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Review

A review: Structure-activity relationship and antibacterial activities of Quinoline based hybrids

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ABSTRACT

The drug resistance problem is most acute in the case of bacteria. There is always a need to develop novel antibacterial drugs with better mechanisms of action. Most of the quinoline-based antibiotics developed are potential antibacterial drug candidates. This review represents quinoline-based hybrids with antibacterial activity and their structure–activity relationship (SAR), which provide further insight into the improvement of quinoline-based antibiotics especially against multidrug-resistant bacterial strains.

1. Introduction

Bacterial infection has evolved once again a serious threat worldwide [1,2]. One-third of the global population is infected by bacterial strains [3]. Bacterial infection is a major health problem due to the widespread multidrug-resistant microorganisms such as *S. aureus* [4,5], *P. aeruginosa* [6,7], *S. epidermidis* [8,9], *E. faecium* [10,11], *S. apiospermum* [12] and *E. coli* [13,14]. Antibiotics are generally used to fight bacterial infections but due to overuse and misuse of antibiotics, bacteria develop resistance to available drugs [15–19].

The ever-increasing number of multidrug-resistant microbial strains and new development in untreatable infections make it difficult to treat bacterial infections. There are enough antibacterial specialists and chemotherapeutics available in the market today. However, there is still a need for a new class of antibacterial agents due to the improvement of old and new opponents of bacterial resistance strains in recent decades [20–30].

Nitrogen-containing heterocycles play a significant role in medicine and are extensively utilized in the design and discovery of drugs [31,32]. From the angle of therapeutic and synthetic science, quinoline is one of the most valuable heterocyclic compound. Among them, quinoline/quinolone and their derivatives have diverse biological significance and are reported to possess anticancer [33], antimalarial [33,34], antihypertensive [35], anti-inflammatory [36,44], antibiotic [34,37], anti-HIV [38], antitubercular [39], anti-cardiovascular [40], analgesic [41], Alzheimer [42], antileishmanial[43], and tyrosine kinase inhibition [45] properties. Quinolones are also known for other treatments such as prostatitis[46], gastroenteritis [47], respiratory diseases [48], skin infection [49] and sexually transmitted diseases [50]. Quinolones are also already available in the medical world as an antibiotic against various bacterial infections, such as ofloxacin, norfloxacin, ciprofloxacin, sparfloxacin, etc [51,52]. This review represents the detailed SAR of potential antibacterial activity counter to pathogens of quinoline-based analogs to get insight into the development of potent antibacterial agents.

2. Quinoline-based derivatives showed potential antibacterial activities

There is always a need for novel antibiotics since many bacterial strains have already generated resistance against antibiotics.

2.1. Benzoindoloquinoline derivatives

Benzoindoloquinoline derivatives were synthesized by Ning Sun and co-workers for their antibacterial activity against *S. aureus* and *E. faecium* pathogens. All the compounds showed excellent activity compared to berberine and were moderately active compared to methicillin and vancomycin with a value of MIC 4–64 μg/ml, Fig. 3**.** Compounds **(1)a, (1)b** and **(1)c** showed potent activity compared to methicillin against *E. faecium* ATCC 700,221. The SAR envisioned that benzoindoloquinoline moiety would have better activity as compared to benzofuroquinoline. Substitution on the phenyl ring is required for biological evaluation. Substitution at R_1 by

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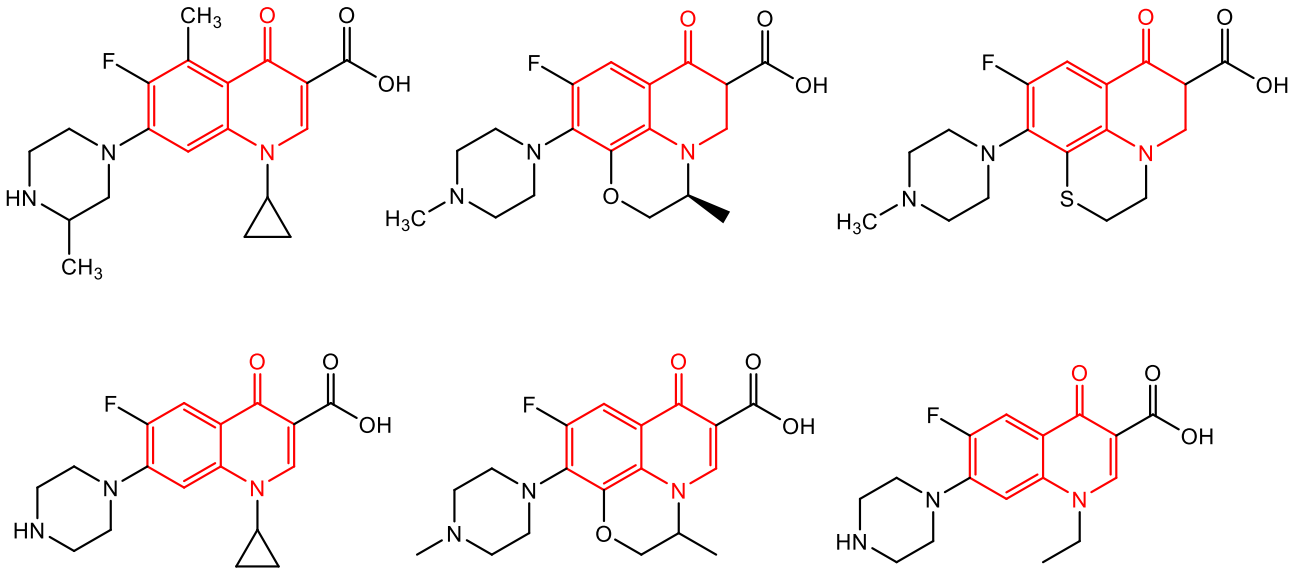


Fig. 1. Structures of the standard 4-quinolones as antibiotics.

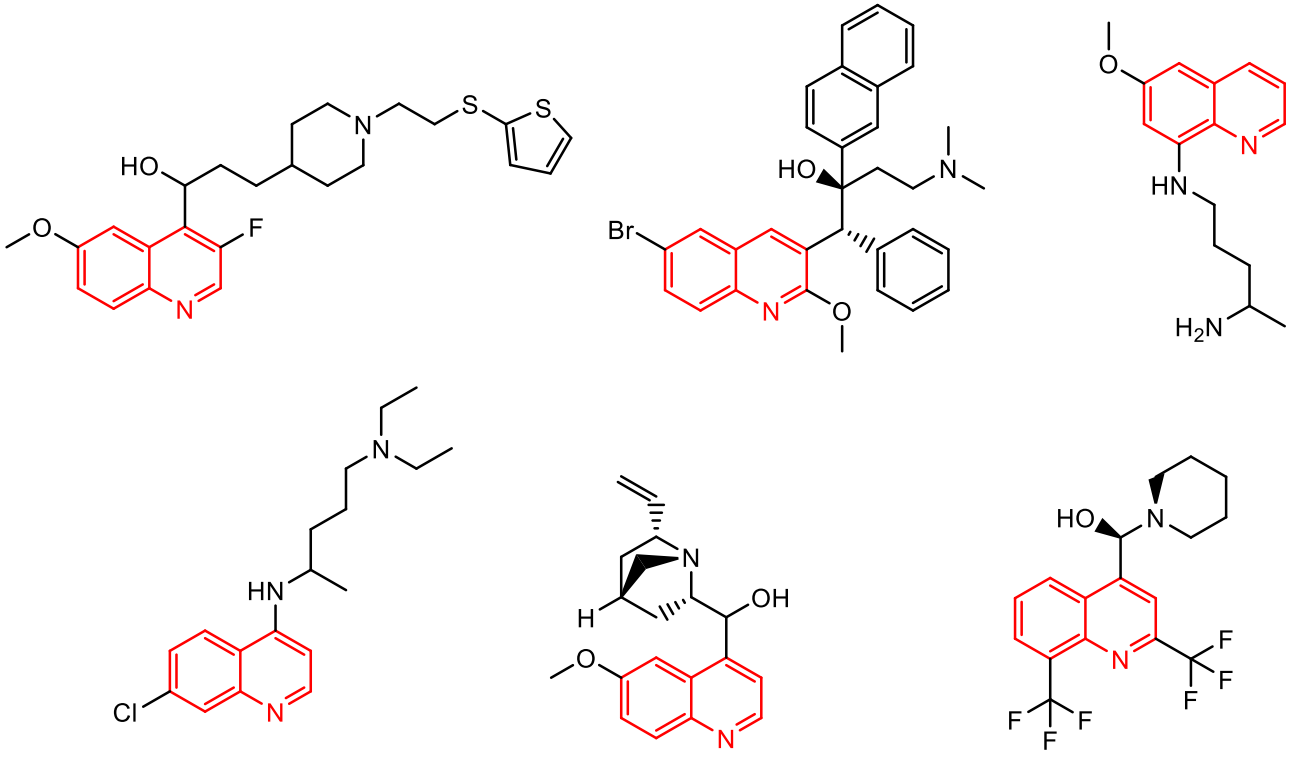


Fig. 2. Structures of quinoline based antibacterial agents.

