COMPREHENSIVE REVIEW

Quinoline derivatives volunteering against antimicrobial resistance: rational approaches, design strategies, structure activity relationship and mechanistic insights

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Abstract

Emergence of antimicrobial resistance has become a great threat to human species as there is shortage of development of new antimicrobial agents. So, its mandatary to combat AMR by initiating research and developing new novel antimicrobial agents. Among phytoconstituents, Quinoline (nitrogen containing heterocyclic) have played a wide role in providing new bioactive molecules. So, this review provides rational approaches, design strategies, structure activity relationship and mechanistic insights of newly developed quinoline derivatives as antimicrobial agents.

Graphical abstract
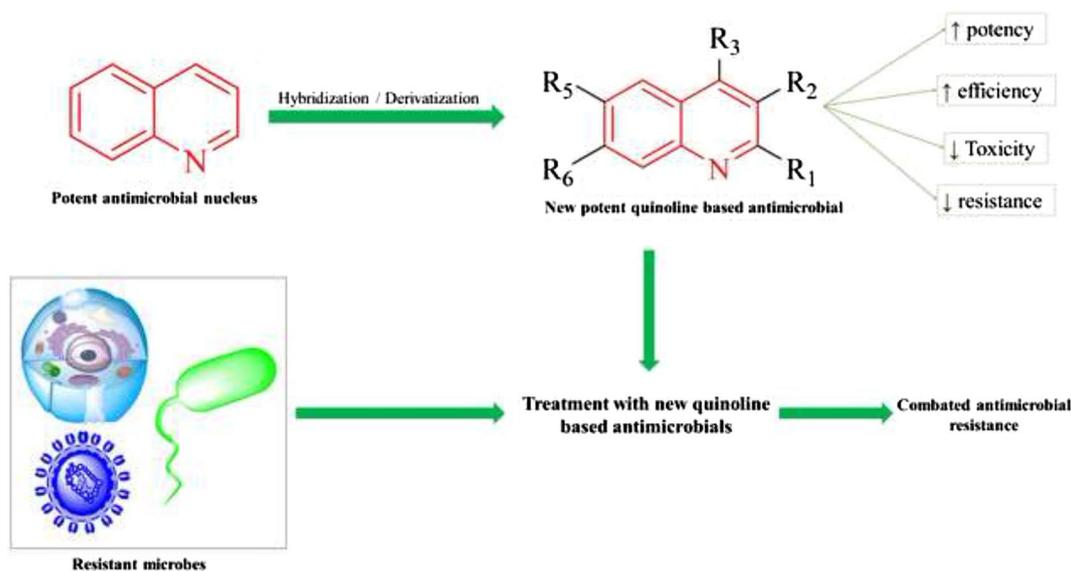
Abbreviations

μg	Microgram
μM	Micromolar

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2D-QSAR	Two-dimensional quantitative structure activity relationship
A549	Hypotriploid alveolar basal epithelial cells
ADMET	Absorption distribution metabolism excretion and toxicity
Ala	Alanine
AMR	Antimicrobial resistance

Arg	Arginine
Asn	Asparagine
Asp	Aspartic acid
AUC	Area under curve
BVDV	Bovine viral diarrhea virus
CNS	Central nervous system
COVID-19	Coronavirus 2019
Cys	Cysteine
D6	Chloroquine-sensitive strain
DENV	Dengue Virus
DNA	Deoxyribonucleic acid
EC50	Half maximal effective concentration
EV-A71	Enterovirus A71
FtsZ	Filamenting temperature- sensitive mutant Z
Gln	Glutamine
Glu	Glutamic acid
Gly	Glycine
HEK	Human epidermal keratinocytes
Hela	First immortal human cell line
His	Histidine
Huh7	Hepatocyte-derived carcinoma cell line
HUVEC	Human umbilical vein endothelial cells
IC50	Half maximal inhibitory concentration
LD50	Lethal dose
Leu	Leucine
Lys	Lysine
MDBK	Madin-Darby bovine kidney
Met	Methionine
MetAP1	Methionine aminopeptidase
MIC	Minimum inhibitory concentration
mL	Millilitre
RNA	Ribonucleic acid
MRSA	Methicillin-resistant staphylococcus aureus
MTB	Mycobacterium tuberculosis
PANC-1	Human pancreatic cancer cell line
Phe	Phenylalanine
Pro	Proline
RdRp	RNA dependent RNA polymerase
ROS	Reactive oxygen species
rRNA	Ribosomal ribonucleic acid
Ser	Serine
SNB-19	Human glioblastoma cell line
THP-1	Human leukemia monocytic cell line
Thr	Threonine
Trp	Tryptophan
Tyr	Tyrosine
Val	Valine
W2	Chloroquine-resistant strain
ZIKV	Zika virus

Introduction

Antimicrobials, the magic bullets to target microbial infections has come to verge of losing efficacy due to emergence of antimicrobial resistance (AMR) [1, 2]. As per Darwin's theory of evolution, evolution is the key to adapt the changes in the environment, in turn increasing the probability of survival [3]. Therefore, bacteria, fungi, viruses, and parasites evolve (mutations) to adapt the environmental changes (attack of antimicrobials) [4]. This evolution and indiscriminate use antimicrobials have led to rise of antimicrobial resistance (Fig. 1a) [5]. Moreover, this resistance has led physicians to increase the dose of antimicrobials which in turn increases the drug toxicity or emergence of multidrug-resistant microbes. This emergence has led to arise of antimicrobial resistance (AMR) and has led to scarcity of novel drugs that can combat this resistance [6]. Therefore, AMR confers a serious challenge to the healthcare system worldwide in the terms of mortality, morbidity, and economic burden [7]. In fact, the Centers for Disease Control and Prevention claimed 23,000 deaths per year in the US due to antibiotic resistance and this could reach millions in the coming decades [8].

Since the discovery of medicines, natural products have played a vital role in controlling and preventing various diseases [9]. These natural products are directly used as crude extract or as a lead for the development of various bioactive molecules [10]. Among these natural products, nitrogen containing derivatives have played a significant role in the development of various clinical candidates [11]. Among these heterocyclic compounds, Quinoline is regarded as the most important molecule as it provides great flexibility to the medicinal chemist to modify and synthesize various derivatives (Fig. 1b) [12]. Quinoline nucleus was first isolated from coal tar by a German chemist Friedlieb Ferdinand Runge in 1834. But later it was isolated from quinine, strychnine, cinchonine by dry distillation, by a French Chemist Charles Gerhardt and then it was widely synthesized in labs from anilines, acylaminoacetophenone, β-ketoanalide and isatin, to get differentially substituted derivatives of quinoline [13].

Quinoline has a pyridine ring with benzene ring fused at C2 and C3 position and is also known as benz[b]pyridine or 1-aza-naphthalene. Quinoline (C_9H_7N) has a molecular weight of 129.16, dipole moment of 2.21 D and acts as a weak base and can react with acids to form salts. It is involved in various coupling reaction, electrophilic and nucleophilic substitution reaction. Its reactivity is dependent upon the type and position of the substitution on the rings for e.g., substitution of halogen at 7th position increases its the tendency to get involved in coupling reactions. But the reactivity pattern is similar to that of benzene and pyridine.
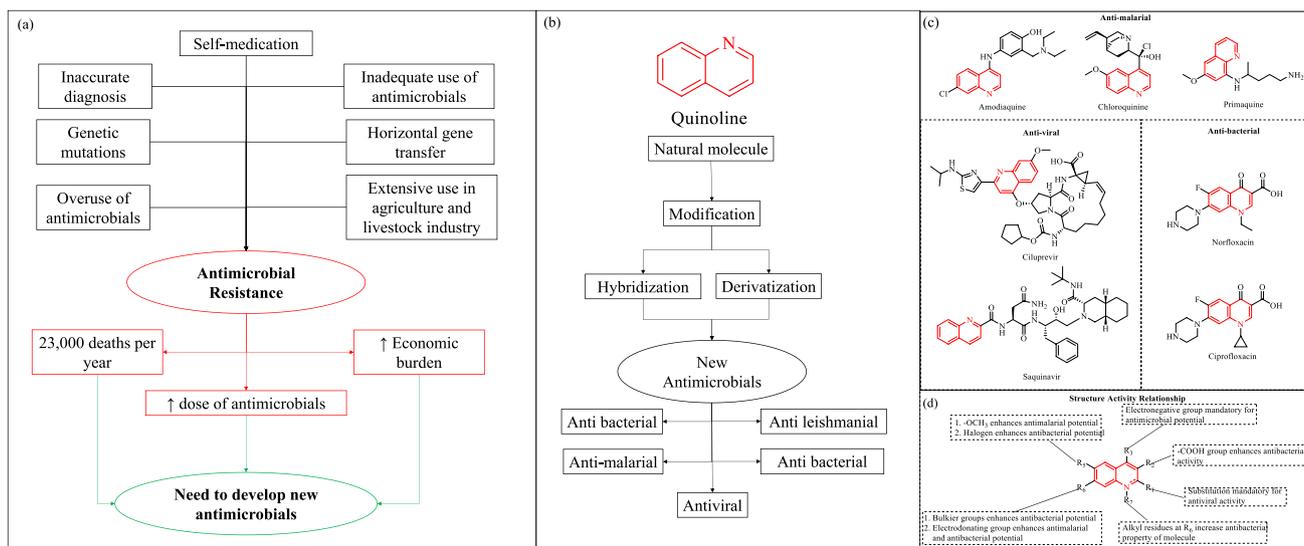
Fig. 1 a Factors leading to antimicrobial resistance and its consequences, **b** Process involved in using quinoline as a lead molecule for the development of various antimicrobials, **c** Structures of few quino-line derivatives in clinical use now, **d** Structure activity relationship of quinoline derivatives

Quinoline nucleus has no biological importance, but its derivatives have a wide range of biological activity. Most of its derivatives are antimalarial (chloroquinine, primaquine, amodiaquinine) but their biological profile is dependent on the position and type of substitution on the ring as shown in Fig. 1c and d [14]. In contrast of antimicrobials, various substitutions on quinoline led to development of a wide class of antimicrobials comprising anti-viral, anti-fungal, antiprotozoal, anti-tubercular, etc. [15, 16]. As shown in Fig. 2, quinolines are targeting a wide range of enzymes that engage in the replication of a microorganism but there are several enzymatic targets that can be targeted by developing new

derivatives by lead modification to combat anti-microbial resistance [17–19]. These activities made quinoline derivatives an important class of chemistry and gained the prime focus of researchers worldwide.

Till now, researchers have successfully modified quinoline by substituting various atoms or molecules on the ring or by hybridizing the nucleus, to get a wide range of biological activities. During literature survey, we came across various articles that are describing only the structure and biology activity of the quinoline derivatives, but they were missing the mechanistic insights and enzymatic targets of quinoline derivatives and their molecular docking studies
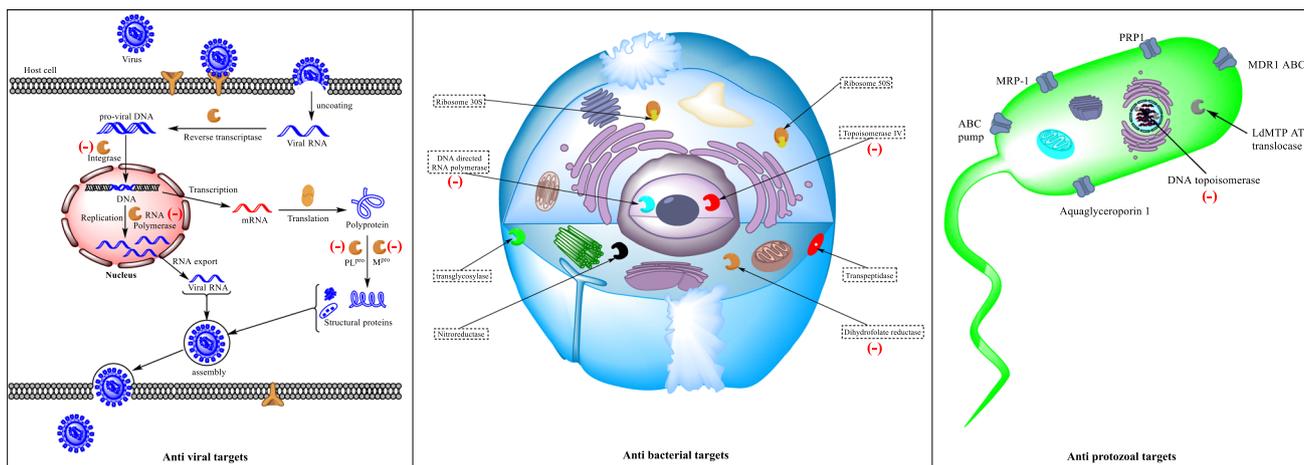

Fig. 2 Mechanistic insights and a general represent of proteins involved in replication of various microorganisms and also the protein being targeted by quinoline (shown as red "(-)" mark) derivatives

[20, 21]. Therefore, to mask these limitations, we have summarized rational approaches, designing strategies, molecular docking studies and mechanistic insights of recently developed quinoline derivatives within a time of 2015 to till date.

Viral resistance

Viruses are seen to be more prone to mutation as they utilize host's cell for their replication (Fig. 2) which increases chances of misreading of their genetic material than other microbes [22]. As seen in case of COVID-19 pandemic, SARS-COV-2 produced more than 4 variants in just two years i.e., due to higher mutational rates [23, 24]. In Fig. 2, we have enlightened the basic process of replication of virus and key enzymes involved in the replication of the virus [19]. Moreover, during literature we came to know that enzyme such as Reverse transcriptase, RNA polymerase, Integrase and other main protease enzymes were readily targeted by quinoline derivatives [25]. But these enzymes are more prone to mutation, and this leads to development of antiviral resistance [26]. Therefore, to counter this antiviral resistance, researchers are continuously working on developing new antiviral molecules and few of quinoline based antivirals are discussed below:

Carta et al., designed and synthesized a series of linear aromatic N- polycyclic system as potent bovine viral diarrhea virus (BVDV) inhibitors. Among all the synthesized compounds, compound **1** was found to be most potent with EC_{50} value of 0.3 μM and IC_{50} value of 0.48 μM against BVDV. On further evaluation, it has been revealed that the compound **1** significantly binds to BVDV RNA dependent RNA polymerase (RdRp) NS5B thus inhibiting the growth the BVDV. Furthermore, in-silico/in vitro studies illustrated the fundamental binding interactions and thus led to the identification of two RdRp amino acids namely Arg295 and Tyr674 as H-bond donors, two hydrophobic cavities i.e., cavity 1 with residues Ala221, Ile261, Ile287

and Tyr289 and cavity 2 with residues Val216, Tyr303, Lys307, Pro408 and Ala412 and these residues were mutagenized into alanine which resulted in significant decrease in BVDV RdRp affinity and thus weakened the stabilizing molecular interactions. Lastly, the compound **1** was found to be non-cytotoxic towards mock-infected MDBK cells (Fig. 3) [27].

Barbosa-Lima et al., designed and synthesized a series of twenty *N*-(2-(arylmethylimino) ethyl)-7-chloroquinolin-4-amine derivatives using thermal and ultrasonic methods as potent antiviral agents against Zika Virus. Among all the synthesized compounds, compound **2** was found to be most potent with an EC_{50} value of 0.8 ± 0.07 μM against Zika Virus. This inhibition was found to be potent than standard drug chloroquine. On further evaluation, it has been revealed that the compound **2** inhibited Zika virus by hampering its replication. Lastly, the cytotoxicity of compound **2** was found to be comparable to the chloroquine when evaluated against Vero cells (Fig. 4) [28].

Ching Lee et al., designed and synthesized a series of novel diarylpyrazolylquinoline derivatives as potent anti-dengue virus agents against various sero-types of Dengue Virus (DENV) namely DENV-1, DENV-2, DENV-3 and DENV-4. Among all the synthesized compounds, compound **3** was found to be most potent with an IC_{50} values of 1.21 ± 0.16 μM, 0.81 ± 0.07 μM, 0.73 ± 0.14 μM and 1.56 ± 0.09 μM against DENV-1, DENV-2, DENV-3 and DENV-4, respectively. This inhibition was found to be 10 times more potent than the standard drug ribavirin. On further evaluation, it has been revealed that the compound **3** decreased the DENV replication in both viral protein and mRNA levels. Furthermore, the compound **3** exhibited very less cytotoxicity towards Huh7 cells. Lastly, the compound **3** protected mice from DENV infection by reducing the symptoms of disease like paralysis, anorexia and asthenia and thus decreased the mortality of mice infected with DENV (Fig. 5) [29].
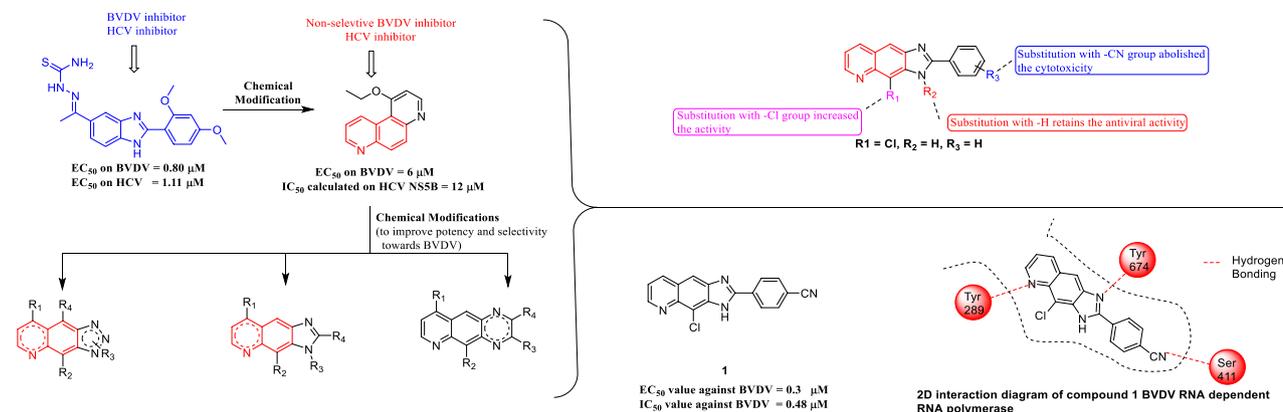

Fig. 3 Linear aromatic *N*-polycyclic system as potent bovine viral diarrhea virus (BVDV) inhibitors
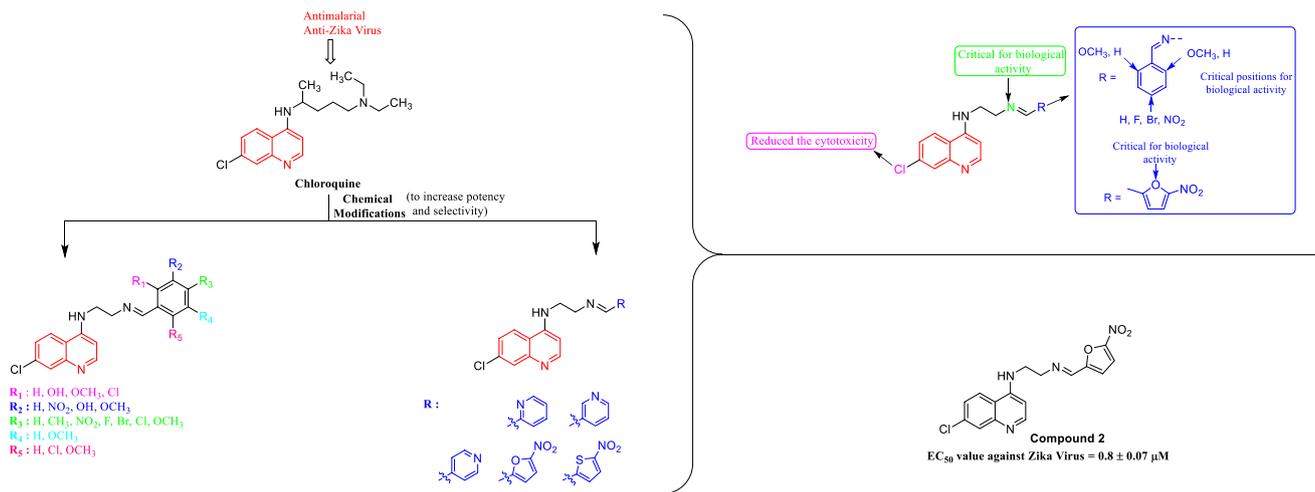
Fig. 4 *N*-(2-(arylmethylimino) ethyl)-7-chloroquinolin-4-amine derivatives using thermal and ultrasonic methods as potent antiviral agents against Zika Virus
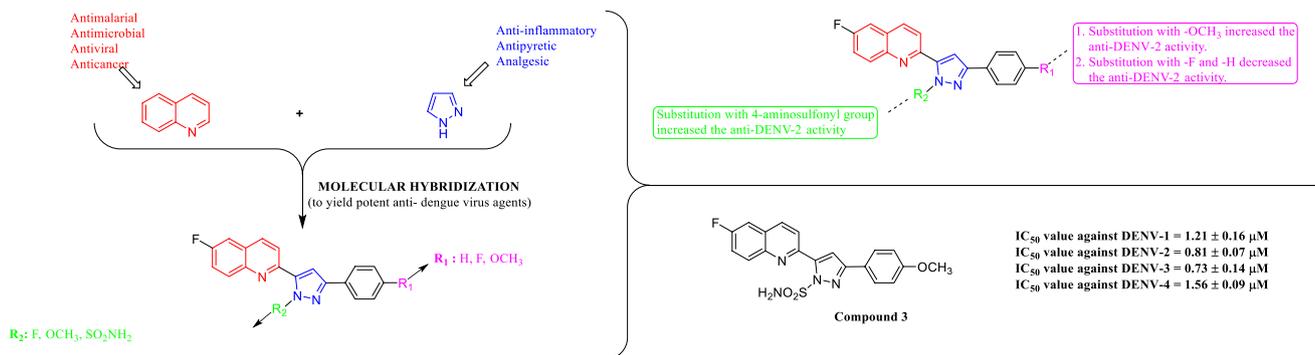

Fig. 5 Novel diarylpyrazolylquinoline derivatives as potent anti- dengue virus agents

Feng Li et al., designed and synthesized a series of twenty-four andrographolide derivatives as potent anti-Zika Virus (ZIKV) agents. Among all the synthesized compounds, compound **4** and **5** was found to be most potent with an EC_{50} values of 1.31 ± 0.1 μM and 4.5 ± 0.2 μM respectively against Zika virus. On further evaluation, it has been revealed that compound **4** and **5** exhibited anti-ZIKV action by inhibiting the replication of Zika virus. Lastly, the compound **4** was found to be significantly cytotoxic towards SNB-19 cells and Vero cells, whereas the compound **5** exhibited very less cytotoxicity (Fig. 6) [30].

