirzazadeh, R., Barzegari, E., Mohammadi-Khanaposhtani, M., Azizian, H., Asgari, M.S., Hosseini, S., Zabihi, E.,Mojtabavi, S., Faramarzi, M.A., Mahdavi, M.(2021). Quinazolinone-dihydropyrano [3, 2-b] pyran hybrids as new α-glucosidase inhibitors: Design, synthesis, enzymatic inhibition, docking study and prediction of pharmacokinetic. Bioorganic chemistry, 109: 104703.

**50.** Osarumwense, P.O., Edema, M.O., Usifoh, C.O.(2020). Synthesis andAnagesic activities of Quinazolin-4 (3H)-One, 2-Methyl-4 (3H)-Quinazolinone and 2–Phenyl-4 (3H)-quinazolin-4 (3H)–one. Journal of Drug Delivery and Therapeutics, 10(4-s): 87-91. doi: 10.22270/jddt.v10i4-s.4209

**51.** Osarumwense, P.O. (2019).Synthesis and Analgesic Activity of 5, 6-difluoro-2-Methyl-4H-benzo (d)(1, 3)-Oxazin-4-one and 3-Amino-5, 6-difluoro-2-Mehtyl-quinzolin 4 (3H)-One. American Journal of Biomedical Science and Research. 5(2): 127-130. doi: 10.34297/AJBSR.2019.05.000892

**52.** Patel, R., Saraswat, R.,Pillai, S (2021). Synthesis, characterization and biological evaluation of novel quinazolinone derivatives as anti-inflammatory agents. ***International Journal of Pharmaceutical Sciences and Research***, 12(4): 2296-2305.

**53.** Prinsloo, I.F., Zuma, N.H., Aucamp, J., N'Da, D.D.(2021). Synthesis and in vitro antileishmanial efficacy of novel quinazolinone derivatives. Chemical Biology and Drug Design, 97(2): 383-398.doi: 10.1111/cbdd.13790

**54.** Pieterse, L., Van der Walt, M.M. TerreBlanche, G. (2020). C2-substituted quinazolinone derivatives exhibit A1 and/or A2A adenosine receptor affinities in the low micromolar range. Bioorganic and Medicinal Chemistry Letters, 30(16): 127274.doi: 10.1016/j.bmcl.2020.127274

**55.** Hajimahdi, Z., Zabihollahi, R., Aghasadeghi, M.R., Zarghi, A.(2019). Design, Synthesis, Docking Studies and Biological Activities Novel 2, 3-Diaryl-4-Quinazolinone Derivatives as Anti-HIV-1 Agents. Current HIV research, 17(3): 214-222.doi: 10.2174/1570162x17666190911125359

**56.** Faraji, A., Motahari, R., Hasanvand, Z., Bakhshaiesh, T.O., Toolabi, M., Moghimi, S., Firoozpour, L., Boshagh, M.A., Rahmani, R., Ketabforoosh, S.H., Bijanzadeh, H.R.(2021). Quinazolin-4 (3H)-one based agents bearing thiadiazole-urea: Synthesis and evaluation of anti-proliferative and antiangiogenic activity. Bioorganic Chemistry, 108: 104553.doi: 10.1016/j.bioorg.2020.104553s