OCH_3, OC_2H_5 and -OCF_3 enhances the antibacterial properties. In contrast, R_1 is replaced by H and CH_3 (MIC: 8 μg/ml against *E. faecium* ATCC 700,221 and 6 μg/ml against *S. aureus* ATCC BAA41) which reduces activity. These results suggested that H and CH_3 substitution at R_1 were unfavorable for improved activity. Substitution of benzofuran was inauspicious to amplify the activity instead of indole, Table 1 [53]. To recognize potential binding affinity, molecular modeling was used which is bind near the T7-loop. Benzoindoloquinolines docked with FtsZ protein WITH PDB ID: 4DXD. **(1)b** interacted with Thr309 amino acid *via* H-bonding with the carbonyl and other interactions hydrophobic side chains of Asp199, Leu200, Val297 and Val307 as per docking prediction.

2.2. Indolylquinolinium derivatives

Indolylquinolinium derivatives screened for their antibacterial activity against Gram-positive and Gram-negative bacteria were synthesized by Senyuan et al. All the hybrids showed moderate to good activity with MIC from 1.0 to 64 μg/ml against Gram-negative bacteria, Fig. 4. The SAR analysis revealed that substitution of diamine and -H to the quinoline ring at R_1 diminishes the activity, whereas substitutions on indole favor the activity. Unsubstituted compound displayed relatively weak antibacterial potency against all the strains. Piperidine substituted analog **(3)** showed remarkable activity against *S. aureus* (MIC: 1.0 μg/ml) on

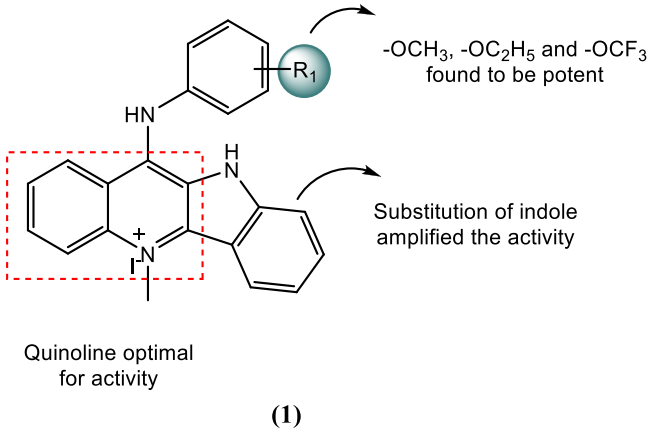


Fig. 3. Graphical SAR of benzoindoloquinoline as an antibacterial agent.

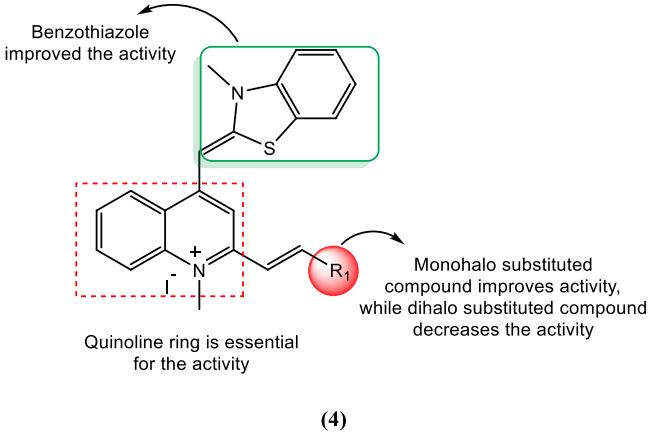


Fig. 5. Graphical SAR of benzothiazole quinolinium salt as an antibacterial agent.

Table 1
Potent antibacterial benzoindoloquinoline hybrids.

Compound	R_1	Antibacterial activity (MIC: μg/ml)		
		S. aureus ATCC BAA41	*E. faecium* ATCC 49,624	*E. faecium* ATCC 700,221
(1)a	OC_2H_5	2	4	4
(1)b	OCH_3	2	4	4
(1)c	OCF_3	2	4	4
Methicillin		>192	4	6
Vancomycin		2	2	>64

par with a reference drug. Piperidine substituted 1-methyl quinolinium compounds had stronger potency than ethylamine substituted compounds, Table 2 [54]**.** Molecular docking of compound **(2)b** was performed with FtsZ protein (PDB ID: 4DXD). Compound **(2)b** binds to a four-stranded β-sheet a hydrophobic and narrow cleft constituted by the H7-helix and T7-loop shows hydrophobic interactions with Gln192, Gly196, Leu200, Val203, Leu209, Met226, Gly227, Ile 228, and Val297. Two carbon-hydrogen bond interactions with Leu200 and Val203 amino acid.

2.3. Benzothiazolequinolinium derivatives

Sun et al. synthesized a series of benzothiazole substituted quinoline derivatives and analyzed their antibacterial activity with MIC of 1.5–64 μg/ml. Some of them were most powerful than the reference drugs, Fig. 5. The SAR study indicated that the compounds were found to be more active than Berberine against all bacteria. Substitution at R_1 has a significant impact on activity. Dihalo substitutions were shown incredible antibacterial movementthan monohalo. Amongst benzothiazole substituted quinoline derivatives, **(4)a** was found to be more than 100-fold better activity, a great movement against *E. faecium, E. faecalis* and *E. coli* (MIC: 2.0 μg/ml) compared to a reference Methicillin drug. Compound **(4)b** can also effectively inhibit the growth of bacterial cells. Due to steric factor, substituent with increased molecular weight diminished the bacterial activity, Table 3 [55]. Molecular modeling of benzothiazolequinolinium derivatives were performed using Biovia Discovery studio. (PDB ID: 4DXD)**(4)a** docked with the active site of T7-loop and H7-helix of FtsZ protein shown hydrophobic interactions with Asp199, Leu200, Met226, Ile228, Val297, Thr309 and Ile311 residues.

2.4. Sulfur-bearing quinolinium derivatives

Empel and co-workers synthesized sulfur-containing quinolinium salts and inspected their antibacterial activity. Compounds with thiobenzyl and thiobenzoyl substitution are more effective than the reference drug, and the remaining hybrids showed low to moderate activity with 0.5–256 μg/ml MIC, Fig. 6. SAR perusal indicated that even though the benzyl group at R_1 position was potent against *E. faecalis, M. luteus* and *B. subtilis* pathogens with a 0.5 μg/ml MIC value, allyl groups at this position reduced activity. Introduction of thioalkyl substituent instead of alkyl amine amplified their antibacterial activity. Quinolinium bromine deriva-

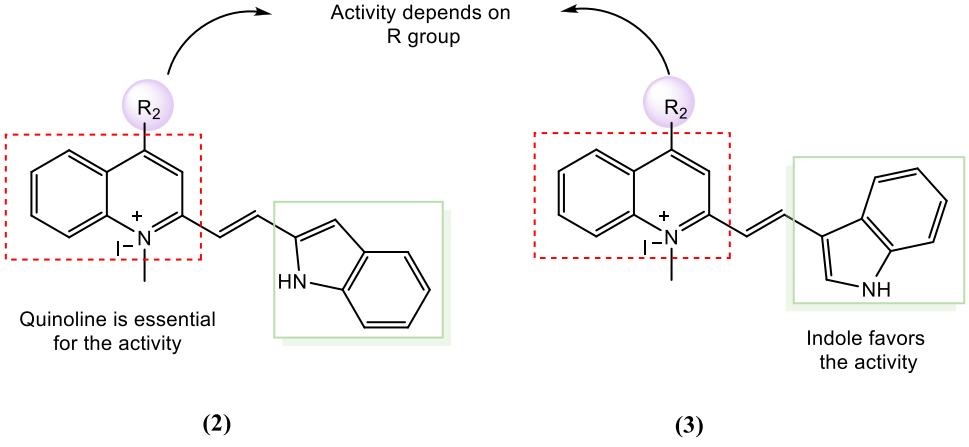


Fig. 4. Graphical SAR of Indolyl-quinolinium salt as an antibacterial agent.