Qi Tang et al., designed and synthesized a series of dibucaine derivatives as potent anti-Enterovirus A71(EV-A71) agents. Among all the synthesized compounds, compound **6** was found to be most potent with an EC_{50} value of 1.238 ± 0.122 μM against EV-A71. On further evaluation, it has been revealed that the compound **6** exhibited anti-EV-A71 activity by inhibition of 2C helicases and VP1 which resulted in impending EV-A71 replication and thus RNA

remodeling and metabolism in a dose-dependent manner. Furthermore, it has been illustrated by the time course assay that the compound **6** showed maximum antiviral efficacy during the early stage of the life-cycle of Enterovirus A71. Lastly, the molecular docking studies demonstrated that the compound **6** binds with EV-A71 2C protein by the formation of five hydrogen binds with the residues Asp177, Ser136, Gly132 and the remaining two hydrogen bonds with the residue Lys135; hydrophobic interactions with the residues Leu261, Ala263, Leu137, Pro131 and Pro159 and finally a π–π interaction with Pro131 (Fig. 7) [31].

Bacterial resistance

Bacterial replication in a controlled manner is not a threat to living beings, but if uncontrolled, they can lead to death of the patient or can create pandemic like situation. Therefore, their replication needs to be controlled and herein antibacterial plays a significant role by controlling bacterial growth
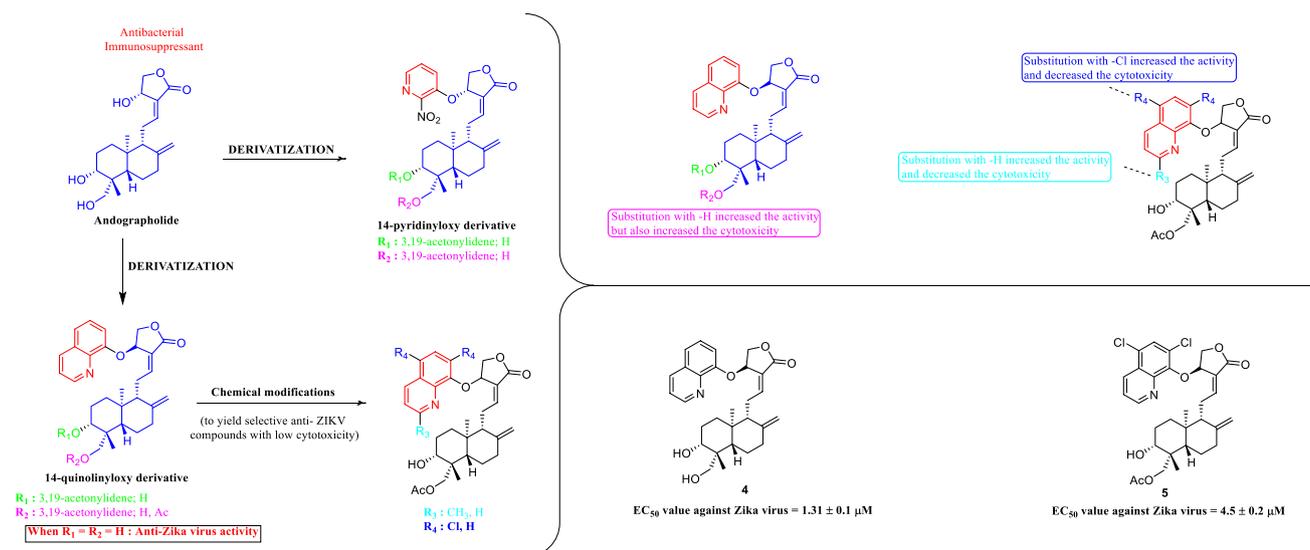
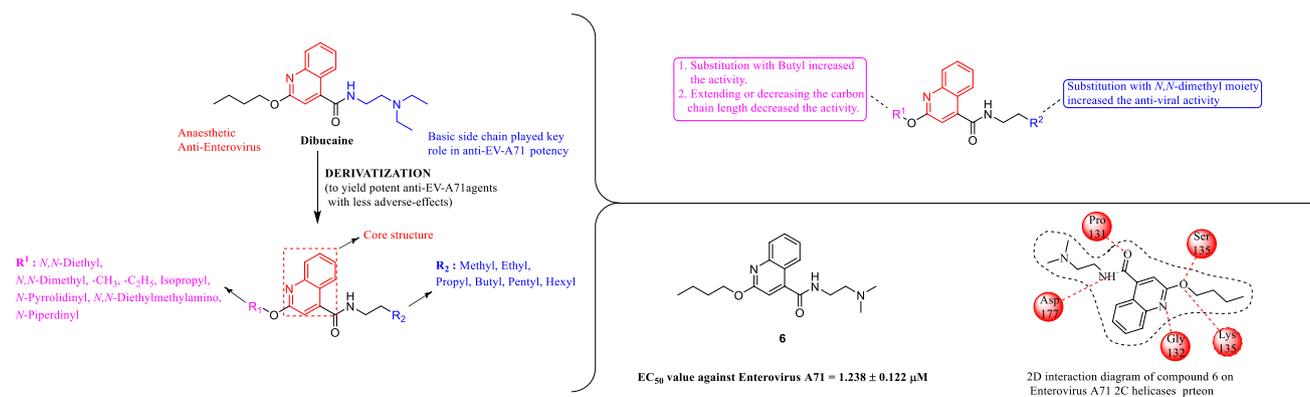**Fig. 6** Andrographolide derivatives as potent anti-Zika Virus agents

Fig. 7 Dibucaine derivatives as potent anti-Enterovirus A71(EV-A71) agents

[32]. They either work by killing the bacteria or halting their replication. These antibacterial aims crucial enzymes such as DNA directed RNA polymerase, topoisomerases, and trans-glycosylases. . which engage in either maintaining integrity of the cell or are involved in replication of the cell as shown in Fig. 2 [33]. Furthermore, bacterial resistance occurs when an enzyme gets mutated, and this results in decrease to no response to antibacterial and arise of antibacterial resistance [34]. So, to counter this problem continuous research is required to synthesize new antibacterial that are effective and non-toxic [35]. Fluroquinolones, a class of quinoline derivatives, are very safe and most widely used antibacterial. But the mutation of DNA gyrase, or topoisomerase and other enzymes has led to development of resistance and need to search for new antibacterial [34]. Few of quinoline derivatives are recently designed by various researcher are mentioned below:

Antibacterial

Yang et al., designed and synthesized a series of twenty-eight highly soluble 9-bromo substituted indolizinoquinoline-5,12-dione derivatives as potent antibacterial agents against one strain gram positive and seven gram-negative strains of bacteria especially Methicillin-resistant *Staphylococcus aureus* (MRSA). Among all the synthesized compounds, compound **7** was found to be most potent with MIC value of 2 μg/mL against both *E. coli* ATCC25922 and *S. pyrogens* ATCC19615, 0.031 μg/mL against *S. aureus* ATCC25923, 0.063 μg/mL against MRSA ATCC43300 and this activity was found to be 16-fold higher than that of vancomycin, 0.125 μg/mL against both *S. haemolytic*-β CICC10373 and *e. faecalis* ATCC29212, 0.5 μg/mL against *s. pneumoniae* ATCC6305 and finally ≤ 0.0078 μg/mL against *S. epidermidis* ATCC12228. Lastly, it has been revealed that the

compound **7** has fairly good water solubility of 1.98 mg/mL (Fig. 8) [36].

Ning sun et al., designed and synthesized a series of novel *N*-methylbenzofuro[3,2-*b*]quinoline and *N*-methylbenzoindolo[3,2-*b*]-quinoline derivatives as potent antibacterial agents. Synthesized compounds were screened for their inhibitory activities against various bacterial strains such as drug-resistant strains like methicillin-resistant *S. aureus* and vancomycin-resistant *E. faecium.* Among all the compounds, compound **8** was found to be active against vancomycin-resistant *E. faecium* with an MIC value of 4 µg/mL which was much lower than vancomycin with MIC value of > 64 µg/mL. In addition, the compound **8** was also shown to inhibit *B. subtilis* 168, *S. aureus* ATCC 29213, *S. aureus* ATCC BAA41, *E. faecium* ATCC 49624, *E. faecium* ATCC 700221, *E. coli* ATCC 25922, *E. coli* ATCC BAA2469, *P. aeruginosa* ATCC BAA2108 and *K. pneumoniae* ATCC BAA2470 with MIC values of 2 µg/mL, 2 µg/mL, 2 µg/mL, 4 µg/mL, 4 µg/mL, 6 µg/mL, 6 µg/mL, 48 µg/mL and 48 µg/mL respectively. On further evaluation, it has been deciphered that that compound 8 strongly inhibited the *S*aFtsZ polymerization in a dose-dependent manner. Also, compound 8 was found to have inhibitory effect on GTPase activity of FtsZ thus leading to abnormal bacterial cell division and eventually causing the cell death. Molecular docking studies revealed that the non-polar compound **8** interacted with number of hydrophobic chains of ASP199, Leu200, Val297, Val307 and Thr309 and also the imino group of the potent participated in one hydrogen bond formation with the backbone carbonyl of Thr309 which resulted in better inhibition of FtsZ polymerization and GTPase (Fig. 9) [37].

Faidallah et al., designed and synthesized a series of twenty-one 1,2,3-triazole incorporated quinoline antibiotic conjugates as potent antibacterial agents against various strains of gram positive and gram-negative bacteria by using microwave assisted click chemistry technique. Among all the synthesized compounds, **9, 10, 11, 12, 13** and **14** were found to be most potent when tested against *Staphylococcus aureus*, *Streptococcus pyrogens*, *Salmonella typhi*, *Pseudomonas aeruginosa* and *Escherichia coli* and the MIC values of the compound **9** were found to be 0.12 µg/mL, 8 µg/mL, 0.12 µg/mL, > 1024 µg/mL, 0.12 µg/mL against the above-mentioned strains of bacteria respectively.
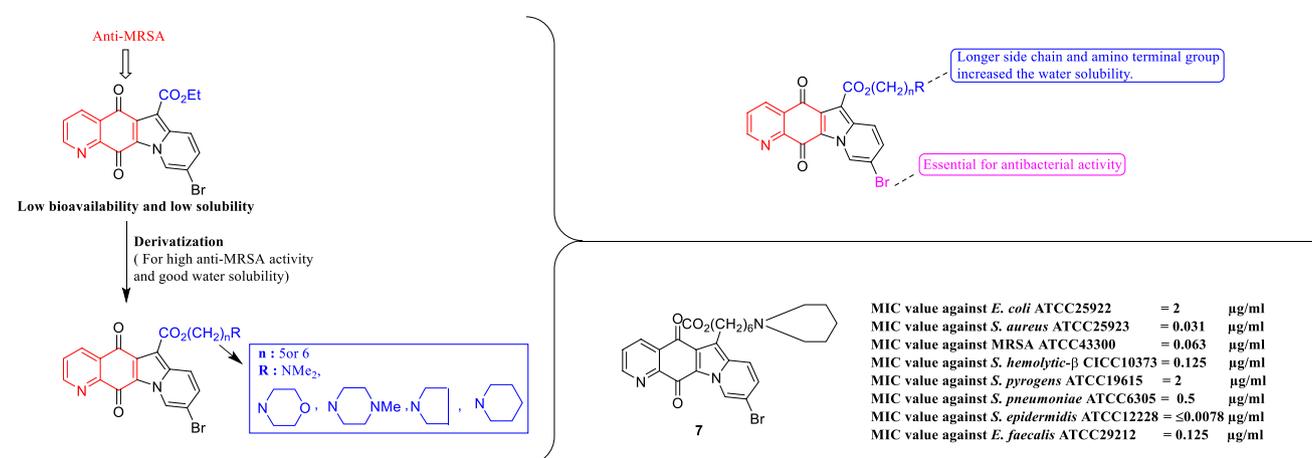

Fig. 8 9-bromo substituted indolizinoquinoline-5,12-dione derivatives as potent antibacterial agents
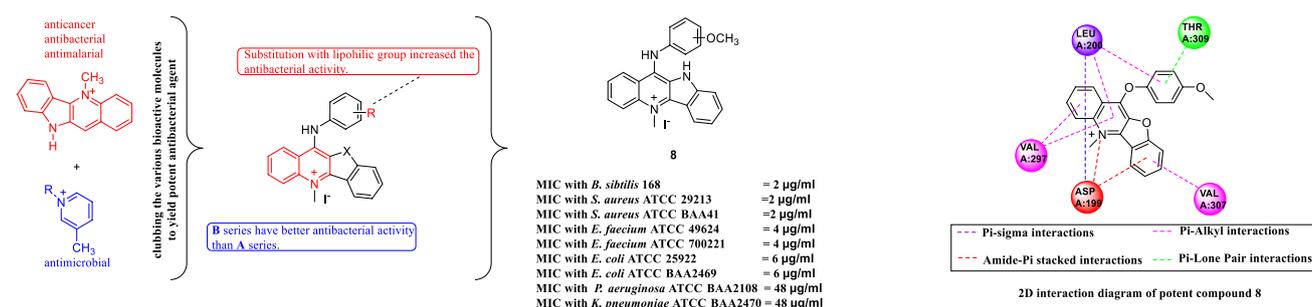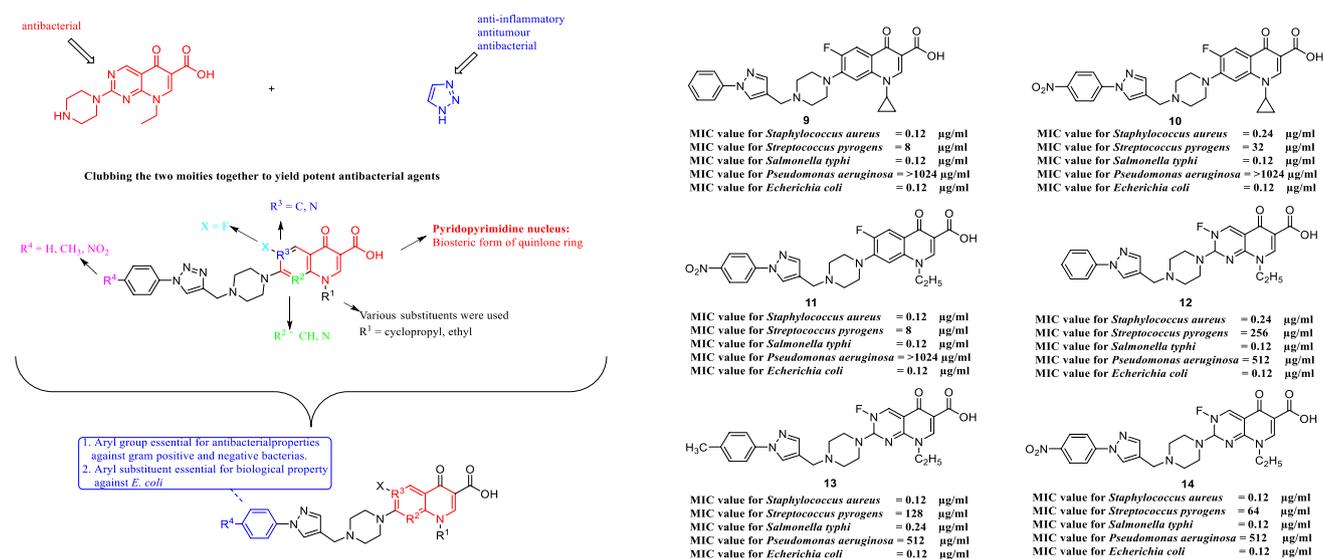

Fig. 9 Novel *N*-methylbenzofuro[3,2-b]quinoline and N-methylbenzoindolo[3,2-b]-quinoline derivatives as potent antibacterial agents

Similarly, the MIC values for the compound **10** were found to be 0.24 μg/mL, 32 μg/mL, 0.12 μg/mL, > 1024 μg/mL and 0.12 μg/mL, respectively. The MIC values for the compound **11** were calculated as 0.12 μg/mL, 8 μg/ mL, 0.12 μg/mL, > 1024 μg/mL and 0.12 μg/mL, respectively. For compound **12**, the MIC values were found to be 0.24 μg/ mL, 256 μg/mL, 0.12 μg/mL, 512 μg/mL and 0.12 μg/mL, respectively. Similarly, for conjugate **13**, the MIC values were revealed to be 0.12 μg/mL, 128 μg/mL, 0.24 μg/mL, 512 μg/mL and 0.12 μg/mL, respectively. Lastly, the MIC values for the compound **14** were calculated as 0.12 μg/mL, 64 μg/mL, 0.12 μg/mL, 512 μg/mL and 0.12 μg/mL, respectively. Out of all the potent compounds, **12** showed excellent ADMET levels especially for plasma protein binding and blood brain barrier penetration. Furthermore, 2D-QSAR studies were performed for *S. aureus, S. pyrogens* and *S. typhi* and the potent compounds **9, 10, 11, 12, 13** and **14** validated the observed biological properties shown by these compounds (Fig. 10) [38].

Kehan Xu et al., designed and synthesized a series of novel 2-sulfoether-4-quinolone scaffolds via free radical process as potential antibacterial agents against gram positive bacteria *Staphylococcus aureus* and *Bacillus cereus*. Among all the synthesized compounds, compound **15** was found to be most potent against both *S. aureus* and *B. cereus* with MIC values of 0.8 μM and 1.61 μM, respectively. This inhibition was found to be comparable to the commercially used antibacterial agents such as gentamicin, ofloxacin and tetracycline. Furthermore, transmission microscopy analysis of compound **15** against *S. aureus* displayed cell wall destruction which might facilitate the penetration of the active compound into the bacteria. Also, the DNA supercoiling analysis

demonstrated the fluoroquinolone character of the compound **15**. Lastly, the molecular docking studies showed that the compound **15** fairly bounds to the DNA gyrase complex via extensive interactions including conventional two hydrogen-bonds with nucleotide DG-9 and one hydrogen-bond with residue Arg458, halogen bonding with nucleotides DG-8, DG-13 and residue Arg458 and finally hydrophobic interactions with nucleotides DG-8 and DG-9 (Fig. 11) [39].

Xuan Ma designed and synthesized a series of thirty-six 2-fluoro 9-oxime ketolides and carbamoyl quinolones hybrids as an antibacterial agent against various strains of drug-resistant pathogens. Among all the synthesized compounds, **16, 17** and **18** were found to be most potent with the MIC values of ≤ 0.008 μg/mL each against *S. pneumoniae* ATCC 49619. The MIC values were calculated as 0.25 μg/mL, 0.25 μg/mL and 0.5 μg/mL respectively against *S. pneumoniae* PU09,mef; 0.215 μg/mL, 0.062 μg/mL and ≤ 0.008 μg/mL respectively against *S. pneumoniae* 07P390,c-ermB; 16 μg/mL, 32 μg/ mL and 16 μg/mL respectively against *H. influenzae* ATCC 49247; ≤ 0.002 μg/mL each against *S. pyrogens* 12–207,mef; 0.125 μg/mL, 0.5 μg/mL and 0.016 μg/mL respectively against *S. pyrogens* 12–206,c-erma; 1 μg/ mL, 0.5 μg/mL and 0.025 μg/mL respectively against *S. aureus* PU32, MRSA, i-erma; 128 μg/mL, 128 μg/mL and ≥ 256 μg/mL respectively against *s. aureus* PU20, MRSA, c-ermC; 4 μg/mL, 4 μg/mL and 0.5 μg/mL respectively against *M. catarrhalis* 132332. Also, **16, 17** and **18** were found to have 2.5–3.6 times prolonged half-life and 2.3–2.6-fold longer mean residence time *in vivo* over the standard drug telithromycin. Molecular docking studies revealed that the compounds **16, 17** and **18** oriented their

Fig. 10 1,2,3-triazole incorporated quinoline antibiotic conjugates as potent antibacterial agents against various strains of gram positive and gram-negative bacteria
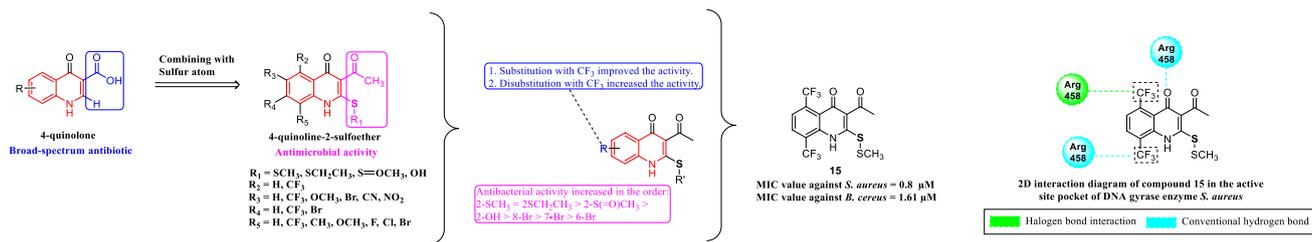
Fig. 11 2-sulfoether-4-quinolone scaffolds via free radical process as potential antibacterial agents against gram positive bacteria Staphylococcus aureus and Bacillus cereus

side chains similar to cethromycin but extended into a new pocket formed by A764, c803, C1772 and A802. Also, the 4-oxygen of quinoline ring of **17** hydrogen-bonded to the rRNA base C1772. Furthermore, the compound **18** oriented its side chains differently from cethromycin, and to a pocket surrounded by U2588, G2587, C2589, G2560 and C2565. The nitrogen atom of compound **18** hydrogen bonded to the phosphate of U2588. Lastly, it has been found that the compounds **16**, **17** and **18** were

metabolically stable than the conventional drug telithromycin with improved AUC (Fig. 12) [40].

Anti-tubercular

Duggirala et al., designed and synthesized a group of 1,2–dihydroquinolines as an antitubercular agents which were screened against Mycobacterium Tuberculosis (MTB) and Mycobacterium smegmatis which exerted
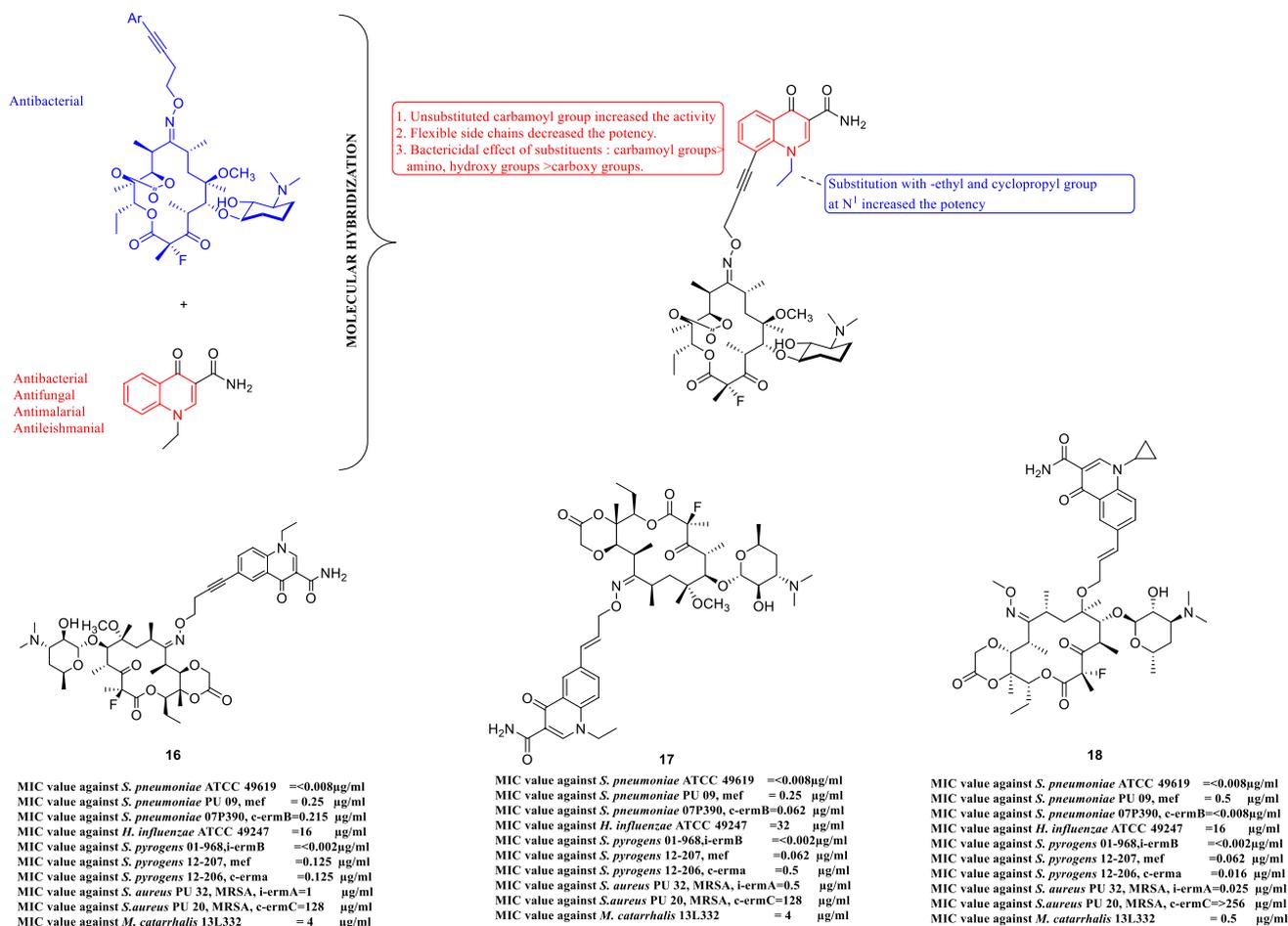

Fig. 12 2-fluoro 9-oxime ketolides and carbamoyl quinolones hybrids as an antibacterial agent against various strains of drug-resistant pathogens

antibacterial effect through two pathways i.e., by targeting key cell division protein FtsZ and by causing redox imbalance in the target cells. Among all the synthesized compounds, **19, 20, 21, 22, 23** and **24** were found to inhibit the growth of Mycobacterium smegmatis mc2 155 with the IC_{50} value in the range of 0.9 – 7.5 μg/mL. IC_{50} values of the active compounds were measured by using two different assays. In light scattering assay, the IC_{50} values of the compounds **19, 20, 21, 22, 23** and **24** were found to be 77.3 ± 2.5 μM, 88.6 ± 3.8 μM, 33.4 ± 4.4 μM, 34.0 ± 3.7 μM, 40.9 ± 2.5 μM and 209.88 μM, respectively. Further, the cytotoxicity analysis of the synthesized compounds was done on 3T3 swiss fibroblasts and compounds **21, 22, 23** and **24** showed brilliant selectivity with the IC_{50} values of 104 ± 2.3 μM, 51.39 ± 2.9 μM, 283.1 ± 4.7 μM and 153.8 ± 6.9 μM, respectively. Further, the active compounds also inhibited the polymerization of MTBFtsZ and its GTPase activity. In addition, the active compounds also tend to undergo oxidation to quinolinium ions through electron transfer to oxygen. Also, these compounds exerted a global cellular effect by causing redox—imbalance that was evident from overproduction of ROS in the treated cells. Lastly, the active compounds exerted a multiple lethal effect on the target organism using a single chemical entity rather than using combination therapy (Fig. 13) [41].

A. Abdelrahman et al., designed and synthesized two different series of novel pyridine and quinolone hydrazone derivatives as potent antimicrobial and antitubercular agents against various strains of bacteria and fungi. Among all the synthesized compounds, **25** and **26** were found to be most potent with the MIC value of 0.98 μg/mL each against *Aspergillus fumigatus*, 0.49 μg/mL and 0.98 μg/mL, respectively against *Candida albicans*, 0.49 μg/mL each against *Streptococcus pneumoniae*, 1.95 μg/mL and 0.98 μg/mL, respectively, against *Staphylococcus aureus*, 0.49 μg/mL each against *Escherichia coli* and finally 0.78 μg/mL and 0.39 μg/mL, respectively, against MTB but both the compounds **25** and **26** were found to be inactive against *Pseudomonas aeruginosa*. On further evaluation, it has been revealed that the compounds **25** and **26** possessed extremely low cytotoxicity against human lung fibroblast normal cells (WI-38). Furthermore, the compounds **25** and **26** were predicted to be CYP2D non-inhibitors and excellently followed the Lipinski's rule of five. Lastly, the compounds **25** and **26** were found to possess good lipophilicity and hence remarkable absorption levels (Fig. 14) [42].

D. Subhedar et al., designed and synthesized a series of novel rhodamine incorporated quinoline derivatives using reusable DBU acetate as an ionic liquid. The synthesized derivates were evaluated for their in vitro antitubercular potency against MTB H37Ra (ATCC 25177) and
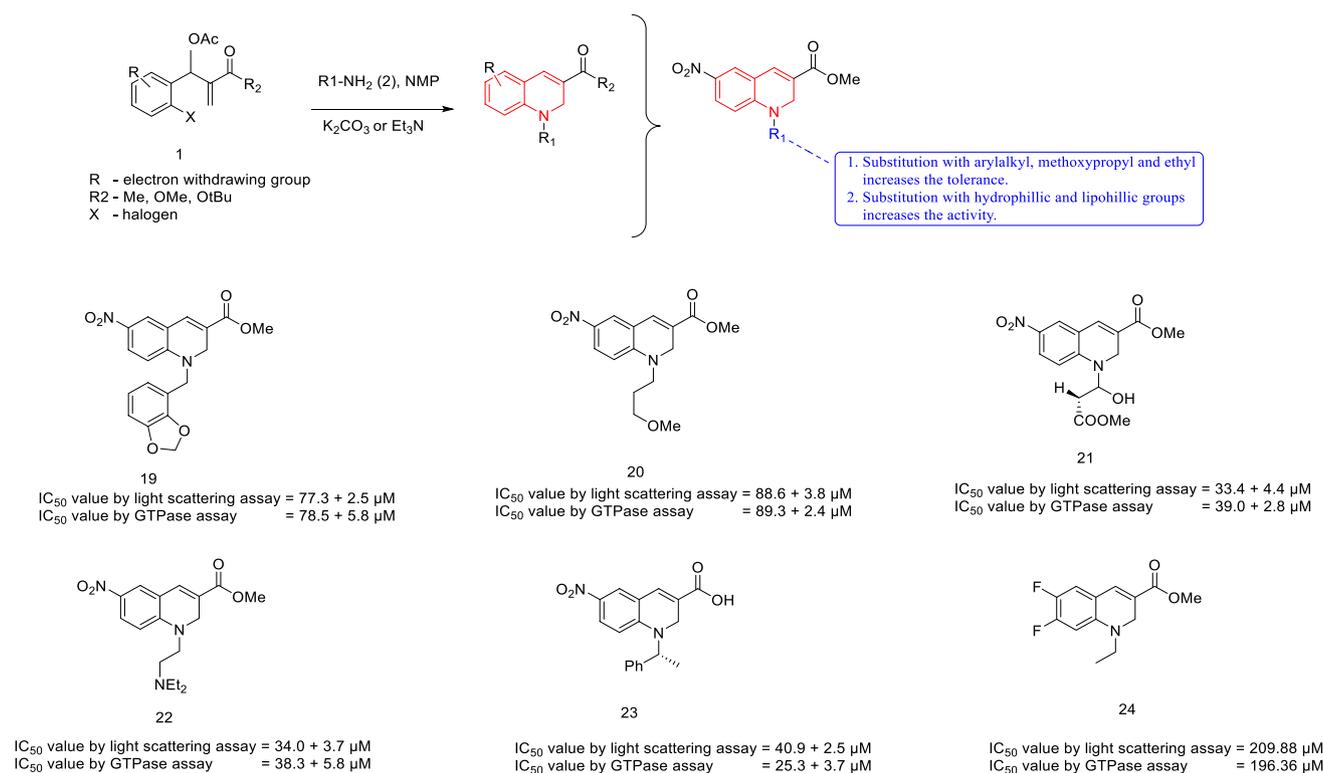

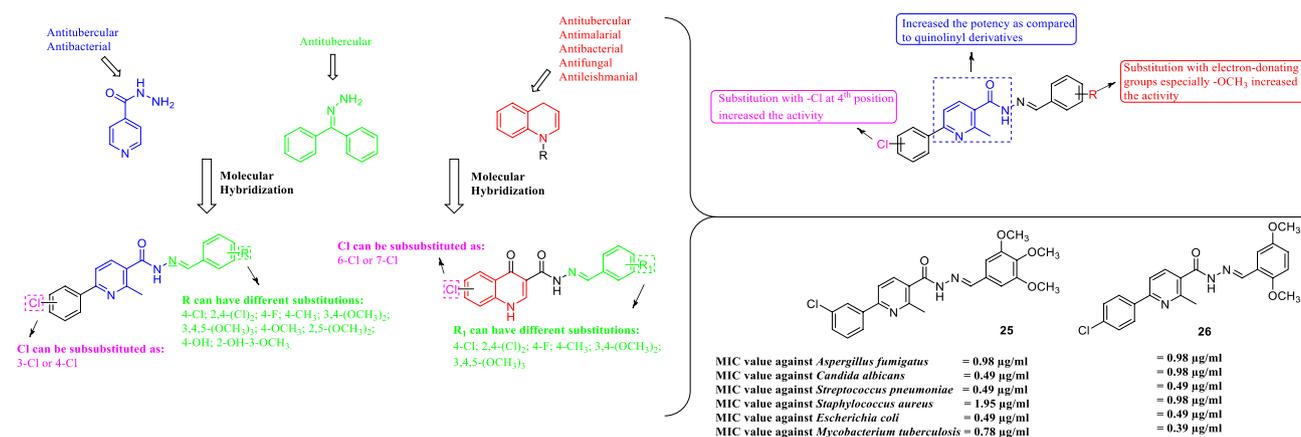**Fig. 13** 1,2—dihydroquinolines as an antitubercular agents

Fig. 14 Novel pyridine and quinolone hydrazone derivatives as potent antimicrobial and antitubercular agents

Mycobacterium bovis BCG (ATCC 35743) both in active and dormant states. Among all the synthesized quinolidene-rhodanine conjugates, **27**, **28**, **29**, **30**, **31** and **32** were found to be most active with MIC value of 1.66–9.57 μg/mL. The IC_{50} values of the compounds **27**, **28**, **29**, **30**, **31** and **32** were calculated for both active and dormant states of MTB and *M. bovis*. For dormant state of MTB H37Ra, the IC_{50} values of **27**, **28**, **29**, **30**, **31** and **32** were found to be 7.6 μg/mL, 10 μg/mL, 3.3 μg/mL, 2.3 μg/mL, 2.2 μg/mL, and 5.1 μg/mL, respectively. For active state of MTB H27Ra, the IC_{50} values were found to be 4.8 μg/mL, 5.7 μg/mL, 6.9 μg/mL, 1.9 μg/mL, 1.9 μg/mL, and 5.4 μg/mL, respectively. Similarly, the IC_{50} values for the dormant state of *M. bovis* BCG were calculated as 5.1 μg/mL, 2.9 μg/mL, 1.1 μg/mL, 1.3 μg/mL, and 3.9 μg/mL, respectively, and for the active state, the IC_{50} values were found to be 1.7 μg/mL, 3.7 μg/mL, 1.4 μg/mL, 1.0 μg/mL, and 2.4 μg/mL, respectively. In addition, the synthesized compounds were screened for their antifungal activity against various fungal strains. Out of all the synthesized compounds, **32**, **33** and **34** showed excellent antifungal activity against various fungal strains. Compounds **32** and **33** were found to be active against *F. oxysporum*, *A. niger, C. neoformans* with MIC value of 25 μg/mL and *A. flavus* with *MIC* value of 12.5 μg/mL. Also, the compound **34** was found to be active against *A. flavus*, *A. niger* and *C. neoformans* with the MIC value of 25 μg/mL. Furthermore, the molecular docking studies of the synthesized compounds revealed that the conjugates have a high affinity towards the active site of Zinc-dependent metalloprotease 1 enzyme of MTB H37Ra. Lastly, the cytotoxic studies of the active compounds against HUVEC, THP-1, macrophages, A549, PANC-1 and HeLa cells using modified MTT assay revealed that the synthesized compounds were non-cytotoxic (Fig. 15) [43].

Kumar et al., designed and synthesized a series of thirty 1,2-dihydroquinoline carboxamide derivatives via

Friedlander annulation method as potent antitubercular agents against MTB H37Rv. Among all the synthesized compounds, **35** and **36** were found to be most potent with an IC_{50} values of 0.39 μg/mL and 0.78 μg/mL, respectively against MTB H37Rv. This inhibition was found to be comparable to the control drug isoniazid and rifampicin. On further evaluation, it has been revealed that the compounds **35** and **36** were non-cytotoxic against MTT cells. Furthermore, compounds **35** and **36** were found to be CNS inactive due to their inability to cross blood brain barrier. Lastly, the compounds **35** and **36** exhibited fairly good pharmacological properties like QPlogkhsa (human serum albumin), QPP-MDCK (MDCK cell permeability) and skin permeability as demonstrated by in-silico ADME studies (Fig. 16) [44].