Table 2
Potent antibacterial Indolylquinolinium hybrids.

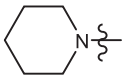
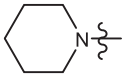
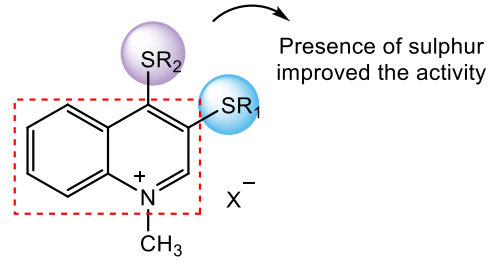
Compound	R_1	Antibacterial activity (MIC: μg/ml)			
		S. aureus ATCC 25,923	*S. aureus* ATCC 29,213	*S. aureus* ATCC BAA-41c	*S. aureus* ATCC 43,300
(2)a	H	32	32	32	64
(2)b		2	1	2	4
(3)c		1	1	2	2
Vancomycin		2	2	2	2

Table 3
Potent antibacterial benzothiazole quinolinium hybrids.

Compound	R_1	Antibacterial activity (MIC: μg/ml)		
		E. faecium ATCC 49,624	*E. faecalis* ATCC 29,212	*E. coli* ATCC 25,922
(4)a	4-F	2	2	3
(4)b	4-CH_3	4	4	3
(4)c	2,4-Cl	16	16	32
Vancomycin		2	>64	2
Methicillin		4	6	4
Berberine		>192	>192	>192



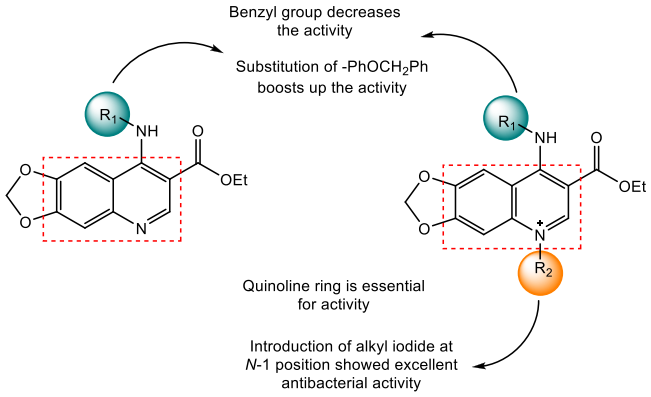
(5)

Fig. 6. Graphical SAR of sulfur-bearing quinoline as an antibacterial agent.

tives were found to be more active than quinolinium methyl sulfate derivatives. The outcome revealed that **(5)b** showed promising activity counter to *B. subtilis* with MIC 0.5 μg/ml closer to ciprofloxacin Table 4 [56].

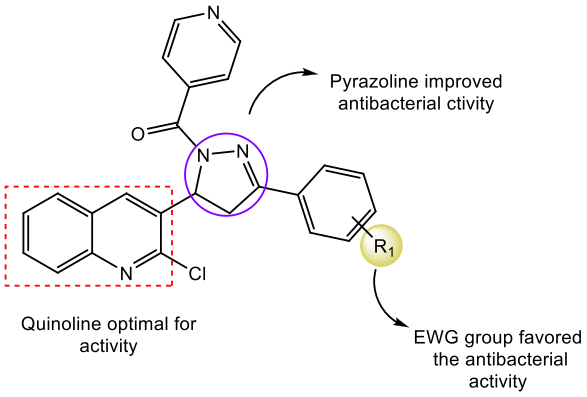
2.5. Benzodioxolequinoline derivatives

A few quinolinebenzodioxole were evaluated for their antibacterial activity against *E. coli* and *S. aureus* strain by Jin et al. All compounds persuaded moderate to excellent antibacterial activity with MIC 3.125–50 μg/ mL, Fig. 7. Compounds **(6)c** and **(6)d** were seen as intensely active against bacteria with an MIC of 3.125 μg/ml as reference. The SAR revealed that alkyliodine substituted quinolines had a stronger inhibition than the unsubstituted quinoline compound. Quaternary ammonium salt showed excellent activity against both strains while substitution of the benzyl group decreases the action, Table 5 [57]. Benzodioxolequinoline docked with *S. aureus* DNA gyrase protein. Quinoline ring of compound **6(d)** interact with DT8 of DNA gyrase protein (PDB ID:



(6)

Fig. 7. Graphical SAR of benzodioxolequinoline as an antibacterial agent.



(7)

Fig. 8. Graphical SAR of pyrazoline quinoline as an antibacterial agent.

2XCT) showed a free binding affinity of −9.2 kcal/mole mainly π-π interaction.

2.6. Pyrazoline-bearing quinoline derivatives

Pyridine and pyrazoline bearing quinoline derivatives were constructed and screened for their in vitro antibacterial activity against *S. aureus, S. pyogenes, E. coli* and *P. aeruginosa* pathogens by Desai et al. in 2016 Fig. 8. The SAR study argued that EWG (Cl, F and NO_2) at *para* position on the aryl ring highly improved antibacterial action against all Gram-positive and Gram-negative pathogens. At the same time, EDG reduces the activity. Results revealed that **(7)a** and **(7)c** showed promising activity

Table 4
Potent antibacterial sulfur derivatives of quinolinium salt.

Compound	R_1	R_2	X	Antibacterial activity (MIC: µg/ml)		
				E. faecalis	*M. luteus*	*B. subtilis*
(5)a	Benzyl	Butyl	Br	0.5	0.5	0.5
(5)b	Benzoyl	Butyl	Br	1.0	1.0	0.5
(5)c	Allyl	Benzyl	Cl	32	32	32
Ciprofloxacin				0.5	1.0	2.0

Table 5
Potent antibacterial benzodioxolequinoline hybrids.

Compound	R_1	R_2	Antibacterial activity (MIC: µg/ mL)	
			E. coli	*S. aureus*
(6)a	$-CH_2Ph$	–	> 50	> 50
(6)b	$-PhOCH_2Ph$	–	6.25	6.25
(6)c	$-PhOCH_2Ph$	$-CH_2CH_3$	3.125	3.125
(6)d	$-PhOCH_2Ph$	$-CH(CH_3)_2$	3.125	3.125
(6)e	$-CH_2Ph$	$-CH_2CH_3$	25	25
Amoxicillin			50	25
Ciprofloxacin			25	12.5

Table 6
Potent antibacterial pyrazoline bearing quinoline hybrids.

Compound	R_1	Antibacterial activity (MIC: µg/ml)			
		E. coli	*P. aeruginosa*	*S. aureus*	*S. pyogenes*
(7)a	4-Cl	12.5	50	250	100
(7)b	4-F	50	12.5	100	50
(7)c	$4-NO_2$	50	50	100	12.5
(7)d	$4-CH_3$	250	250	500	>1000
(7)f	$4-OCH_3$	>1000	500	1000	500
Ampicillin		100	100	250	100

Table 7
Potent antibacterial pyrazoline bearing quinoline hybrids.