Souza Macchi et al., designed and synthesized a series of thirty-nine 1H-benzo[d]imidazoles and 3,4-dihydro-quinazolin-4-ones as antitubercular agents against MTB H37Rv along with four drug-resistant strains that are MTB CDCT10, MTB CDCT16, MTB CDCT27 and MTB CDCT28. Among all the synthesized compounds, **37** and **38** were found to be most potent with MIC values of **37** calculated as 0.08 μg/mL, 0.31 μg/mL, 0.08 μg/mL and 0.31 μg/mL, respectively, against the four drug-resistant strains of MTB mentioned above. Similarly, the MIC values of compound **38** were found to be 0.31 μg/mL, 0.31 μg/mL, 0.31 μg/mL, 0.16 μg/mL and 0.31 μg/mL, respectively. This inhibition was found to be much more potent against the drug-resistant strains CDCT10, CDCT27 and CDCT28 than against MTB H37Rv strain. On further evaluation, it has been demonstrated that the synthesized compounds targeted the membrane-bound type-2 NADH dehydrogenase NdhA based on whole-genome sequencing of resistant strains with extremely insignificant risk of cardiotoxicity and neurotoxicity (Fig. 17) [45].

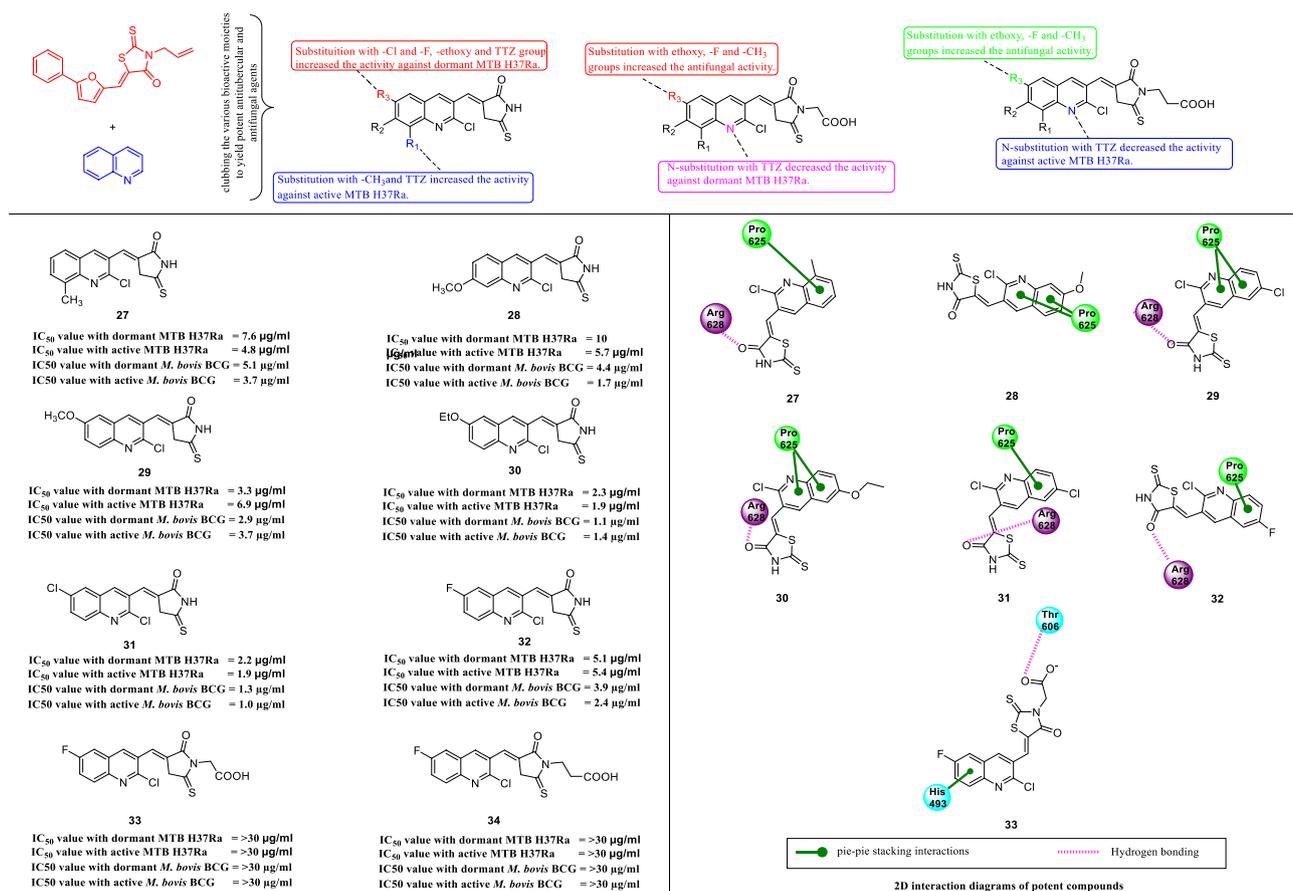Kumar Marvadi et al., designed and synthesized a series of sixteen novel morpholine, thiomorpholine and

Fig. 15 Novel rhodamine incorporated quinoline derivatives as antitubercular agent
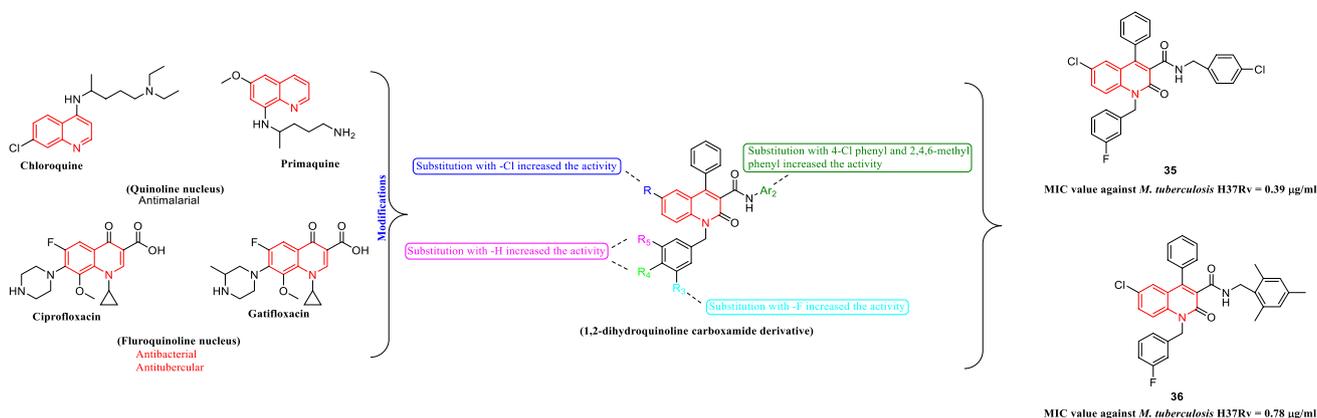

Fig. 16 1,2-dihydroquinoline carboxamide derivatives via Friedlander annulation method as potent antitubercular agents

N-substituted piperazine coupled 2-(thiophen-2-yl) dihydroquinolines as potent antitubercular agents against MTB H37Rv. Among all the synthesized compounds, **39** and **40** were found to be most potent with the MIC value of 1.56 μg/mL each. This inhibition was found to be much more potent than the conventionally used drug ethambutol and equipotent to the standard drug ciprofloxacin. Lastly, the in vitro

cytotoxicity studies showed that the compounds **39** and **40** has extremely low cytotoxicity against mammalian HEK-293 T cells (Fig. 18) [46].

Borsoi et al., designed and synthesized 36 novel 2-(quinoline-4-yloxy) acetamide-based antituberculosis agents. On in vitro screening of designed compounds against MTB, **41** and **42** was found to have potent bacteriostatic
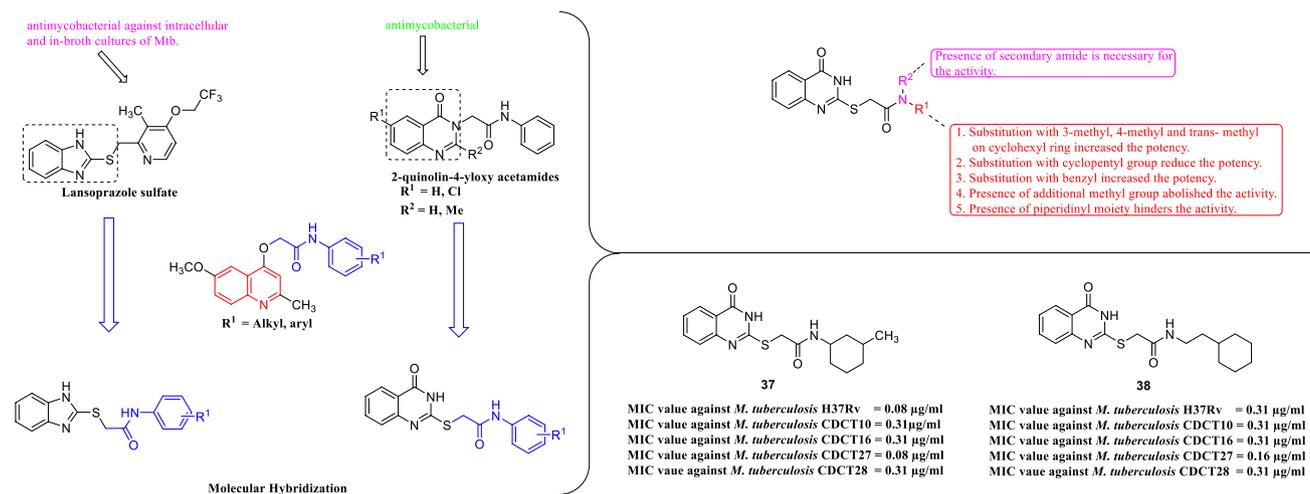
Fig. 17 1H-benzo[d]imidazoles and 3,4-dihydroquinazolin-4-ones as antitubercular agents
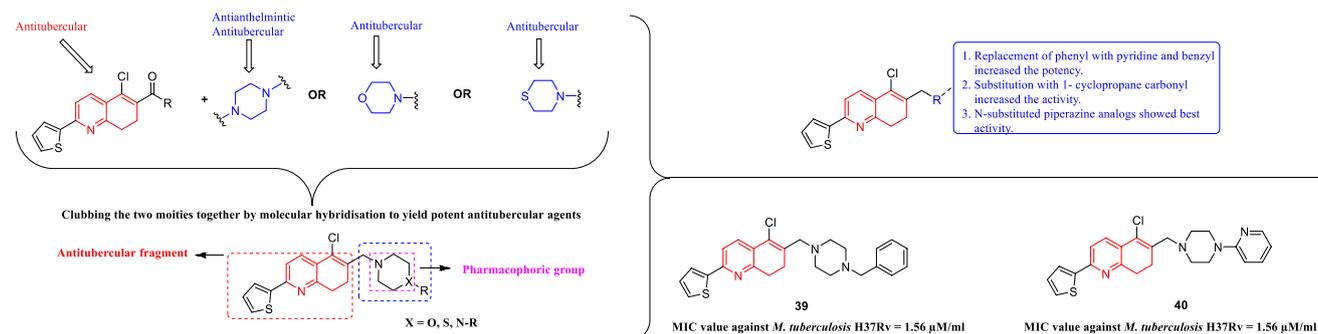

Fig. 18 Novel morpholine, thiomorpholine and N-substituted piperazine coupled 2-(thiophen-2-yl) dihydroquinolines as potent antitubercular agents

effect on intracellular growth of MTB H37Rv reference strain with an MIC value of 1.8 μM and 0.3 μM, respectively. On further evaluation, it was found that compounds **41** and **42** showed selective activity against drug sensitive and multidrug-resistant MTB strain. Furthermore, compounds **41** and **42** were active against multidrug-resistant strains, without cross resistance with some first- and second-line drugs. Analyzation of compounds **41** and **42** against a spontaneous mutant strain containing a single mutation in the qcrB gene (T313A) indicated that these compounds targeted the cytochrome bc_1 complex. At last, toxicity studies have confirmed that compounds 41 and 42 were devoid of apparent toxicity to HepG2 and Vero cells and showed moderate elimination rates in human liver S9 fractions. Finally, the ability of compounds 41 and 42 to pass through cell membranes and to inhibit the intracellular growth of bacilli were evaluated in a macrophage model of MTB infection (Fig. 19) [47].

Protozoal resistance

Protozoa are unicellular or multicellular organisms that have abilities to infect living cells of either plants or animals [48]. These organisms usually enter the cell and utilizes the cells nutrients to multiply intracellularly and on completion of replication cycle, they destroy the host cell and are available for infecting other healthy cells [48]. Antiprotozoal agents works either by blocking the influx of nutrient to the protozoal cell or block the production of energy by mitochondria, this leads to starvation of cell which eventually causes cell death. As shown in Fig. 2 various pumps, channels and enzymes engage in providing nutrition to the cell and helps in proliferation of the organism [17, 18]. Various drug such as Meltifosine, Paromomycin, and pentamidine. are available that are efficiently blocking these targets but due to mutation, there
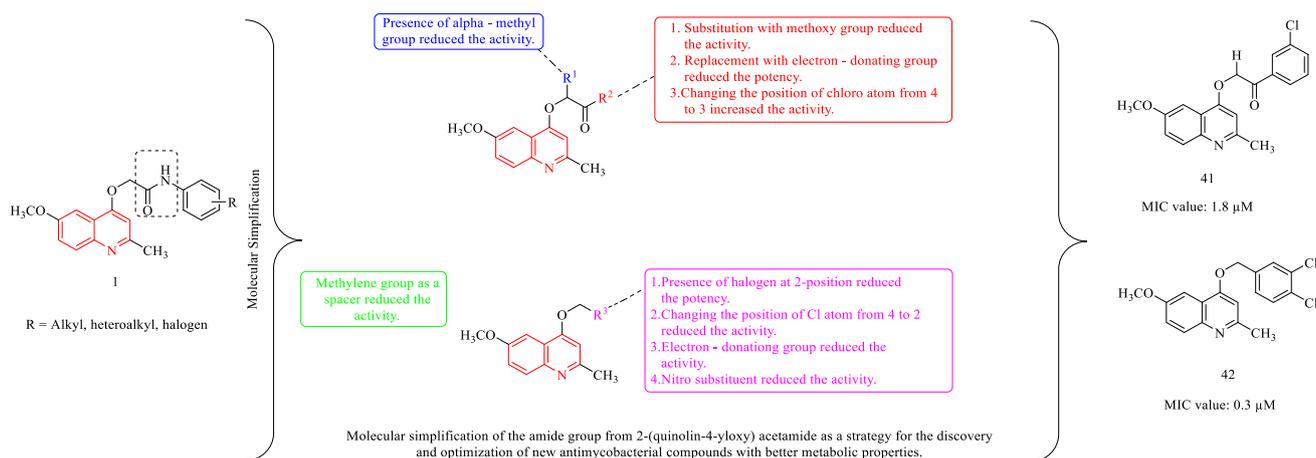
Fig. 19 Novel 2-(quinoline-4-yloxy) acetamide-based antituberculosis agents

was arousal of resistance to these drugs. Overall cause of resistance was due to decreased drug diffusion, modification of drug target due to mutation, increased efflux of drug, inactivation of drug by enzymes, etc. [17]. So, this emergence of resistance develops need for new antimicrobial molecules that have better affinity and potency. few newly developed quinoline based antiprotozoal agents are discussed below:

Anti-leishmanial agents

Yousuf et al., designed and synthesized novel ferrocenylquinoline possessing triazole derivatives as an antileishmanial agents. Synthesized compounds were screened for their inhibitory activity both against promastigote and amastigote stages of *Leishmania donovani*. Among all the synthesized compounds, **43**, **44** and **45** were found to exhibit exorbitant anti – promastigote activity with an IC_{50} values of 28.7 μM, 22.1 μM and 28 μM, respectively. In addition, **43**, **44** and **45** also exhibited excellent activity against the intracellular amastigote stage of *Leishmania donovani* with an IC_{50} values of 16 μM, 8 μM and 16 μM, respectively. This inhibition was found to be much more potent than the conventionally used antileishmanial drug sodium antimony gluconate with an IC_{50} value of 400 μM. On further evaluation, the compounds **43**, **44** and **45** were not found to be cytotoxic towards host phytohemagglutinin (PHA)–induced murine splenocytes. The compounds **43**, **44** and **45** were shown to induce apoptosis in *Leishmania donovani* promastigotes. Also, these compounds showed pro—inflammatory response by generating the primary effector molecule, nitric oxide to abolish *Leishmania donovani* amastigotes from the infected macrophages. In addition, induction of apoptosis by **43**, **44** and **45** was confirmed by the capability of both heterocyclic rings present in these compounds to mechanistically damage parasite membranes by altering sterol composition of the parasitic membrane, or by blocking sterol biosynthesis by inhibiting the enzymatic activity of 14 α—demethylase (CYP51), resulting in parasitic death (Fig. 20) [49].
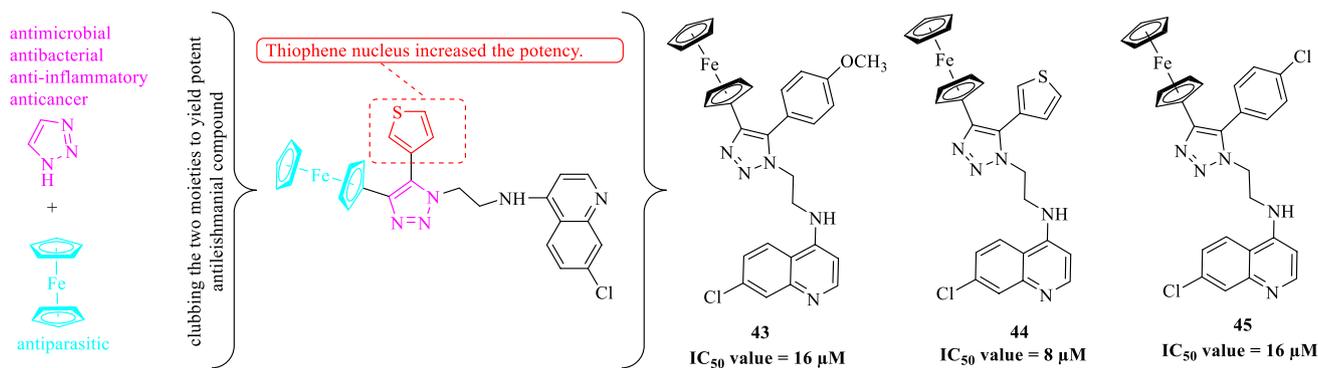

Fig. 20 Ferrocenyl-quinoline possessing triazole derivatives as an antileishmanial agents

Zhang et al., designed and synthesized a series of five neutral N-heterocyclic carbene gold (I) complexes as potent antileishmanial agents against *Leishmania infantum* promastigotes and *Leishmania infantum* axenic amastigotes. Among all the synthesized compounds, **46** was found to be most potent with an IC$_{50}$ values of 10.32 ± 1.29 μM and 2.17 ± 0.14 μM against *L. infantum* promastigotes and *L. infantum* axenic amastigotes, respectively. Also, the compound **46** was found to be more efficient than conventionally used antileishmanial drug miltefosine. Lastly, the compound **46** was found to possess moderately low cytotoxicity against murine macrophages J774A.1 (Fig. 21) [50].