Compound	R_1	Antibacterial activity (MIC: µg/ml)	
		E. coli	*P. aeruginosa*
(8)a	2-F	25	50
(8)b	$2-NO_2$	25	12.5
(8)c	$4-OCH_3$	1000	1000
(8)d	2-OH	250	500
Ciprofloxacin		25	25

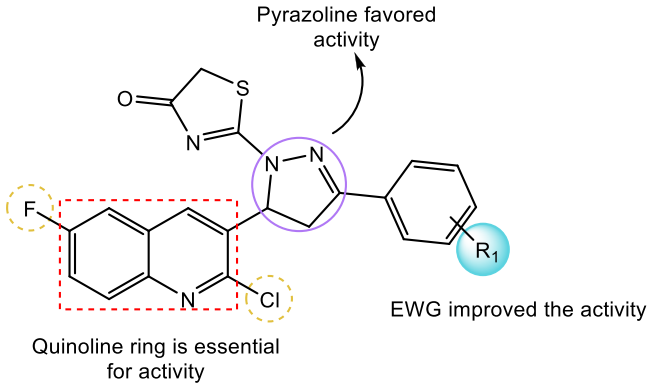


Fig. 9. Graphical SAR of pyrazoline quinoline as an antibacterial agent.

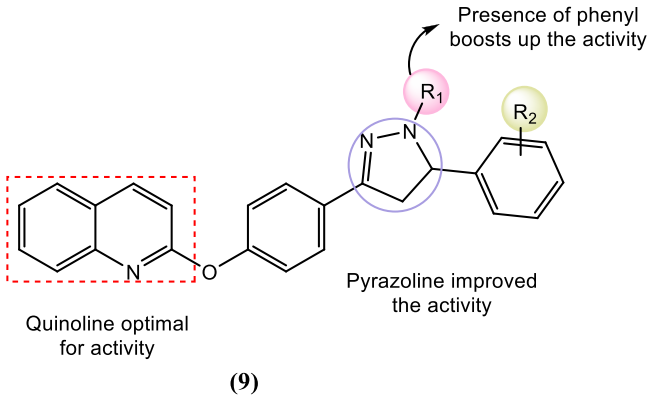


Fig. 10. Graphical SAR of pyrazoline quinoline as an antibacterial agent.

against *E. coli* and *S. pyogenes* bacteria respectively with 12.5 µg/ml MIC. By changing substitution from *para* to *meta* and *ortho*, compounds showed lower antibacterial potency. Unsubstituted quinoline derivative does not display antibacterial activity against all the organisms Table 6 [58].

A series of pyrazoline substituted quinoline derivatives were constructed and examined for their antibacterial activity by Desai and his research group in 2012, Fig. 9. The SAR prompted that the presence of EWG amplified the activity and the presence of EDG diminished the activity. Fluorine at the 2nd and 4th positions amplified the antibacterial activity. This is potentially due to the smaller size of fluorine providing stability and reducing the ring strain. *Ortho* substituted EWG-containing compounds showed promising activity than *meta*- and *para-substituted* EWG compounds. **(8)b** was found to have the most pronounced activity with 12.5 µg/ml MIC against *P. aeruginosa.* **(8)a** showed similar action as ciprofloxacin against *E. coli* with 25 µg/ml MIC, Table 7 [59].

Pyrazoline-bearing compounds were synthesized by Mohamed et al. and screened for their antibacterial activity showed ~ 8.7 to ~ 29 mm ZOI (Zone of inhibition) at concentration of 5 mg/mL against various Gram-positive and Gram-negative strains, Fig. 10. The SAR revealed that the presence of phenyl ring at R_1 in place of hydrogen improved antibacterial activity. Conversion of α,β-unsaturated ketone to pyrazoline moiety enhanced the antibac-

Table 8
Potent antibacterial pyrazoline bearing quinoline hybrids.

Compound	R_1	R_2	Antibacterial activity (MIC: µg/ml)		
			S. epidermidis	*P. vulgaris*	*S. flexneri*
(9)a	H	2-Cl	0.97	0.97	1.95
(9)b	Ph	4–OCH_3	0.24	9.9	0.48
Ampicillin			0.48	–	–
Gentamicin			–	1.95	0.24

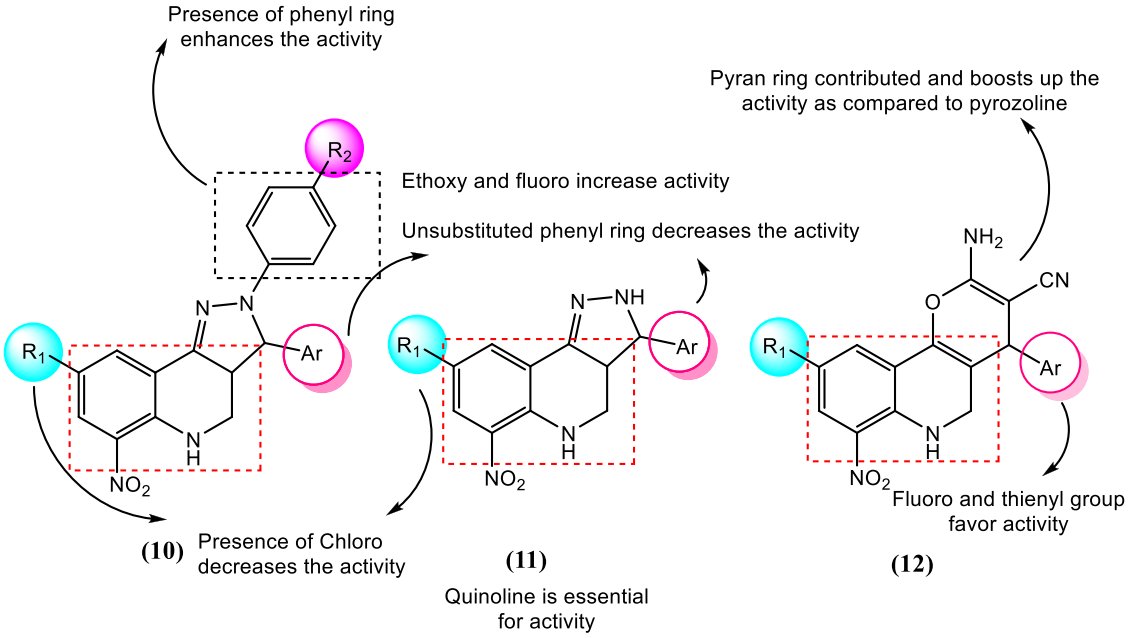


Fig. 11. Graphical SAR of pyrazole and pyrano quinoline as an antibacterial agent.

terial activity. *Para* substituted OCH_3 hybrid **(9)b** has remarkable activity against *S. epidermidis* as ampicillin with 0.24 µg/ml MIC, Table 8 [60].

2.7. Pyrazole and pyrano containing quinoline derivatives

Nitro substituted pyrazole and pyrano quinoline scaffolds developed for their antibacterial activity by Arasakumar et al. against *S. aureus, B. subtilis, E. coli* and *P. aeruginosa*. All compounds were moderately active against Gram-positive and Gram-negative bacteria with MIC value of 5–200 µg/ ml and ampicillin was used as a standard drug, Fig. 11. The SAR study signifies that 4-fluorophenyl on pyran ring has better activity than 4-fluorophenyl on pyrazole. 2-amino-3-cyanopyran compound with thiophene and halogenated aryl group at C-4 position exhibited significant antibacterial activity compared to pyrazolo compound. The presence of fluorine and pyran would be responsible to enhance the antibacterial activity. Unsubstituted phenyl rings diminished the activity Table 9. Due to presence of sulfur in thiophene compound **(12)a** showed excellent activity against all the bacterial strains. The activity order for substituent at 4th position of phenyl ring was *F* > Br > Cl > OCH_3 > CH_3 > H [61]. All 7-nitroquinolines docked with epidermal growth factor receptor (PDB ID: 1M17). Favorable interactions of compound **(12)c** with the active center of EGF receptor shows two hydrogen bond interactions with Glu738 and Arg817 residues.

2.8. Thiazolidinone quinoline derivatives

Sulfur-containing quinoline derivatives have been designed and investigated by Umamatheswari against *S. pneumoniae, B. subtil, C. tetani, E. coli, S. typhi* and *V. cholera* strains established to have 15.6 to 500 µg/ml MIC value, Fig. 12. The SAR study revealed that *para*-substituted halogen-containing compounds showed potent antibacterial activity. Due to the presence of CF_3, compound **(13)** showed better activity than compounds **(14)** and **(15)**. EDG-containing compounds displayed lower potency than EWG containing compound. Fluoro substituted **(13)a** compound has shown excellent activity against *B. Subtilis* and *C. Tetani* (MIC: 31.25 µg/ml & 15.26 µg/ml respectively) as ampicillin and norfloxacin. It also signifies that with increase in the number of alkyl chains, activity decreases, Table 10 [62].

2.9. Thiazolidinone containing quinazolinone derivatives

6-Methylquinoline-based quinazolinone-4- thiazolidinone derivatives were structured by Desai and his group and evaluated for their antibacterial activity against *S. aureus, S. pyogenes, E. coli* and *P. aeruginosa* showed low to moderate activity with MIC 25–1000 µg/ml, Fig. 13. The SAR study revealed that EDG substituted analogs showed better activity than EWG-containing analogs. The presence of thiazolidinone responsible for enhancement of antibacterial activity. 2-OH and 3-OH substituted compounds showed potent activity against *E. coli 0*and *S. aureus* strain with (~50 µg/ml and ~25 µg/ml MIC respectively), Table 11 [63].

Quinoline-based quinazolinone-4- thiazolidinone derivatives synthesized by Desai et al. in 2011 showed moderate bacterial activity against Gram-positive and Gram-negative bacteria, Fig. 14. EDG containing compounds had a stronger antibacterial potency than EWG containing compounds. *Para* chlorophenyl derivative was seen as potent against *P. aeruginosa* strain with ~25 µg/ml MIC. *Para*

Table 9
Potent antibacterial nitro substituted pyrazole and pyrano quinoline hybrids.

Compound	R_1	R_2	Ar	Antibacterial activity (MIC: µg/ mL)			
				S. aureus	*B. subtilis*	*E. coli*	*P. aeruginosa*
(10)a	H	H	C_6H_5	60	60	60	150
(10)b	H	H	2,4-Di $OCH_2CH_3C_6H_3$	10	7.5	34	55.5
(10)c	H	H	4-FC_6H_4	10	12.5	17	55.5
(10)d	Cl	OCH_3	4-ClC_6H_4	50	50	80.5	100
(11)a	Cl	–	4-FC_6H_4	50	50	80.5	200
(11)B	Cl	–	4-ClC_6H_4	17.5	17.5	25.5	55.5
(12)a	H	–	2-thienyl	5	5	17	37
(12)b	H	–	4-FC_6H_4	5	7.5	17	37
(12)c	H	–	4-$OCH_3C_6H_4$	10	12.5	17	37
Ampicillin				2.5	2.5	8.5	18.5

Table 10
Potent antibacterial thiazinanone substituted quinoline hybrids.

Compound	N	R_1	Antibacterial activity (MIC: µg/ml)	
			B. subtilis	*C. tetani*
(13)a	–	F	31.25	15.6
(13)b	–	Br	62.5	31.25
(14)a	2	F	62.5	15.6
(14)b	2	Br	31.25	31.25
(14)c	3	F	62.5	100
(14)d	3	Br	62.5	100
(14)e	4	F	100	125
(14)f	4	Br	100	250
Norfloxacin			100	50

Table 11
Potent antibacterial quinoline based quinazolinone-4- thiazolidinone hybrids.

Compound	R_1	Antibacterial activity (MIC: µg/ml)			
		E. coli	*P. aeruginosa*	*S. aureus*	*S. pyogenes*
(15)a	3-OH	~25	~50	~100	~100
(15)b	2-OH	~100	~500	~50	~500
(15)c	4–OCH_3	~500	~50	~500	~100
(15)d	−3,4,5-$(OCH_3)_3$	~62.5	~500	~100	~500
Ampicillin		~100	~100	~250	~100

Table 12
Potent antibacterial quinoline based quinazolinone-4- thiazolidinone hybrids.

Compound	R_1	Antibacterial activity (MIC: µg/ml)	
		E. coli	*P. aeruginosa*
(16)a	4-Cl	~150	~25
(16)b	4-OH	~50	~200
(16)c	4-CH_3	~500	~50
Ampicillin		~100	~100

Table 13
Potent antibacterial oxadiazole and azetidinone bearing quinoline hybrids.

Compound	R_1	Antibacterial activity (MIC: µg/ml)		
		P. aeruginosa	*S. pyogenes*	*S. aureus*
(17)a	4-Cl	~50	~25	~100
(17)b	3-Cl	~500	~200	~50
(17)c	4-NO_2	~100	~100	~50
Ampicillin		~100	~100	~250

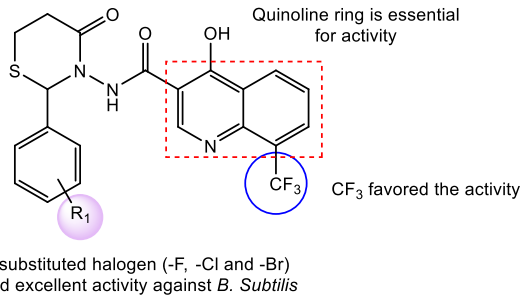
hydroxy and *para* methyl-substituted hybrids also showed better activity against *E. coli* and *P. aeruginosa* pathogens with MIC: ~ 50 µg/ml, Table 12 [64].

2.10. Oxadiazole and azetidinone quinoline derivatives

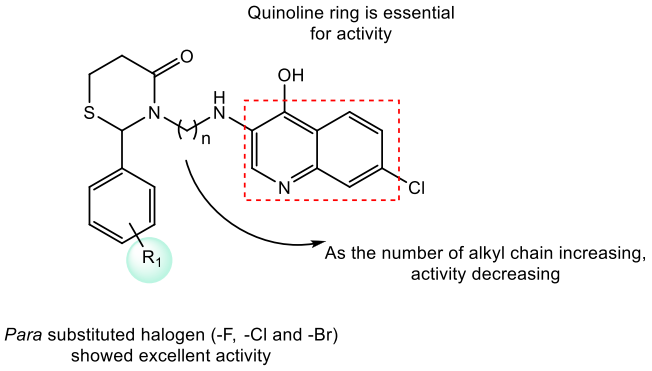
Oxadiazole and azetidinone bearing quinoline derivatives were also designed and developed by Desai and co-workers in 2011. All derivatives were screened for their antibacterial activity against Gram-positive and Gram-negative bacteria with MIC 50–1000 µg/ml, Fig. 15. The SAR persuaded that *para*-substituted chloro analog **(17)a** showed excellent antibacterial activity against *P. aeruginosa* and *S. pyogenes* with ~ 50 µg/ml and ~ 25 µg/ml MIC value respectively and also m*eta* substituted chloro and *para*-substituted nitro compound showed potent activity against *S. aureus*, Table 13 [65].

2.11. Oxadiazolylquinoline derivatives

Oxadiazolylquinoline derivatives were synthesized by Salahuddin et al. and screened for their antibacterial activity, Fig. 16. The SAR study indicated that EWG-containing compounds showed better activity than EDG. 2–chloro quinoline has a great impact to increase the bacterial activity. Benzimidazole possessing 1,3,4-oxadiazole had better activity than 1,3,4-oxadiazole moiety. Nitro substituted compounds **(18)a** and **(18)b** were found to be equipotent as ciprofloxacin against *K. pneumonia* and *B. cereus* strains, Table 14**.** The presence of EWG favors the activity [66].

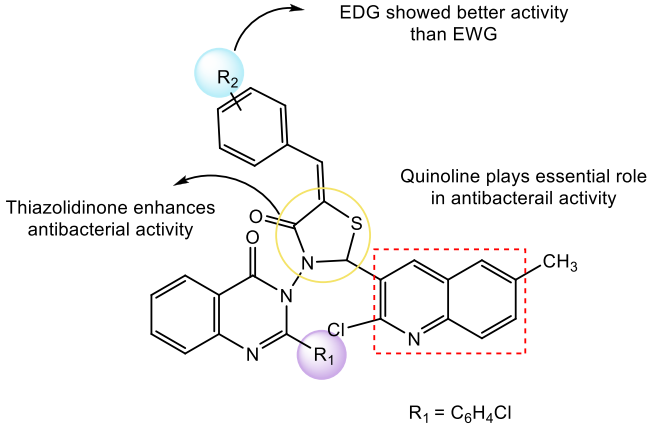


(13)



(14)

Fig. 12. Graphical SAR of thiazolidinone quinoline as an antibacterial agent.