Upadhyay et al., designed and synthesized a series of twenty-five triazolyl-2-methyl-4-phenylquinoline-3-carboxylate derivatives as antileishmanial agents against promastigote and amastigote stages of *Leishmania donovani* using click chemistry inspired molecular hybridization approach. Among all the synthesized compounds, **47** was found to be most potent when screened against promastigote stage with an IC$_{50}$ value of 25 μM and against intracellular amastigote stage with an IC$_{50}$ value of 7 μM. Further, the cytotoxicity studies against J774A cell line using MTT method revealed that the potent compound **47** was found to be less cytotoxic as compared to the standard drugs. The evaluation of the molecular properties of the synthesized derivatives using Mole inspired cheminformatics demonstrated that the potent compound **47** has not more than one violation of "Lipinski rule" (Fig. 22) [51].

Ana Tejeria et al., designed and synthesized a series of novel phosphorated tetrahydroquinoline and quinoline derivatives using multicomponent Povarov reaction as potent antileishmanial agents against both promastigote and intramacrophagic amastigote stages of *Leishmania infantum*. Among all the synthesized compounds, **48, 49,**

50, 51 and **52** were found to be most potent with EC$_{50}$ values calculated against promastigote stage of *L. infantum* to be 3.14 ± 0.04 μM, 27.27 ± 2.36 μM, 10.66 ± 0.53 μM, 6.15 ± 1.24 μM and 6.01 ± 0.80 μM, respectively. Also, the EC$_{50}$ values of compounds **48, 49, 50, 51** and **52** against amastigote stage of *L. infantum* were found to be 1.75 ± 0.51 μM, 5.69 ± 0.91 μM, 0.61 ± 0.18 μM, 1.46 ± 0.16 μM and 1.39 ± 1.08 μM, respectively. This activity was observed to be similar to the standard drug amphotericin B. On further evaluation, it has been revealed that the compound **49** inhibited leishmanial Topoisomerase IB. Furthermore, the stereo electronic properties revealed that the potent compounds bind to the allosteric site of the target enzyme. Lastly, the molecular docking studies was conducted to investigate the plausible binding pattern of the potent compounds and their interaction with the key amino acids and DNA nucleobases in the active site of the enzyme Topoisomerase IB and it has been found that the pi-pi interactions were found to be predominant with various amino acids (Fig. 23) [52].

Staderini et al., designed and synthesized a series of novel 4-aminostyrylquinoline derivatives as antileishmanial agents against *Leishmania donovani* promastigotes and axenic and intracellular *Leishmania pifanoi* amastigotes. Among all the synthesized compounds, **53, 54, 55** and **56** were found to be most potent with an IC$_{50}$ values of 1.6 ± 0.0 μM, 2.1 ± 0.2 μM, 8.4 ± 2.4 μM and 3.4 ± 0.2 μM, respectively against *L. donovani* promastigotes and 1.1 ± 0.1 μM, 0.9 ± 0.1 μM, 1.2 ± 0.8 μM and 1.6 ± 0.4 μM, respectively, against *L. pifanoi* amastigotes. On further evaluation, it has been found that the compounds **53, 54, 55** and **56** showed leishmanicidal activity by interfering with the mitochondrial activity of the parasite which leads to the bioenergetic collapse by ATP exhaustion. Lastly, the compounds **53, 54, 55**
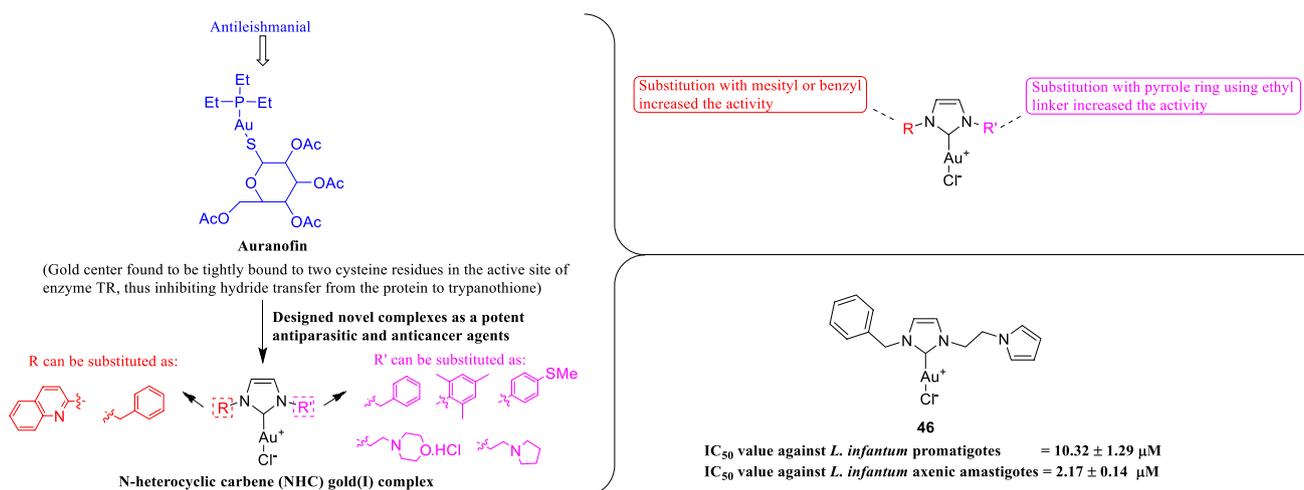

Fig. 21 *N*-heterocyclic carbene (NHC) gold (I) complexes as potent antileishmanial agents
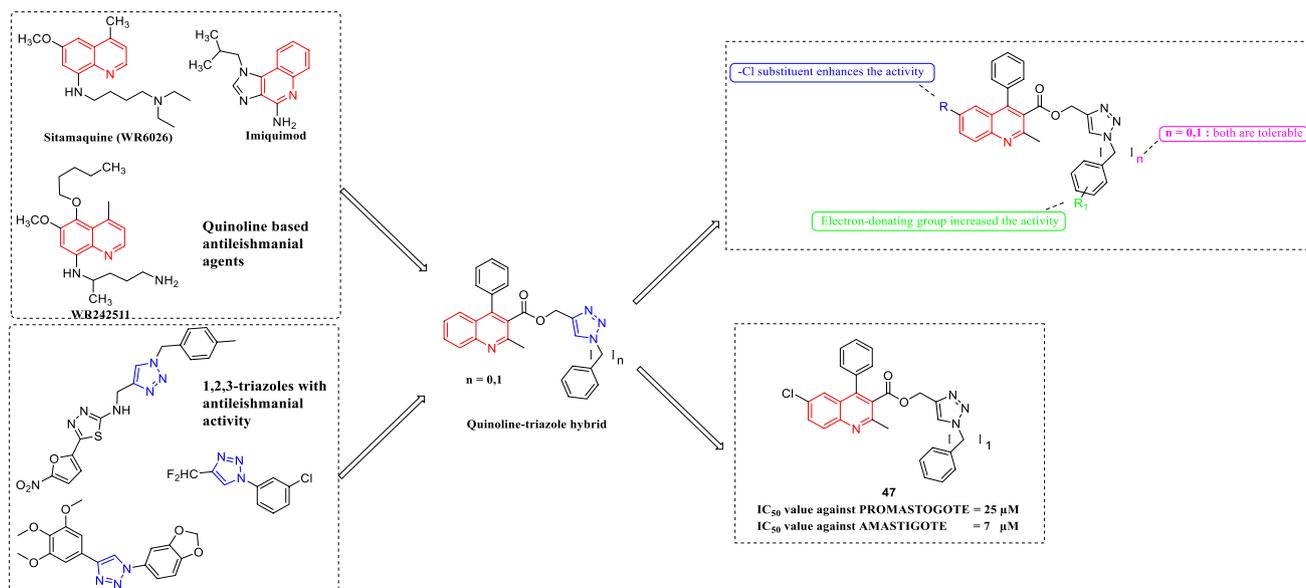
Fig. 22 Triazolyl-2-methyl-4-phenylquinoline-3-carboxylate derivatives as antileishmanial agents
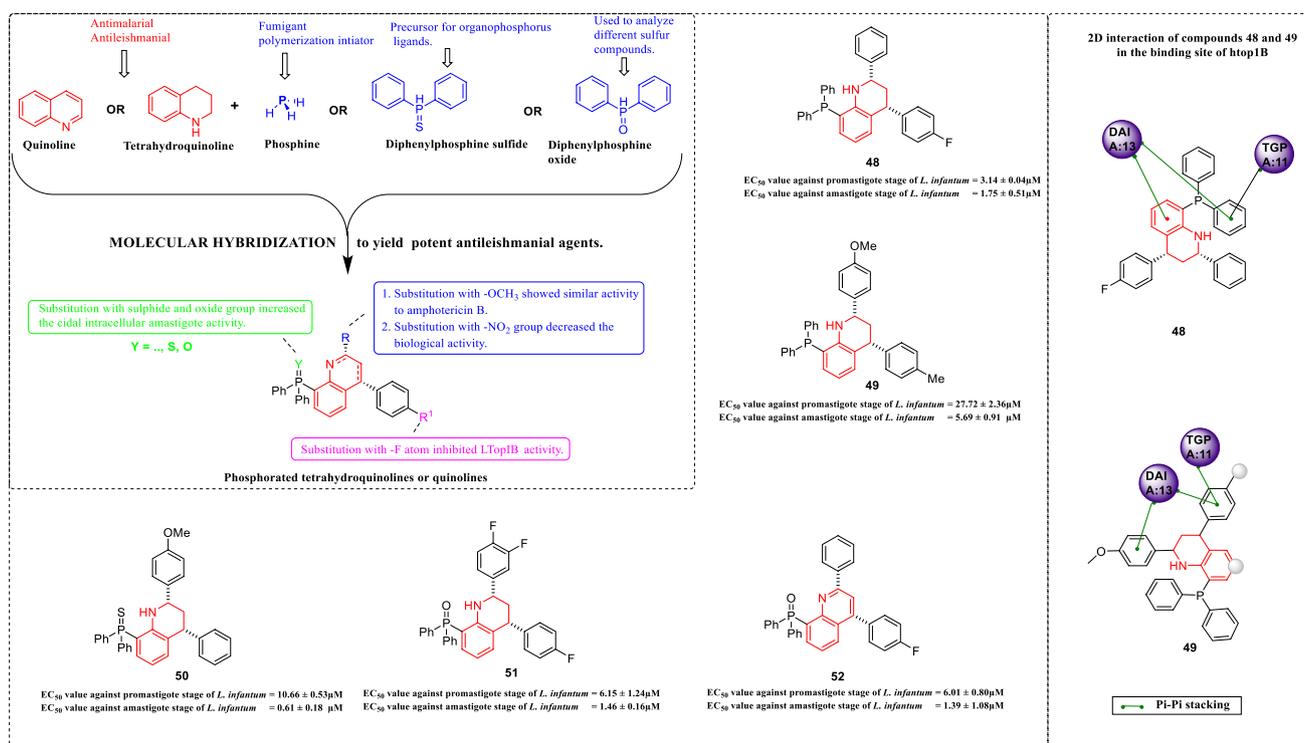

Fig. 23 Novel phosphorated tetrahydroquinoline and quinoline derivatives using multicomponent Povarov reaction as potent antileishmanial agents

and **56** were found to be non-cytotoxic against mammalian macrophage cells (Fig. 24) [53].

Yousuf et al., designed and synthesized a series of novel quinoline-carbaldehyde derivatives as potent

antileishmanial agents against methionine aminopeptidase (LdMetAP1) of *Leishmania donovani*. Among all the synthesized compounds, **57** and **58** were found to be most potent with IC$_{50}$ values of 1.31 μM and 1.10 μM,
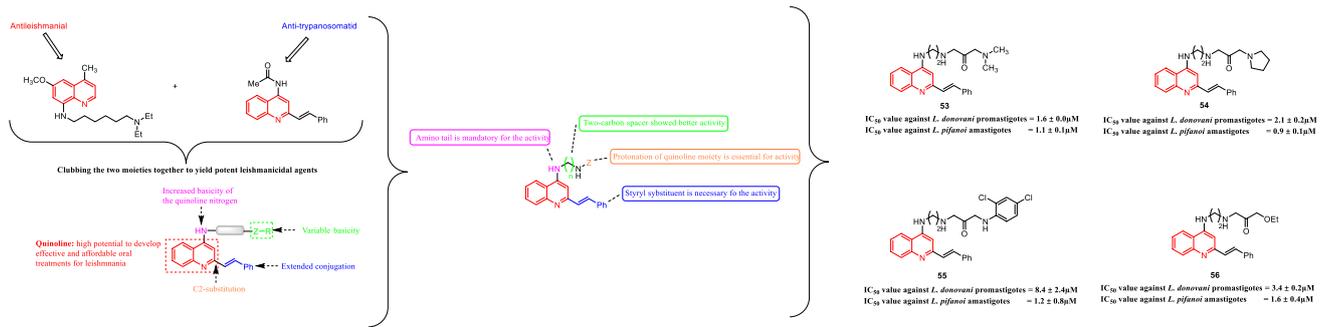
Fig. 24 Novel 4-aminostyrylquinoline derivatives as antileishmanial agents

respectively, against LdMetAP1. Also, the compounds **57** and **58** were found to be less effective against HsMetAP1 with IC$_{50}$ value with **57** and 284.0 μM with **58**. On further evaluation, it has been found that **57** and **58** competitively inhibited LdMetAP1 and possessed promising drug likeness and none of them violated Lipinski's rule and are also found to be non-cytotoxic. Lastly, the molecular docking studies revealed that the compounds **57** and **58** binds to LdMetAP1 by interacting with Thr291, His300 and Asn304 through hydrogen bonding and have

hydrophobic interactions with residues Arg107, Tyr185, Tyr 186, Ser289 and Tyr290 (Fig. 25) [54].

Antimalarial

Valverde et al., designed and synthesized a series of five new dihydroxy isoquine derivatives as potent antimalarial agents against *Plasmodium berghei*. Among all the synthesized compounds, **59**, **60**, and **61** were found to be most potent and inhibited haem polymerization with an IC$_{50}$ values of
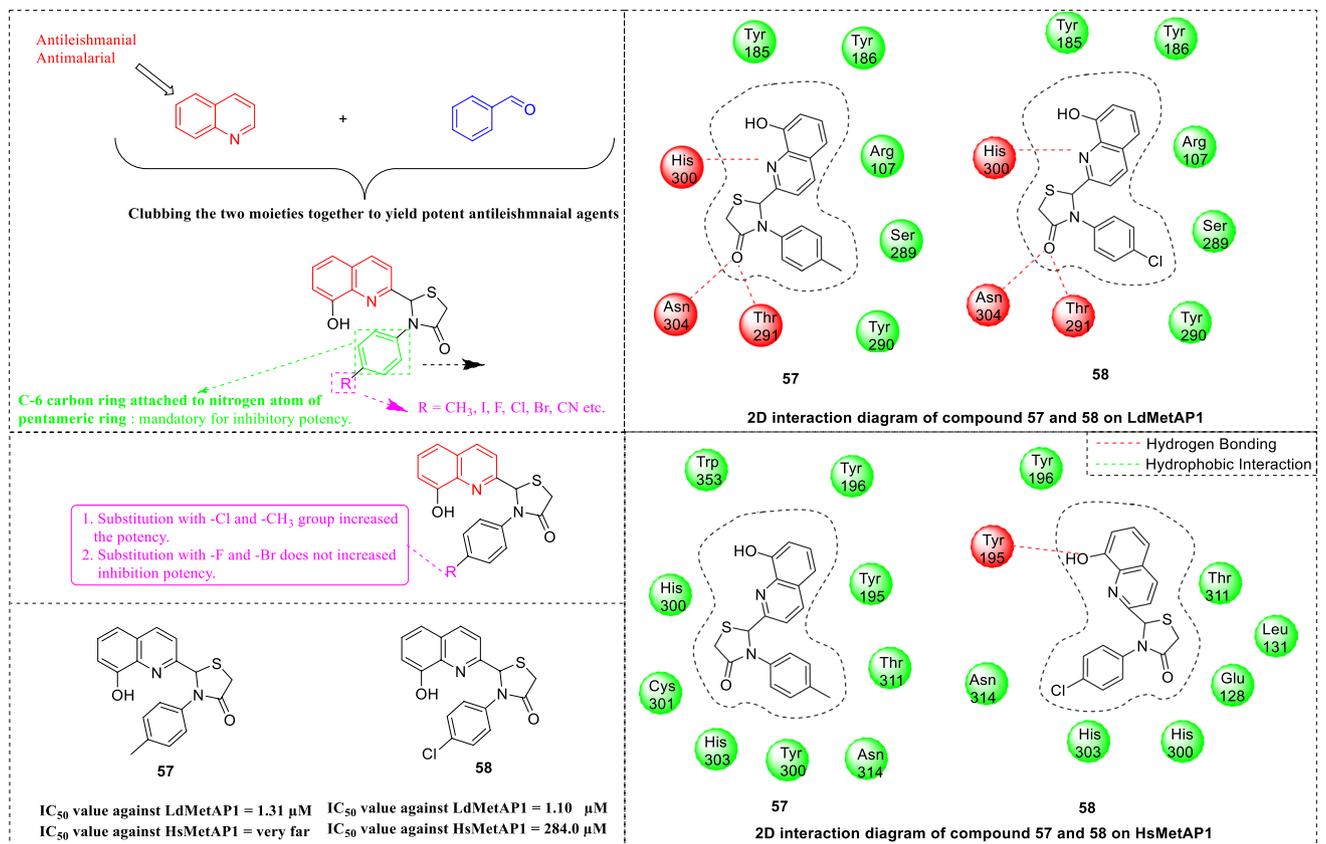

Fig. 25 Novel quinoline-carbaldehyde derivatives as potent antileishmanial agents

1.86 ± 0.22 μM, 1.81 ± 0.23 μM and 1.66 ± 0.11 μM, respectively. On further evaluation, it has been revealed that the compounds 59, 60, and 61 inhibited the haem polymerization which suggested the inhibition of β-hematin and thus exhibited the antimalarial effect. Furthermore, the cytotoxicity studies against macrophage cells demonstrated less cytotoxicity of compounds **59**, **60**, and **61**. Lastly, the molecular docking studies of compounds **59**, **60**, and **61** showed the hydrogen-bond interactions with residues Ser79 and Asp-214, respectively. Also, the π-π interactions has also been seen with the residues Tyr77 and Phe111 (Fig. 26) [55].