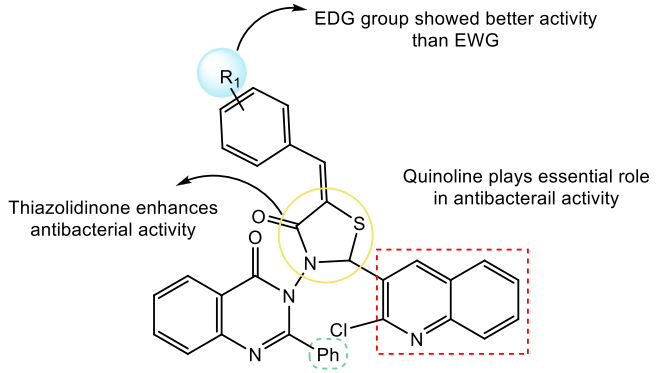


(15)

Fig. 13. Graphical SAR of quinazolinone-4-thiazolidinone as an antibacterial agent.

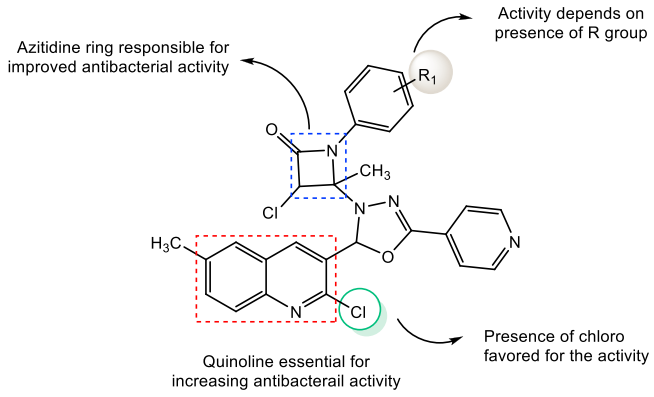
2.12. Sulfur-containing quinoline derivatives

Sulfur-containing derivatives were synthesized by El-Shershaby et al. and screened for their antibacterial activity with ZOI from ~13 to ~ 21 mm against *S. pneumonia, B. subtilis* and *E.coli* pathogens, Fig. 17. The SAR study demonstrated that mono substitution of chlorine on phenyl rings of the compounds had shown better activity than di substitution with chlorine. As the number of carbon increases in the spacer alkyl chain, activity diminishes. Position and type of substituent have an extraordinary impact on antibacterial movement. Except tribromo derivative, amide analogs along with EWG showed better activity than EDG. Regarding ester, acetate derivatives have a greater antibacterial influence than propionate derivatives. The compounds play a leading role in developing an antibacterial agent. R_1 is replaced by the methyl group,



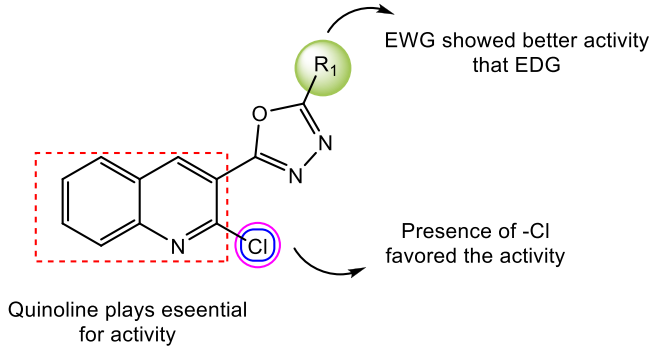
(16)

Fig. 14. Graphical SAR of quinazolinone-4-thiazolidinone as an antibacterial agent.



(17)

Fig. 15. Graphical SAR of oxadiazole and azetidinone quinoline as an antibacterial agent.



(18)

Fig. 16. Graphical SAR of Oxadiazolyl quinoline as an antibacterial agent.

Table 14
Potent antibacterial oxadiazolyl quinoline hybrids.

Compound	R_1	Antibacterial activity (MIC: µg/ml)	
		K. pneumonia	*B. cereus*
(18)a	4-Nitrophenyl	12.5	12.5
(18)b	3,5-Dinitrophenyl	12.5	12.5
(18)c	3,5-Dimethoxyphenyl	100	100
Ciprofloxacin		12.5	12.5

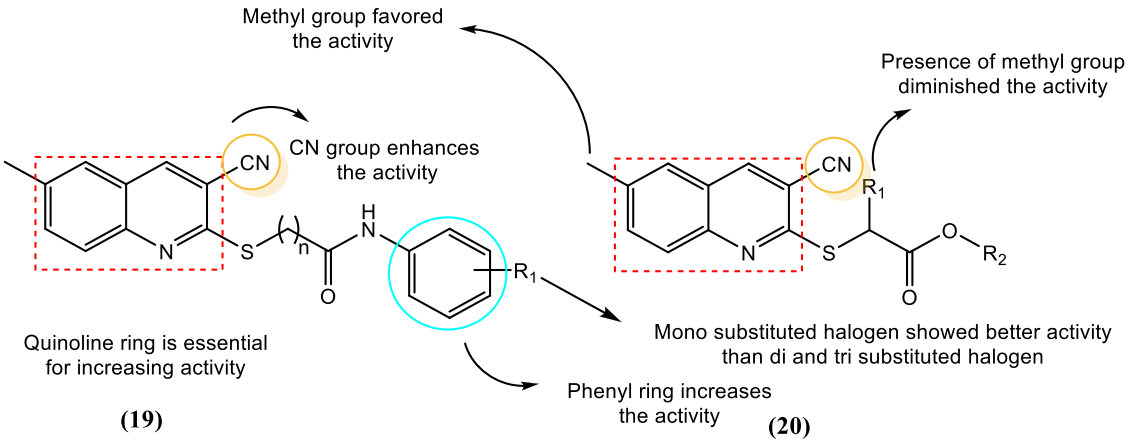


Fig. 17. Graphical SAR of sulfur containing quinoline as an antibacterial agent.

Table 15
Potent antibacterial sulfur bearing quinoline hybrids.

Compound	R_1	n	R_2	Antibacterial activityZOI (mm)		
				S. pneumonia	*B. subtilis*	*E. coli*
(19)a	3-CH_3	1	–	~17.4	~19.1	~15.2
(19)b	3-CH_3	2	–	~13.6	~15.2	~12.4
(19)c	4-Cl	1	–	~18.1	~20.2	~16.6
(19)d	2,6- Di Cl	1	–	~19.3	~20.8	~19.2
(20)a	H	–	C_2H_5	~15.7	~16.1	~15.2
(20)b	CH_3	–	C_2H_5	~18.3	~20.4	~17.5
Ampicillin				~23.8	~32.4	NT

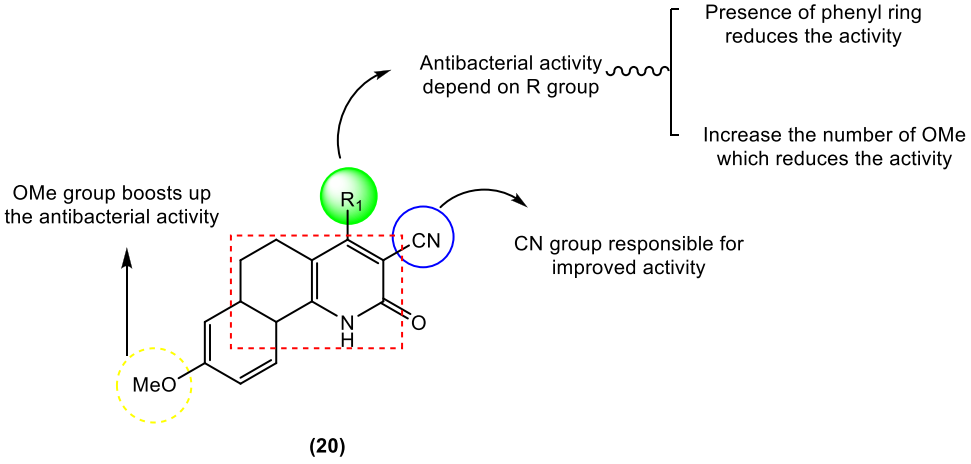


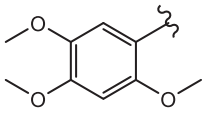
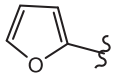
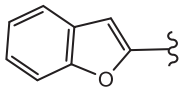
Fig. 18. Graphical SAR of quinoline-3-carbonitrile as an antibacterial agent.

reducing the activity, Table 15 [67]. All the compounds were individually docked with active sites of DNA gyrase protein (PDB ID: 4DUH). Compound **(19)d** showed the highest binding affinity value of −13.59 kcal/mol. The carbonyl oxygen of **(19)d** interacted with a hydrogen bond with Arg136 and another hydrogen bond interaction with a sulfur atom with Glu50 amino acid was also observed. Due to these interactions (19)**d** was potentially found to have remarkable antibacterial potency.

2.13. Quinoline-3-carbonitrile derivatives

Khan et al. have developed quinoline-3-carbonitrile derivatives and assessed them for their antibacterial activity against Gram-negative bacteria *S. aureus, S. pyogenes, E. coli* and *S. typhimurium* revealed 4–64 μg/ml MIC, Fig. 18. All compounds were moderately active. The SAR study demonstrated that activity of quinoline carbonitrile derivatives depend on R_1 group. Increasing number of methoxy group and presence of phenyl ring reduces the activity. Presence of cyano group favored for the activity. **(20)b** has shown better action than other compounds with 4 μg/ml MIC against *S. pyogenes, S. typhimurium* and *E. coli* strains which was more profoundly active than the standard, Table 16 [68]. Quinoline carbonitrile derivatives were docked with DNA gyrase protein (PDB ID: 1KZN). Compound **(20)b** showed the best binding affinity and most binding interactions, such as hydrogen bonding with GLU50, ASP73, and GLY77 residues. A strong hydrogen bond interaction with NH and C=O of the quinoline ring concludes its good antibacterial efficacy.

Table 16
Potent antibacterial quinoline-3-carbonitrile hybrids.

Compound	R_1	Antibacterial activity (MIC: µg/ml)			
		S. aureus	*S. pyogenes*	*S. typhimurium*	*E. coli*
(20)a		32	64	64	32
(20)b		8	4	4	4
(20)c		32	16	32	16
Ciprofloxacin		<1	2	<1	<1

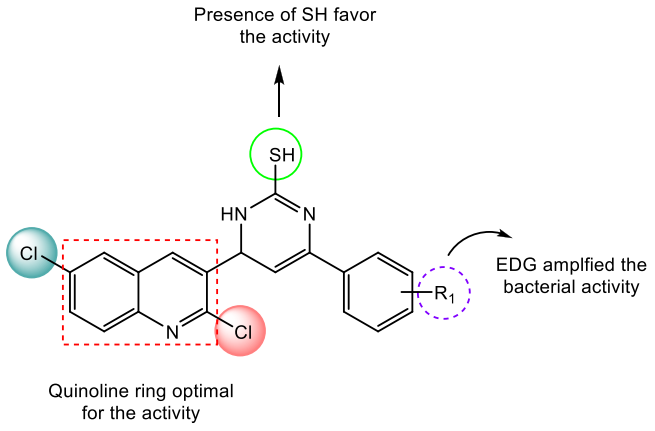


Fig. 19. Graphical SAR of pyrimidine substituted quinoline as an antibacterial agent.

Table 17
Potent antibacterial pyrimidine bearing quinoline hybrids.

Compound	R_1	Antibacterial activity (MIC: µg/ml)	
		S. aureus	*S. pyogenes*
(21)a	3–OCH_3	50	100
(21)b	4–OCH_3	12.5	25
(21)c	3-OH	100	100
(21)d	4-OH	25	12.5
(21)e	4-Cl	250	500
(21)f	3-F	125	250
Ciprofloxacin		50	50

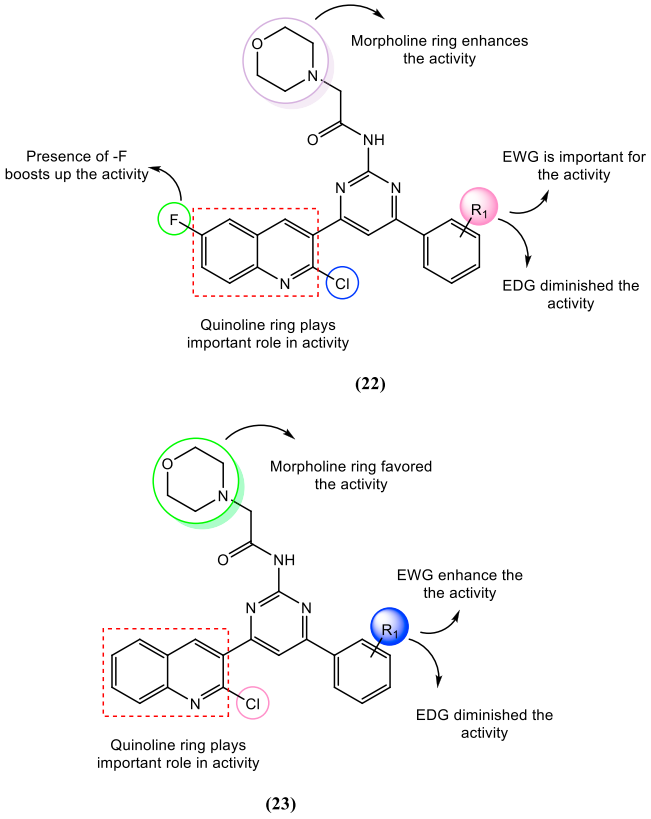


Fig. 20. Graphical SAR of morpholine containing quinoline as an antibacterial agent.

2.14. Pyrimidine-bearing quinoline derivatives

Desai and co-workers developed pyrimidine substituted quinoline and screened for their antibacterial activity against *S. aureus* and *S. pyogenes* pathogens with MIC values from 12.5 to 1000 µg/ml, Fig. 19. The SAR study revealed that EDG substituted quinoline showed more potent activity than EWG substituted quinoline. *Para* substituted EWG compounds showed better activity than the *meta* substituted compounds. **(21)b** and **(21)d** showed noticeable activity against *S. aureus* and *S. pyogenes*, Table 17 [69].

2.15. Morpholine-bearing quinoline derivatives

Morpholine-bearing quinoline hybrids showed potent antibacterial activity against *E. coli* and *P. aeruginosa* pathogens, Fig. 20. The SAR demonstrated that fluorine substitution at the position of R_1 plays a vital role in activity with 12.5 µg/ml MIC against *E. coli* as compared to ciprofloxacin. The activity was affected by different substitutions on the phenyl ring of pyrimidine moiety. The absence of fluorine in the quinoline ring slightly increases the activity against *E. coli* [70]. Antibacterial activity increased by the EWG substitution at the R_1 position, whereas it was reduced by the EDG, Table 18 [71]. Compounds **(22)a** and **(23)b** had stronger bacterial

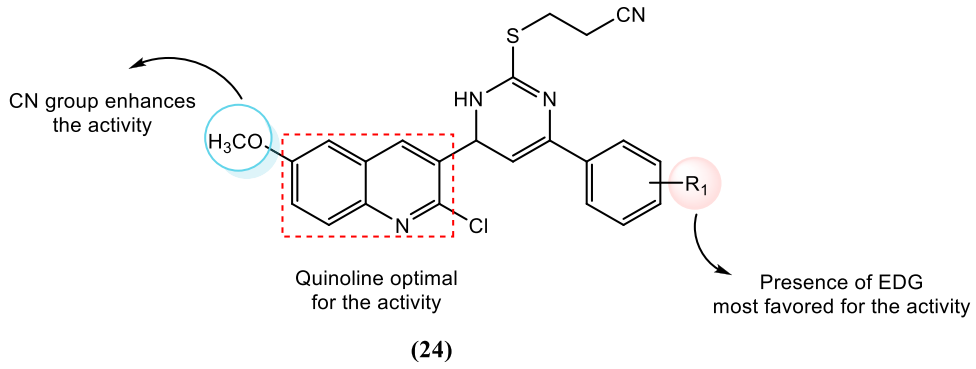


Fig. 21. Graphical SAR of sulfur-pyrimidine containing quinoline as an antibacterial agent.