Singh et al., designed and synthesized a series of aliphatic and aromatic substituted 1H-1,2,3-triazole-tethered 4-amino-quinoline-ferrocenylchalcone conjugates as potent anti-plasmodial agents. Synthesized compounds were screened for their inhibitory activity against the chloroquine-resistant W2 strain of Plasmodium falciparum. Out of all the synthesized compounds, **62** was found to be most potent with an IC_{50} value of 0.37 μM. On further evaluation, it has been found that the anti-plasmodial activity of the compound **62** and in general of chalcones was due to their ability to function as inhibitors of plasmodial aspartate proteases, cysteine proteases and cyclindependent protein kinases. In addition, compound **62** also inhibited the new permeation pathway induced by the parasite in the erythrocytic membranes. Furthermore, it was seen that the conjugates with flexible aliphatic (aminoethanol or aminopropanol) substituents on the quinoline ring showed better anti-plasmodial activities compared to those with cyclic (piperazine or aminophenol) substituents. Lastly, **62** was found to be non-toxic when screened against the mammalian HeLa cells (Fig. 27) [56].
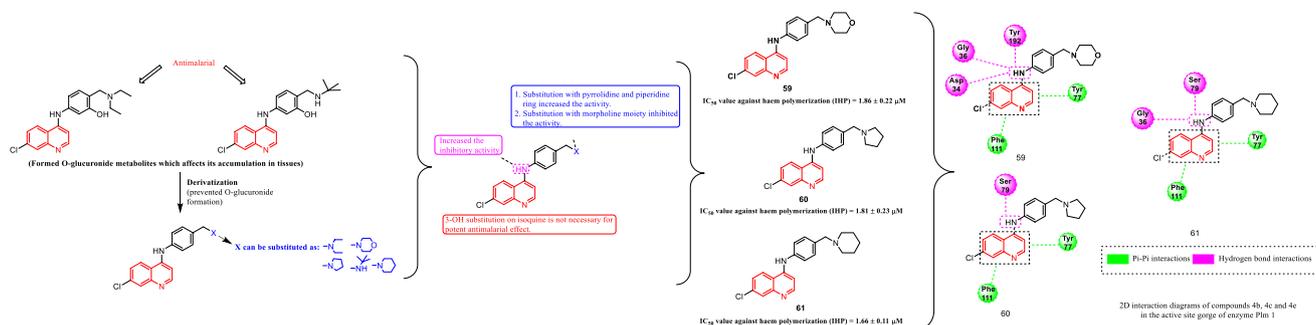

Fig. 26 New dihydroxy isoquine derivatives as potent antimalarial agents
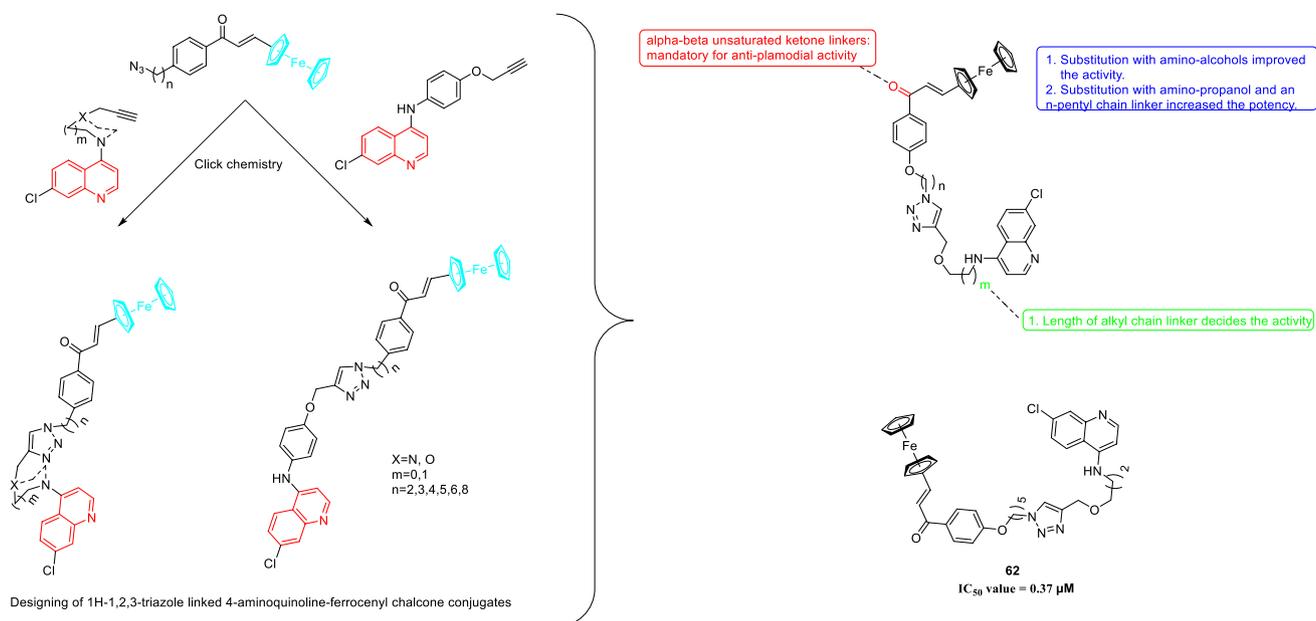

Fig. 27 Aliphatic and aromatic substituted 1H-1,2,3-triazole-tethered 4-amino-quinoline-ferrocenylchalcone conjugates as potent anti-plasmodial agents

Kholiya et al., designed and synthesized a series of novel twenty-two 4-aminoquinoline-piperonyl–pyrimidine hybrids as potent anti-plasmodial agents. Synthesized hybrids were screened in vitro for their antimalarial activity against cultured chloroquine-resistant (W2) and chloroquine-sensitive (D6) strains of *Plasmodium falciparum*. Among all the synthesized compounds, **63** was found to be most active against W2 strain of *Plasmodium falciparum* with an IC_{50} value of 0.05 μM and also against D6 strain of *Plasmodium falciparum* with an IC_{50} value of 0.02 μM. This inhibition was found to be 8 times more potent than conventionally used drug chloroquine. On further evaluation, it has been found that the compound **63** exerted its action by binding with monomeric and dimeric heme. Furthermore, the cytotoxicity studies revealed that the potent compound **63** was found to be non-cytotoxic towards mammalian cells. Molecular docking of **63** both wild and mutant type *Pf*-DHFR-TS demonstrated that the compound **63** showed good π–π interactions with Phe116 in case of mutant *Pf*-DHFR and with Phe58 in case of wild *Pf*-DHFR. Also, the protonated nitrogen of piperazine of the compound 63 formed H-bond interactions with Asp54 in the wild and mutant *Pf*-DHFR which was found to be extremely important for the anti-plasmodial activity (Fig. 28) [57].

Kumar et al., designed and synthesized a series of 1H-1,2,3-triazole linked 4-aminoquinoline-chalcones/-N-acetyl pyrazoline conjugates for their anti-plasmodial

activity against the chloroquine-resistant W2 strain of *Plasmodium falciparum*. Among all the synthesized compounds, **64** was found to be most potent with an IC_{50} of 53.7 ± 25.0 nm. This inhibition was found to be comparable to that of chloroquine. On further in vitro cytotoxicity analysis against mammalian HeLa cells, compound **64** was found to be non-cytotoxic (Fig. 29) [58].

Capela et al., designed and synthesized a series of 1,2,4,5-tetraoxane-8-aminoquinoline hybrids as dual stage antimalarial agents found to be active against both symptomatic erythrocytic stage of Plasmodium infection caused by multidrug-resistant *Plasmodium falciparum* W2 strain and *Plasmodium berghei* liver stage parasite. Among all the synthesized compounds, **65, 66, 67** and **68** were found to be most potent with an EC_{50} values of 0.287 μM, 0.916 μM, 4.19 μM and 5.67 μM, respectively. Cytotoxicity studies revealed that synthesized compounds have exceptionally low cytotoxicity against mammalian cells. Furthermore, the stability studies demonstrated that the potent compounds displayed high metabolic susceptibility in rat liver microsomes. Also, these compounds were found to be much more stable than their primaquine counterparts without the loss of dual stage antimalarial activity (Fig. 30) [59].

Sharma et al., designed and synthesized a series of novel vanillin-based bischalcones as antimalarial agents against erythrocytic stages of *Plasmodium falciparum*. Among all the synthesized compounds, **69** displayed
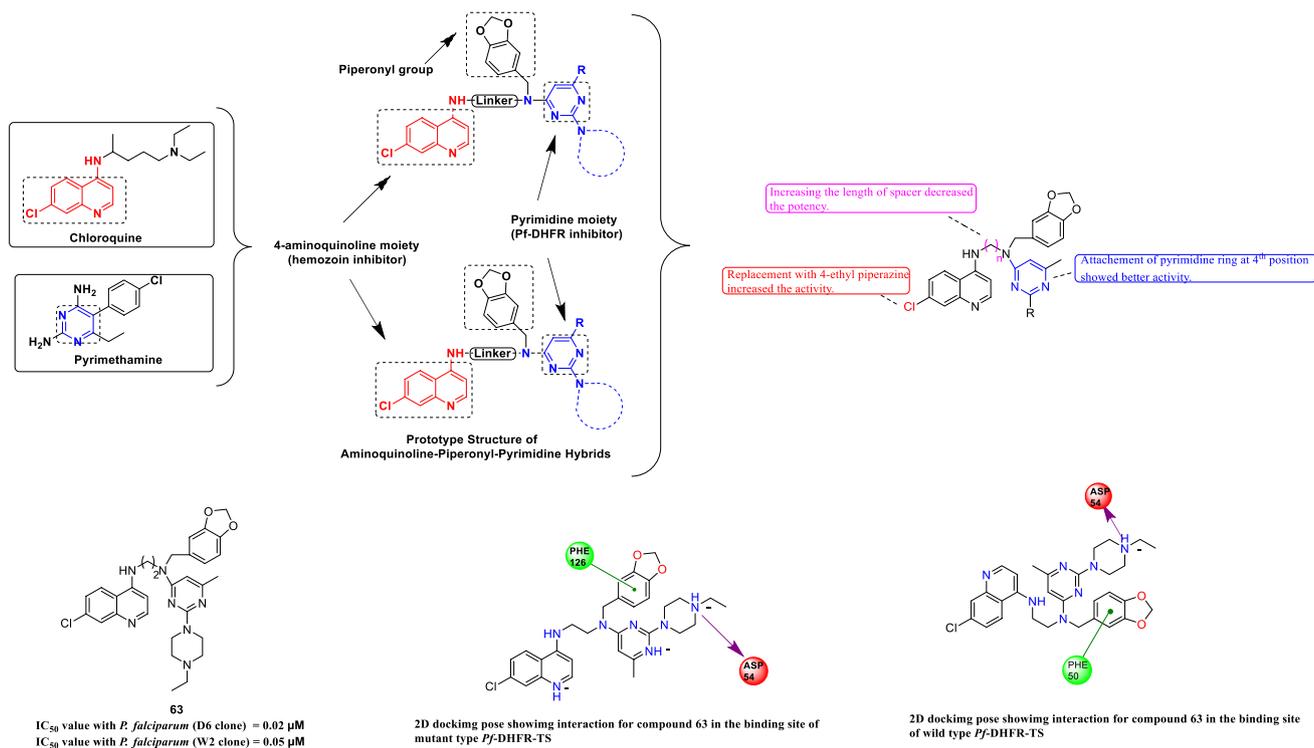

Fig. 28 Novel twenty-two 4-aminoquinoline-piperonyl–pyrimidine hybrids as potent anti-plasmodial agents
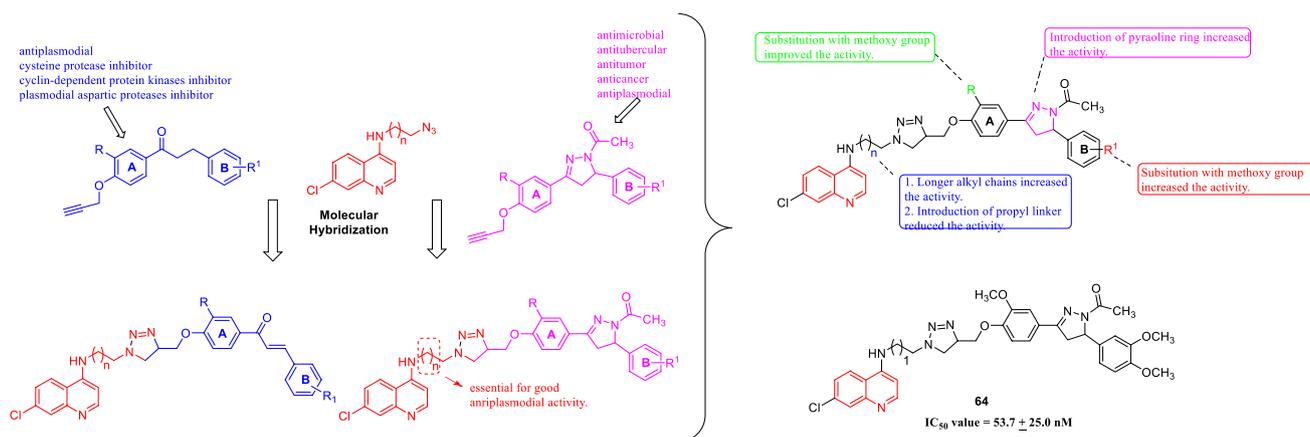
Fig. 29 1H-1,2,3-triazole linked 4-aminoquinoline-chalcones/-*N*-acetyl pyrazoline conjugates for their anti-plasmodial activity
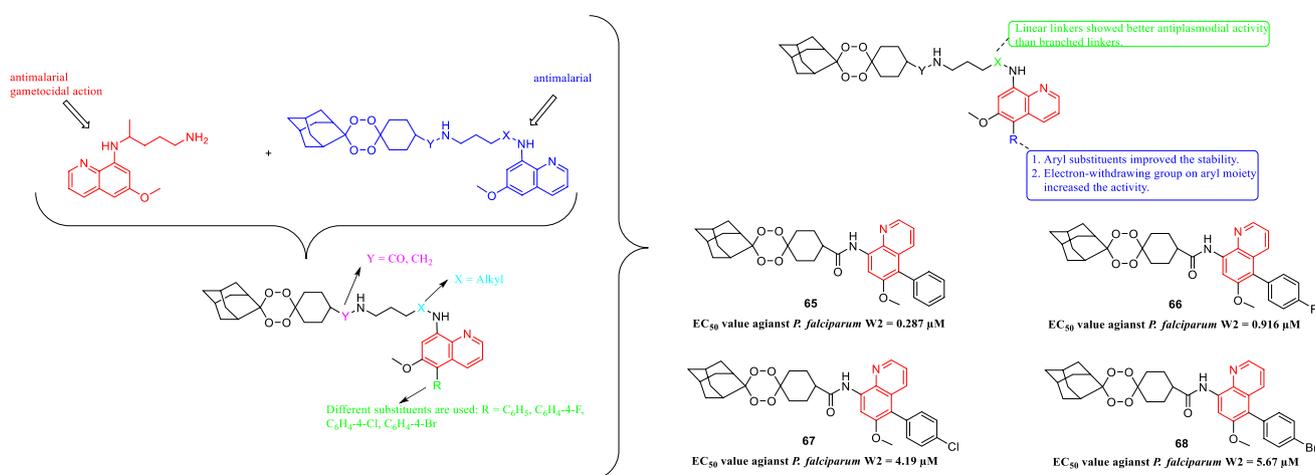

Fig. 30 1,2,4,5-tetraoxane-8-aminoquinoline hybrids as dual stage antimalarial agents

potent against the chloroquine-resistant PfDd2 and PfIndo strains with an IC_{50} values of 3.5 μM and 3.8 μM, respectively. Also, **69** has been found to be active against chloroquine-sensitive Pf3D7 strain with an IC_{50} value of 2.5 μM. On further evaluation, it has been revealed that **69** inhibited *Plasmodium falciparum* at all stages of its life cycle including ring, trophozoite and schizont stages. Furthermore, it has been found that **69** induced apoptosis and finally programmed cell death in *P. falciparum* by mechanisms like arrested growth, chromatin fragmentation, loss of mitochondrial potential, externalisation of phosphatidylserine and by activation of CASPASE like proteases. Lastly, it has been demonstrated that combination of **69** + Artemisinin exhibited strong synergy ($SFIC_{50}$: 0.46 to 0.58) while **69** + chloroquine ($SFIC_{50}$: 0.7 to 1.23) exhibited mild synergy to antagonism against PfIndo. In contrast, both combinations showed marked antagonism against Pf3D7 (Fig. 31) [60].

Bonilla-Ramirez et al., designed and synthesized a series of novel chloroquine and primaquine-quinoxaline 1,4-di-N-oxide hybrids as antimalarial agents against chloroquine-sensitive and multidrug-resistant *Plasmodium falciparum*. Among all the synthesized compounds, **70** was found to be most potent against *P. falciparum* 3D7 and *P. falciparum* FCR-3 with an IC_{50} values of 67.18 ± 3.12 μM and 68.20 ± 3.26 μM, respectively. Furthermore, compound **70** showed good bioavailability and showed no violation to Lipinski's rule of five or Veber's criteria. On further evaluation, it has been revealed that the compound **70** was found to be most active hybrid compound against the exoerythrocytic forms, 1.5-fold more active against *P. yoelii* than primaquine and also exhibited moderate activity against liver stage of *P. falciparum*. Furthermore, compound **70** showed potent activity in the asexual phases of parasitic development with a remarkable parasitaemia inhibition of 95.97% which is slightly less than primaquine (100%). Compound
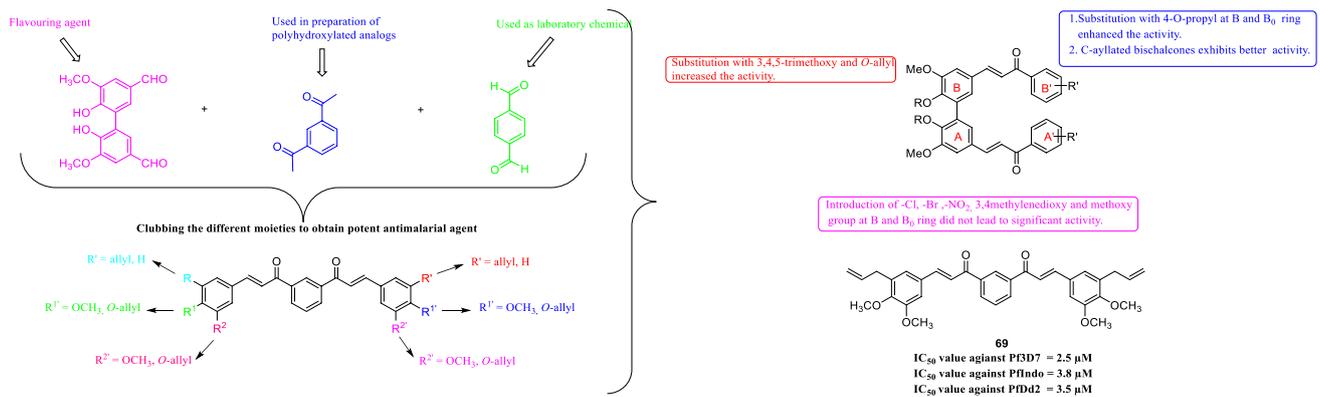
Fig. 31 Novel vanillin-based bischalcones as antimalarial agents

70 was also found to inhibit *P. berghei* oocyte formation and also inhibited sporogony with 92% blocking of transmission. Lastly, the cytotoxicity evaluation revealed that the compound **70** showed no genotoxicity and in vivo acute toxicity at doses of 300 mg/kg (Fig. 32) [61].

Levatic et al., designed and synthesized six different series of novel primaquine derivatives containing sixty-four different compounds: amides, ureas, semicarbazides, acylsemicarbazides, bis-ureas and ureidoamides as potent antimalarial agents *Plasmodium falciparum* NF54 strain. Among all the synthesized compounds, **71** and **72** belonging to primaquine ureidoamide class were found to be most potent against *Plasmodium falciparum* NF54 strain with an IC$_{50}$ values of 1.4 μM and 1.8 μM, respectively. This inhibition was found to be much more potent than Primaquine. Lastly, cytotoxicity studies relative to Primaquine revealed that the compounds **71** and **72** were found to be 2.7 and 2.5-fold less cytotoxic against L6 rat skeletal myoblasts,

13-fold less toxic than Primaquine against human cell lines and finally much less toxic to the G6PD-deficient patients (Fig. 33) [62].

Maurya et al., designed and synthesized a series of novel *N*-substituted aminoquinoline-pyrimidine hybrids as potent antimalarial compounds against both chloroquine-sensitive D6 strain and chloroquine-resistant W2 strain of *Plasmodium falciparum*. Among all the synthesized compounds, **73** was found to be most potent with IC$_{50}$ value of 0.027 μM against D6 strain of *P. falciparum* and 0.142 μM against W2 strain of *P. falciparum*. On further evaluation, it has been revealed through heme binding studies that the compound **73** exerted its action by binding with hematin. Also, the compound **73** was found to be non-cytotoxic towards the mammalian VERO cell lines up to the concentration of 10 μM. Lastly, the docking studies demonstrated excellent binding interaction of compound **73** with Pf-DHFR (Fig. 34) [63].
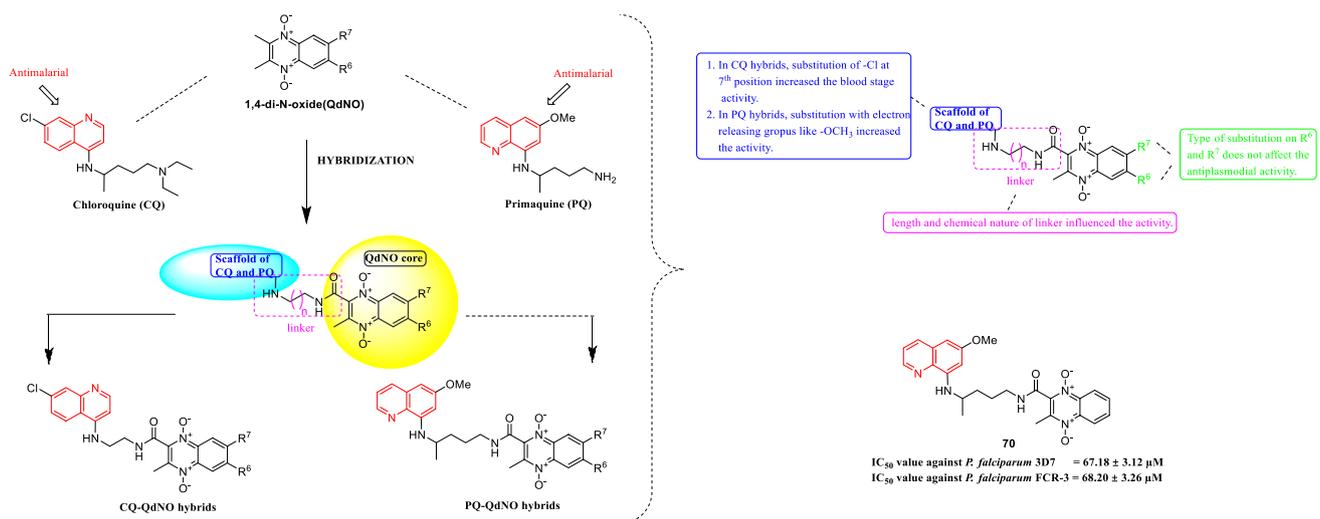

Fig. 32 Novel chloroquine and primaquine-quinoxaline 1,4-di-*N*-oxide hybrids as antimalarial agents
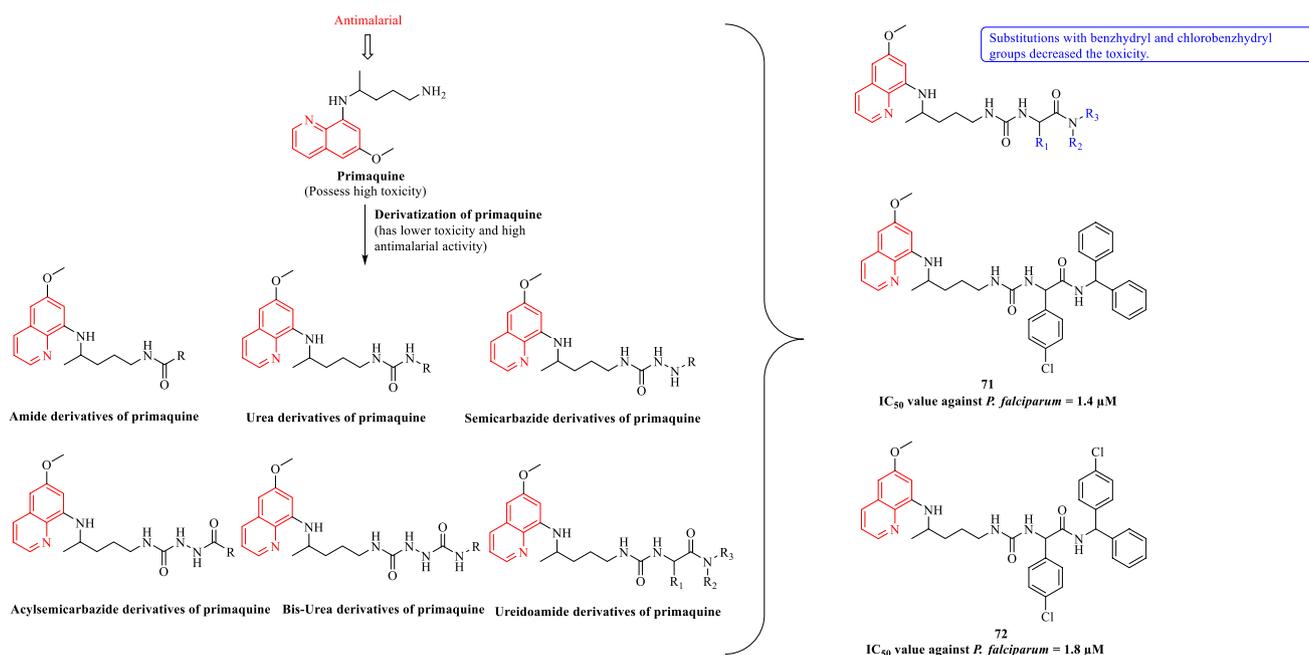
Fig. 33 Novel primaquine derivatives as antimalarial agents
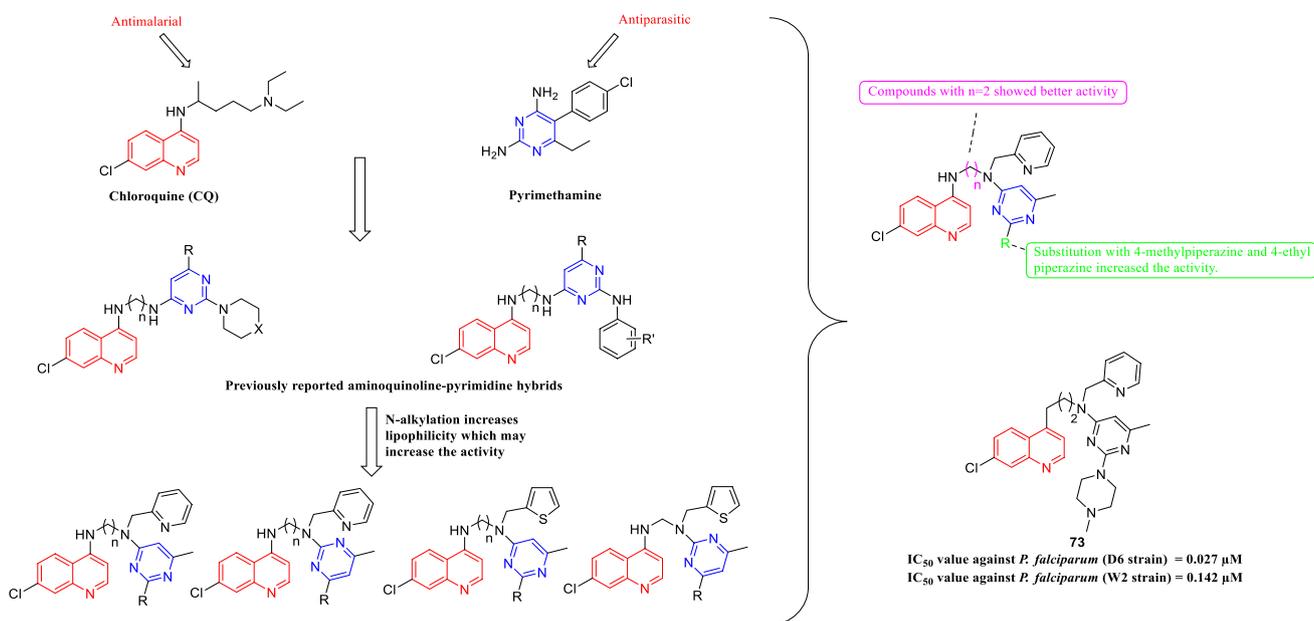
Fig. 34 *N*-substituted aminoquinoline-pyrimidine hybrids as potent antimalarial compounds

Miscellaneous

Qinggang Ji et al., designed and synthesized a series of novel 5-(piperazin-1-yl) quinoline-2(1H)-one derivatives as potential chitin synthase inhibitors and antifungal agents against various strains of fungi. Among all the synthesized compounds, **74**, **75** and **76** were found to be most potent with an IC$_{50}$ values of 0.10 μM, 0.36 μM and 0.47 μM, respectively,

against chitin synthase enzyme. Also, the MIC values of **74**, **75** and **76** were calculated to be 32 μg/mL each against fungi *Candida albicans* ATCC 76,615, 128 μg/mL, 256 μg/mL and 512 μg/mL, respectively, against *Cryptococcus neoformans* ATCC 32,719 and finally 128 μg/mL, 256 μg/mL and 128 μg/mL, respectively, against *Aspergillus flavus* ATCC 16,870. On further evaluation, it has been revealed that the compounds **74**, **75** and **76** were found to be extraordinarily

little potent against various gram positive bacteria like *S. aureus*, MRSA, *B. subtilis* and gram-negative bacteria *B. proteus*, *E. coli* and *P. aeruginosa* (Fig. 35) [64].

Karad et al., designed and synthesized a series of novel morpholino-quinoline based conjugates with pyrazoline moiety under microwave irradiation as antimicrobial, antitubercular and antimalarial agents. Synthesized antibacterial agents were screened for their inhibitory potential against gram positive strains i.e., *Bacillus subtilis* MTCC 441, *Clostridium tetani* MTCC 449, Streptococcus *Pneumoniae* MTCC 1936 and against three gram-negative strains i.e., *Salmonella typhi* MTCC 98, *Escherichia coli* MTCC 443, *Vibrio cholera* MTCC 3906. Further, synthesized antifungal compounds were screened for their impeding effect against *Candida albicans* MTCC 227. In vitro screening of newly synthesized antitubercular agents were conducted against MTB H_{37}Rv strain. Finally, the synthesized antimalarial pyrazoline derivatives were screened against *Plasmodium falciparum*. Among all the compounds, **77** and **83** showed significant antibacterial activity with an IC_{50} value of 145 μM and 148 μM. This inhibition was found to be much more potent than ampicillin, chloramphenicol, and ciprofloxacin. Out of all the synthesized antifungal compounds, **78** with IC_{50} of 597 μM, **80** with IC_{50} of 518 μM, **81** with IC_{50} of 470 μM and **82** with IC_{50} of 537 μM showed excellent activity as compared to griseofulvin with IC_{50} of 1147 μM. Amongst all the synthesized morpholino-quinoline based pyrazoline scaffolds, compounds **81, 78, 83, 77, 82, 79** and with IC_{50} values of 0.015 μM, 0.018 μM, 0.028 μM, 0.034 μM, 0.040 μM, 0.044 μM and 0.051 μM, respectively, displayed splendid inhibitory activity as compared to chloroquine with IC_{50} value of 0.062 μM as well as quinine with IC_{50} value of 0.826 μM. The compounds **79**, **81** and **82** with IC_{50} values of 0.044 μM, 0.015 μM and 0.040 μM, respectively, were identified as dual antimalarial and antitubercular agents. At last, the cytotoxicity of the synthesized compounds was evaluated using bioassay of S. pombe cells

at cellular level and compounds **77**, **78** and **83** were found to have maximum toxicity, whereas compounds **80**, **79**, **82** and **81** were found to be less cytotoxic (Fig. 36) [65].

Duroux et al., designed and synthesized a series of novel napthocyclopentane and quinolinocyclopentane derivatives with various acetamide modulations as potent melatoninergic (MT$_1$ / MT$_2$) and serotoninergic (5-HT$_{2c}$) dual ligands with potent anti-parasitic activity. Among all the synthesized compounds, 84 and 85 were found to be most potent with an EC_{50} values of 5 nm and 8 nm, respectively, on h-MT$_1$ receptors and 3 nm and 6 nm, respectively, on h-MT$_2$ receptors. On further evaluation, it has been revealed that the compounds **84** and **85** showed the enantioselective character i.e., these compounds exist as levogyre enantiomers ()-**84** and ()-**85** and exhibits highest affinity at MT$_1$, MT$_2$ and 5-HT$_{2c}$ receptors (Fig. 37) [66].

El Shehry et al., designed and synthesized three series of quinoline derivatives bearing pyrazole moiety as potent antibacterial and antifungal agents against various strains of gram positive and gram-negative bacteria and fungi. Among all the synthesized compounds, **86** was found to be most potent against *S. aureus, S. epidermidis, B. subtilis, P. vulgaris, K. pneumonia, S. flexneri, A. fumigatus, A. clavatus* and *C. albicans* with MIC values of 0.49 μg/mL, 0.12 μg/mL, 0.98 μg/mL, 0.49 μg/mL, 0.12 μg/mL, 0.98 μg/mL, 0.49 μg/mL and 0.12 μg/mL, respectively. This inhibition was found to be four times more potent against *S. flexneri* and two times more potent against *P. vulgaris* than gentamycin, four times more potent against *A. clavatus* and *C. albicans* than amphotericin B and equipotent against *S. epidermidis, A. fumigatus* when compared to ampicillin and amphotericin B. Furthermore, the animal toxicity studies were performed by LD_{50} (the median lethal dose) by using Spearmane Karber method and it has been revealed that the synthesized compounds were found to have exceptionally low toxicity and good tolerability up to the dose of 1200 mg/kg (Fig. 38) [67].
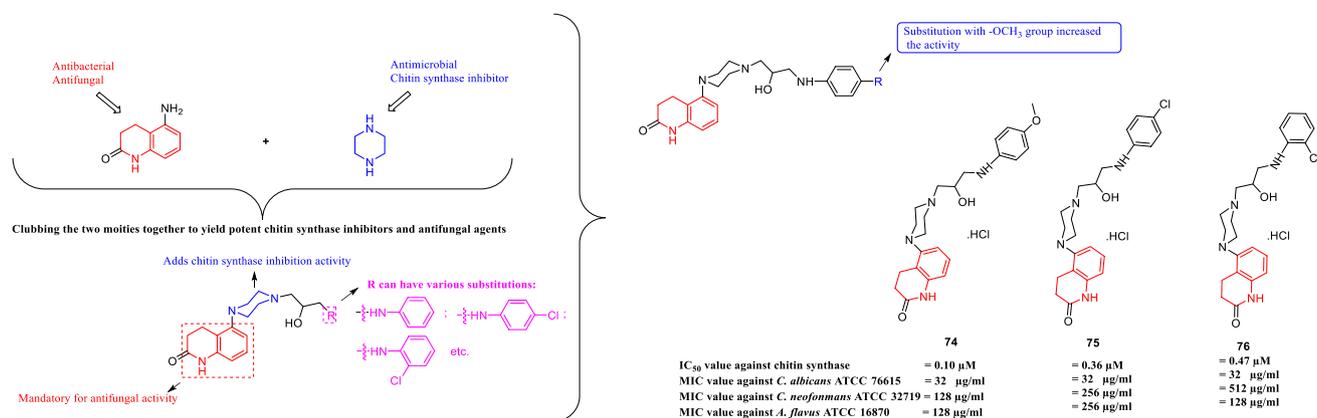
Fig. 35 Novel 5-(piperazin-1-yl) quinoline-2(1H)-one derivatives as potential chitin synthase inhibitors and antifungal agents
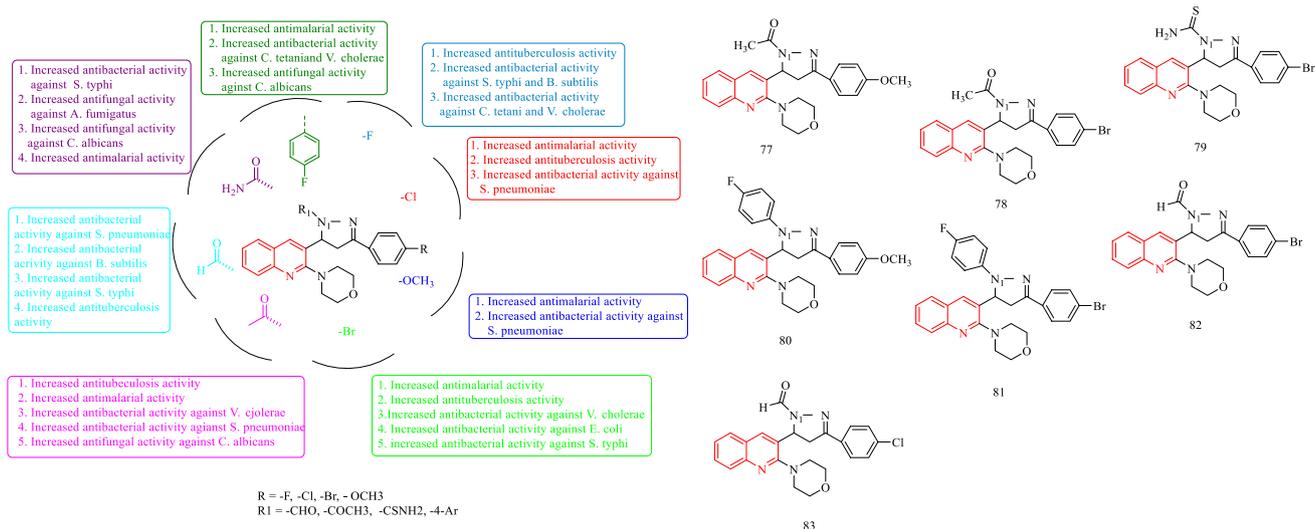
Fig. 36 Novel morpholino-quinoline based conjugates with pyrazoline moiety under microwave irradiation as antimicrobial, antitubercular and antimalarial agents
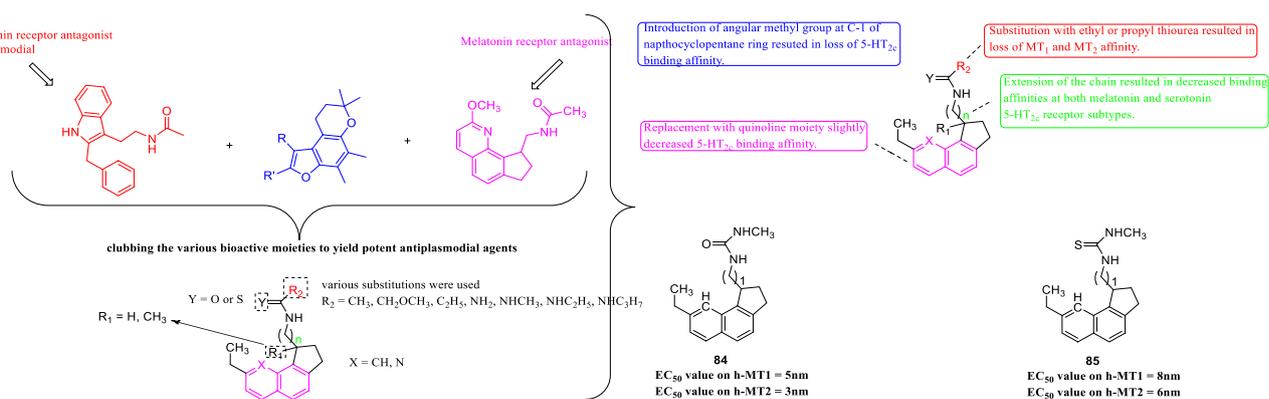
Fig. 37 Novel napthocyclopentane and quinolinocyclopentane derivatives with various acetamide modulations as potent melatoninergic (MT1/MT2) and serotoninergic (5-HT2c) dual ligands with potent anti-parasitic activity

Fig. 38 Quinoline derivatives bearing pyrazole moiety as potent antibacterial and antifungal agents

Pavic et al., designed and synthesized four series of primaquine derivatives: amides, ureas, semi carbazides and bis-ureas as potent antitubercular and anti-plasmodial agents against various mycobacterium and plasmodial strains, respectively. Among all the synthesized compounds, **87** and **88** were found to be most potent anti-mycobacterial agents with MIC values of 2 μg/mL each against *MTB* H37Ra ATCC 25,177: 2 μg/mL and 16 μg/mL, respectively, against *Mycobacterium avium complex* CIT19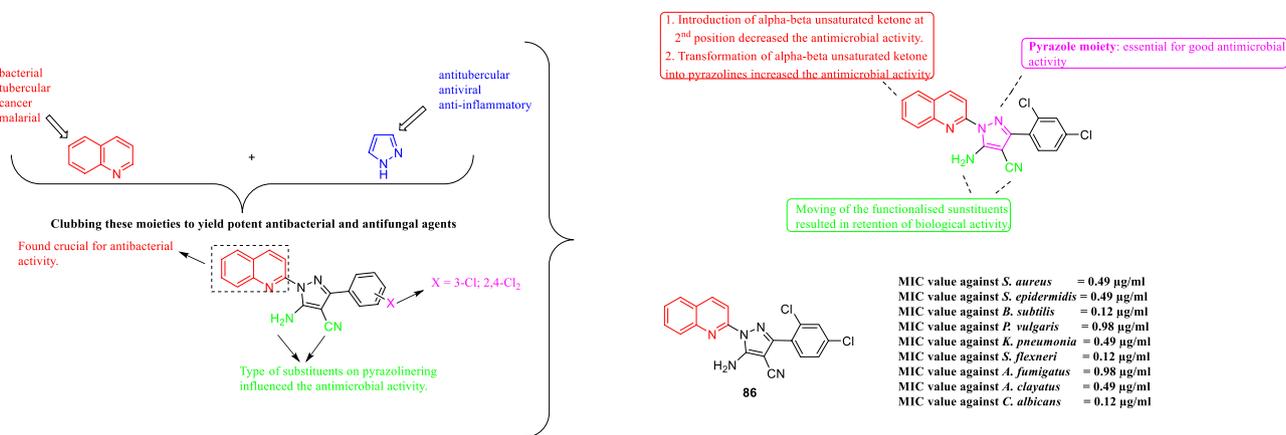106 (MAC) and finally 2 μg/mL and 4 μg/mL, respectively, against *Mycobacterium avium subsp. Paratuberculosis* CIT03 (MAP). Also, the compound **89** was found to be most potent anti-plasmodial agent against liver stage of *Plasmodium berghei* and erythrocyte -stage of *Plasmodium berghei* with an IC_{50} values of 42.0 μM and 17.8 μM, respectively. On further evaluation, it has been revealed that the compounds **87** and **88** exhibited antitubercular action by the inhibition of mycobacterial gyrase, ATP synthase, FtsZ protein, glutathione S-transferase, enoyl-ACP reductase, decaprenyl phosphoryl-β-$_D$-ribose-2'-epimerase (DprE1) or FadD32. Furthermore, docking studies indicated that the compounds **87** and **88** does not interfere with FtsZ as no conclusive binding sites for these compounds have been identified. Lastly, the cytotoxicity studies on L6 cells revealed extremely high cytotoxicity/

activity ratio of compound 89. Also, the compounds **87** and **88** were found to be very less cytotoxic (Fig. 39) [68].

Okumu et al., designed and synthesized a series of Novel Bacterial Topoisomerase Inhibitors (NBTIs) derived from isomannide against fluoroquinolone-resistant MRSA and other gram positive pathogens. Among all the synthesized compounds, **90** was found to be most potent with the MIC_{90} value of 2 μg/mL and 1 μg/mL against fluoroquinolone-resistant MRSA and *Staphylococcus aureus,* respectively. This inhibition was found to be 16-fold more potent than control drug ciprofloxacin. On further evaluation, it has been revealed in a spontaneous frequency of resistant study (FoR) that the compound **90** was unable to suppress the emergence of NBTI-resistant mutants. Furthermore, compound **90** was found to be cardiovascular safe by using hERG inhibition assay with an IC_{50} value of 66 μM. Also, compound **90** was found to be minimally cytotoxic against mammalian HepaRG cells. Also, the compound **90** displayed favorable ADME properties with moderately high protein binding both in mouse and human plasma and finally it has been revealed that the compound **90** inhibited CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP2D6 by 50% and CYP3A4 by 56% at 10 μM concentration and also exhibited rapid metabolism as revealed in microsomal assays (Fig. 40) [69].
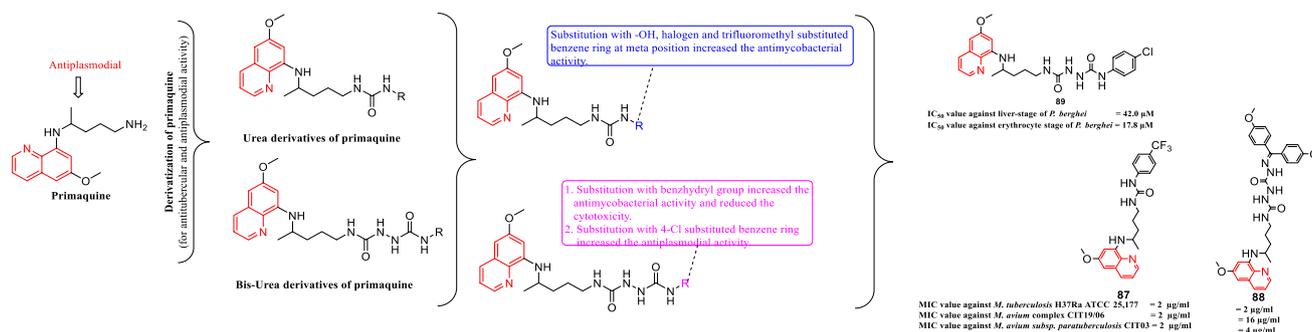

Fig. 39 Primaquine derivatives: amides, ureas, semi carbazides and bis-ureas as potent antitubercular and anti-plasmodial agents
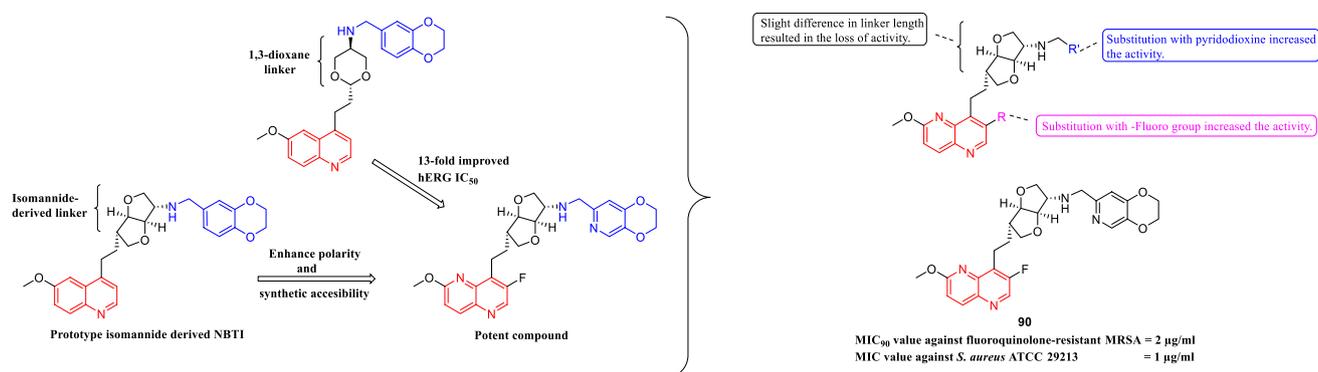

Fig. 40 Novel Bacterial Topoisomerase Inhibitors (NBTIs) derived from isomannide

Mohammed et al., designed and synthesized a series of novel glycosylated-fluoroquinolones derivatives as potent antibacterial and antifungal agents against various strains of bacteria and fungi. Among all the synthesized compounds, **91**, **92** and **95** were found to be most potent against fluoroquinolone-resistant *Escherichia coli* clinical isolate with the MIC values of 0.2608 ± 0.0014 mM, 0.1358 ± 0.0025 mM and 0.0898 ± 0.0014 mM, respectively. The inhibitions displayed by the compounds **91** and **92** were revealed to be twofold more potent as compared to their parent drugs ciprofloxacin and norfloxacin, respectively, and the inhibition by the compound **95** was found to be three times more potent than its parent drug moxifloxacin. Also, the compounds **92**, **93**, **94** and **95** were found to be most active against fungi *Aspergillus flavus* with the MIC values of 0.3620 ± 0.0099 mM, 0.1618 ± 0.0212 mM, 0.2338 ± 0.007 mM and 0.4784 ± 0.0049 mM, respectively. Compound **92** also exhibited potent antifungal activities against *Candida albicans* and *Penicillium chrysogenum* with the MIC values of 0.0056 ± 0.0014 mM and 0.0453 ± 0.0156 mM, respectively. The compounds **92**, **93**, **94** and **95** displayed more potent antifungal activities as

compared to their respective parent drugs. On further evaluation, it has been illustrated that the compound **91**, **92** and **95** exhibited antibacterial activity by inhibiting bacterial DNA gyrase, topoisomerase IV, cell division, energy conversion and motility of the targeted bacteria. Lastly, the cytotoxicity analysis against L6 muscle cell line demonstrated that the compounds **91**, **92**, **93**, **94** and **95** showed similar cytotoxicity profiles as compared to their parent drugs (Fig. 41) [70].

Riboswitches as potential drug targets

An *in-silico* framework has been developed by Mujwar et al. for the prediction of riboswitch to combat the drug resistance against various marketed antibiotics and design of its corresponding inhibitor with the help of case study of *Bacillus anthracis* bacteria. Three molecules ZINC19362650, ZINC01729524 and ZINC19325791 has been identified as potential inhibitors for anthrax by the virtual screening using molecular docking simulations of molecular library consisting of 1880 different ligands out of which the compound ZINC19325791 showed most appreciable binding energy of -12.32 kcal/mol. Furthermore, it has been revealed that
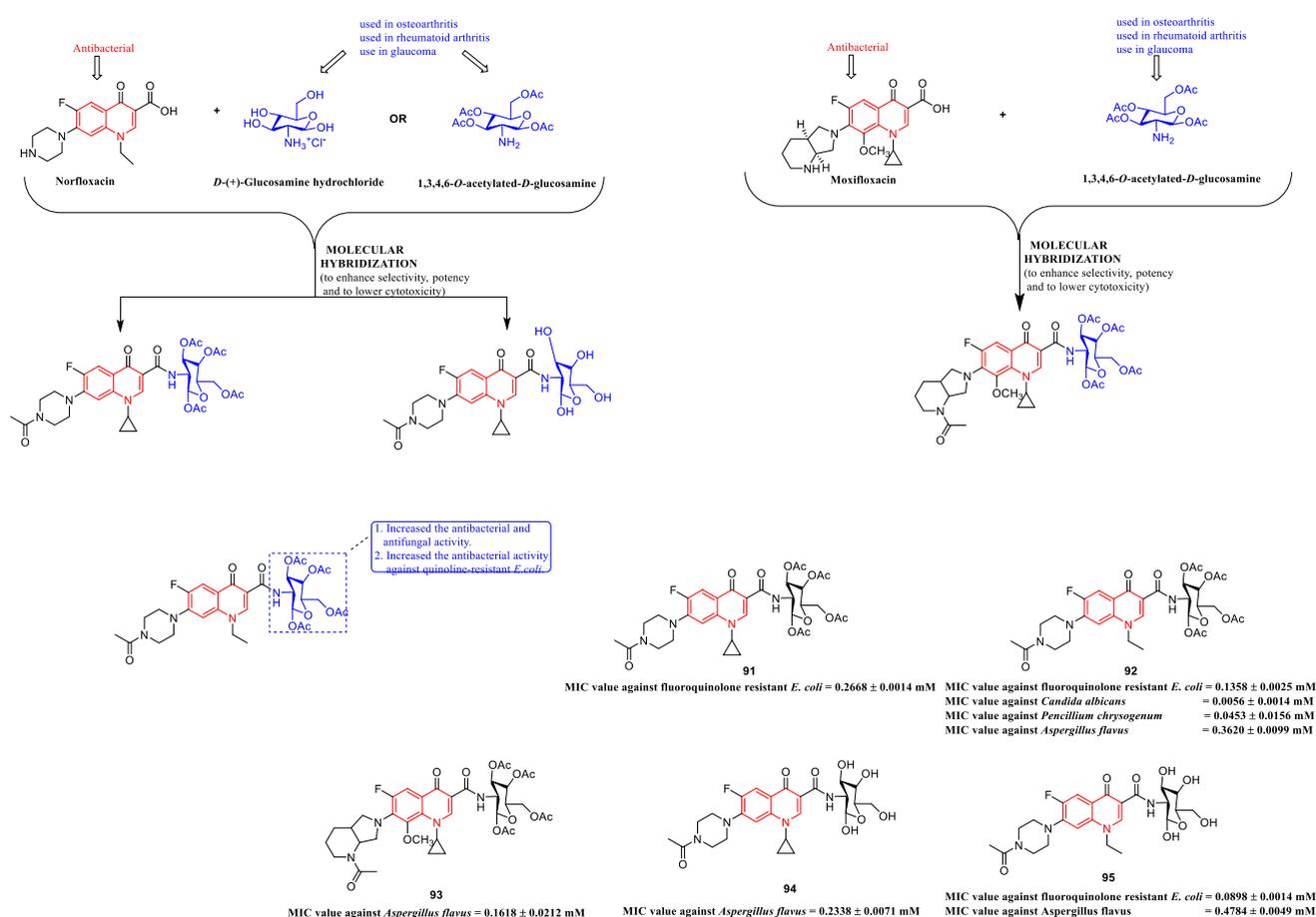

Fig. 41 Novel glycosylated-fluoroquinolones derivatives as potent antibacterial and antifungal agents

the bacterial gene expression has been regulated by the predicted riboswitch thus encoding the synthesis of amino acid efflux protein. Lastly, these three compounds has not shown any toxicity as these riboswitch has no identified role in humans and also showed satisfactory drug-likeness score in the ADME prediction studies. Furthermore, it has been revealed that the bacterial gene expression has been regulated by the predicted riboswitch thus encoding the synthesis of amino acid efflux protein (Fig. 42) [71].

In 2015, Pradhan et al. performed the in- silico prediction of two riboswitches for three strains of influenza virus H1N1, H2N2 and H3N2. On further evaluation it has been revealed that the lysine to be the most efficient ligand amongst all the three strains of influenza virus. Furthermore, compound NCI_81462_a was found to possess most satisfactory binding energy of − 10.06 kcal/mol. Also, all the screened compounds showed no toxicity and satisfactory drug likeness properties. Lastly, the designed compounds have been predicted to be exempted from the adverse effects of antiviral drugs and also itself was found to be very less labile for developing resistance (Fig. 42) [72].

Due to the severe side effects and drug resistance development by the *Norcardia farcinia* against various antibiotics such as ampicillin and third-generation cephalosporins. Amritpreet Kaur et al., designed four lead molecules as the inhibitors against the CBL riboswitch of *N. farcinia* due to their appreciable binding energies with the identified bacterial riboswitch with the optimum pharmacokinetic properties with the most satisfactory binding energy of − 14.45 kcal/mol shown by the ligand ZINC19325788. Furthermore, molecular docking simulation-based virtual screening technique and structure-based pharmacophore development method has been used to obtain the various lead molecules. Also, it has been revealed that the designed lead molecules cannot interact with the mammalian mRNA as they only targeted CBL riboswitch which is only unique to the *N. farcinia*. Lastly, Ligand 1, 2 and ZINC18163421 has feen found to posess almost negligible tendency to be metabolized by the isoenzymes such as CYP1A2, CYP3A4, CYP2C9 and CYP2A1 and thus supposed to show slow metabolism rate which in turn resulted in longer duration of action even with the smaller therapeutic doses (Fig. 42) [73].
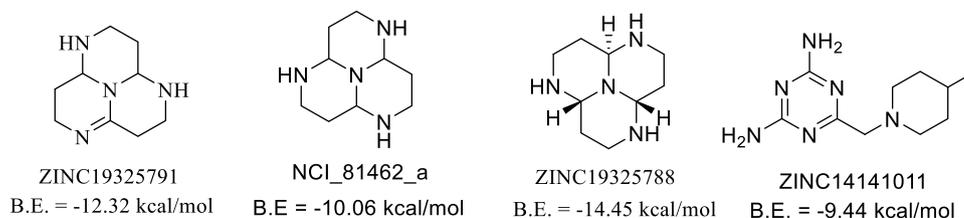
In 2015, Mujwar et al. performed the molecular docking simulation-based virtual screening using molecular library containing 5017 diverse ligands against *Mycobacterium*

tuberculosis riboswitch. Among all the screened compounds, ZINC14141011 has been found to possess most appreciable binding energy of − 9.44 kcal/mol with the *Mycobacterium tuberculosis* riboswitch. On further evaluation, it has been clearly revealed that almost all the five lead molecules followed Lipinski's rule of five, good drug-likeness properties without any toxic effects (except ZINC06375208) and also showed satisfactory physiochemical properties as predicted by studying ADME properties. Also, these lead molecules these compounds does not show side effects and drug resistance when compared to the conventional marketed antibiotics as these leads targeted the riboswitch of the pathogens which are present in 5′-UTR and are rarely reported to undergo mutations (Fig. 42) [74].

Conclusion

AMR has become a serious challenge for the healthcare system which might be due to increased toxicity or lack of novel drug molecules for the treatment. From the extensive literature survey, it can be concluded that quinoline is a unique molecule which has diverse pharmacological activities such as antibacterial, antifungal, antimalarial, antiviral, antitubercular, antileishmanial, anti-inflammatory and anticancer and can be easily modified chemically by derivatizing or by forming hybrids. During reviewing quinoline compounds, it was observed that activities of quinoline derivatives were varying on varying the substitutions on it. After classifying quinoline derivatives according to their pharmacological profiles, compound 1 was found to be the most potent with an IC_{50} value of 0.48 μM against BVDV. Similarly, among anti-bacterial compound 9 was the most potent and was active against *Staphylococcus aureus*, *Streptococcus pyrogens*, *Salmonella typhi*, *Pseudomonas aeruginosa* and *Escherichia coli* with MIC value of 0.12 μg/mL, 8 μg/mL, 0.12 μg/mL, > 1024 μg/mL, 0.12 μg/mL. Among antitubercular, compound 38 was the most potent with MIC value of 0.31 μg/mL, 0.31 μg/mL, 0.31 μg/mL, 0.16 μg/mL and 0.31 μg/mL against MTB CDCT10, MTB CDCT16, MTB CDCT27 and MTB CDCT28 drug-resistant strains. Among anti-protozoal agents, compound 50 was found to the most potent with EC_{50} value of 0.61 ± 0.18 μM as anti-leishmanial agent and compound 73 as the most potent antimalarial compound with IC_{50} value of 0.027 μM against D6 strain of *P.*

Fig. 42 Potent riboswitches inhibitors to combat antimicrobial resistance

ZINC19325791
B.E. = -12.32 kcal/mol

NCI_81462_a
B.E = -10.06 kcal/mol

ZINC19325788
B.E. = -14.45 kcal/mol

ZINC14141011
B.E = -9.44 kcal/mol

falciparum and 0.142 μM against W2 strain of *P. falciparum.* Moreover, *Mujwar* et al. recommended rarely mutated riboswitches as the potential target for treating infectious diseases as these switches has no identified role in humans. Therefore, they performed various *in-silico* studies on riboswitches of *B. anthracis*, influenza virus (H_1N_1, H_2N_2 and H_3N_2), *Norcardia farcinia and Mycobacterium tuberculosis*; and recommended ZINC19325791 (− 12.32 kcal/mol), NCI_81462_a (− 10.06 kcal/mol), ZINC19325788 (− 14.45 kcal/mol) and ZINC14141011 (− 9.44 kcal/mol) as potent inhibitors of respective riboswitches.

Author contributions NK: Conceptualization, Methodology, Resources, Writing—original draft, Writing—review & editing; AK: Writing—review & editing, KK: Writing—review & editing, HK: Writing—review & editing, AS: Writing—review & editing, PMSB: Supervision, review & editing.

Declarations

Conflict of interest No interest of conflicts.

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