Table 18
Potent antibacterial morpholine bearing quinoline hybrids.

Compound	R_1	Antibacterial activity (MIC: µg/ml)		
		E. coli	*P. aeruginosa*	*S. pyogenes*
(22)a	2-F	12.5	25	100
(22)b	4-NO_2	25	50	50
(22)c	4–OCH_3	500	250	1000
(23)a	2-F	25	250	100
(23)b	4-NO_2	12.5	50	12.5
(23)c	4–OCH_3	250	250	500
Ciprofloxacin		25	25	50
Ampicillin		100	100	100

Table 19
Potent antibacterial sulfur-pyrimidine bearing quinoline hybrids.

Compound	R_1	Antibacterial activity (MIC: µg/ml)			
		S. aureus	*S. pyogenes*	*E. coli*	*P. aeruginosa*
(24)a	4-OH	100	100	25	25
(24)b	4–OCH_3	25	25	12.5	12.5
(24)c	4-Cl	500	500	250	500
(24)d	4-NO_2	1000	>1000	1000	500
Ciprofloxacin		50	50	25	25

potency against organism. EWG on phenyl ring at *para* position showed maximum inhibition of bacterial strains.

2.16. Sulfur-pyrimidine containing quinoline derivatives

The dominant part of sulfur-pyrimidine containing quinoline derivatives were constructed for their antibacterial activity against Gram-positive and Gram-negative bacteria with 12.5–1000 µg/ml MIC, Fig. 21. The SAR revealed that antibacterial action increased by the presence of EDG at R_1 group. *Para* or *meta* substituted hydroxy and methoxy group on phenyl ring attached pyrimidine moiety had a stronger bacterial inhibition. Among them, compound **(24)b** exhibited significant activity with 12.5 µg/ml MIC against *E. coli* and *P. aeruginosa* than the reference drug(MIC: 12.5 µg/ml). The EWG on the phenyl ring showed the least antibacterial activity against all the tested bacterial strains while EDG on phenyl ring at *para* position responsible for improved antibacterial activity, Table 19 [72].

2.17. Phenoxy substituting quinoline derivatives

Quinoline derivatives were designed and developed by Alagumuthu et al. against *E. coli, P. aeruginosa, S. aureus* and *S. pyogenes*

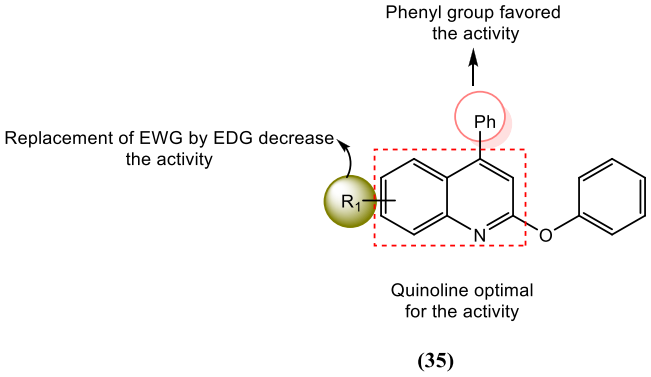


Fig. 22. Graphical SAR of phenoxy substituting quinoline as an antibacterial agent.

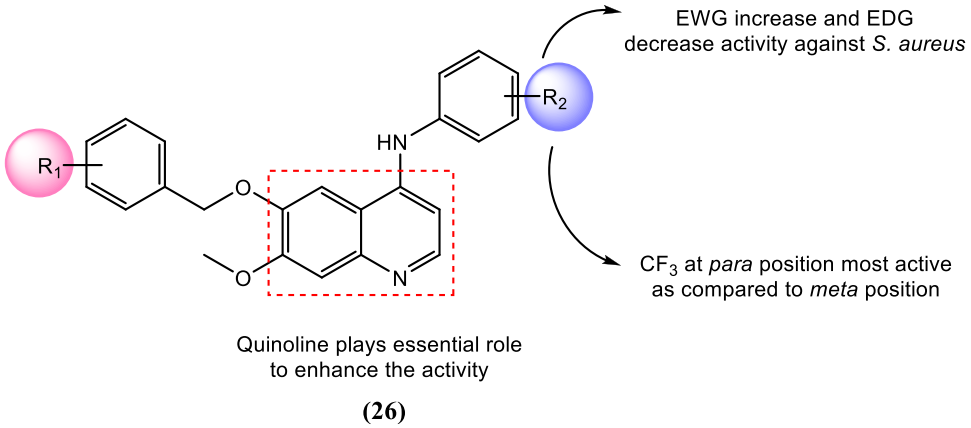
Table 20
Potent antibacterial 6-substituted phenoxy quinoline hybrids.

Compound	R_1	ZOI (mm) against *S. aureus*
(25)a	4-OH	~34.5
(25)b	4-OH, −3,5Cl	~38.48
(25)c	6,7-Di CH_3	~27.53
Ciprofloxacin		~26.36

with 7–38 µg/ml MIC, Fig. 22. The SAR study demonstrated that the presence of the hydroxyl group improves the activity, while compounds with methyl were weakly active because methyl is a deactivator. Replacement of EWG by EDG reduces the inhibitory activity. The presence of hydroxyl along with chlorine was seen to be significant antibacterial action. **(25)b** has remarkable activity against the *S. aureus* pathogen, Table 20 [73]. All analogs docked with DNA gyrase A (PDB ID: 2XCT) and DNA gyrase B (PBD ID: 3G75). Gyrase A protein showed favorable interactions instead of Gyrase B protein. **(25)c** exhibited an excellent binding affinity −19.06 kcal/mol.

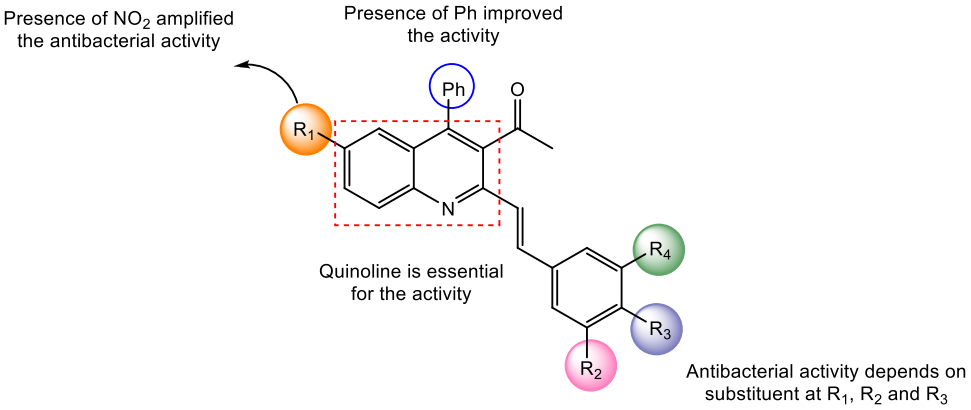
2.18. Facile accessible quinoline derivatives

Teng and co-workers have designed and synthesized a series of facile accessible quinoline derivatives, evaluated for their antibacterial activity against MRSA, VRE, *C. difficile* and MRSE with 0.75–12 µg/ml MIC value, Fig. 23. The SAR study showed that R_1 and R_2 positions have an extraordinary impact on the activity. Two -CH_3 groups at the *para* position reduced the activity while two -CF_3 at the *para* position enhanced the activity which was also more active than the compound with one CF_3 at *para* and another at *meta* position. Compound **(26)a** was recognized as the most potent inhibitor as compared to other analogs Table 21 [74].



(26)

Fig. 23. Graphical SAR of facile accessible quinoline as an antibacterial agent.



(27)

Fig. 24. Graphical SAR of styryl quinoline as an antibacterial agent.

Table 21
Potent antibacterial facile accessible quinoline hybrids.

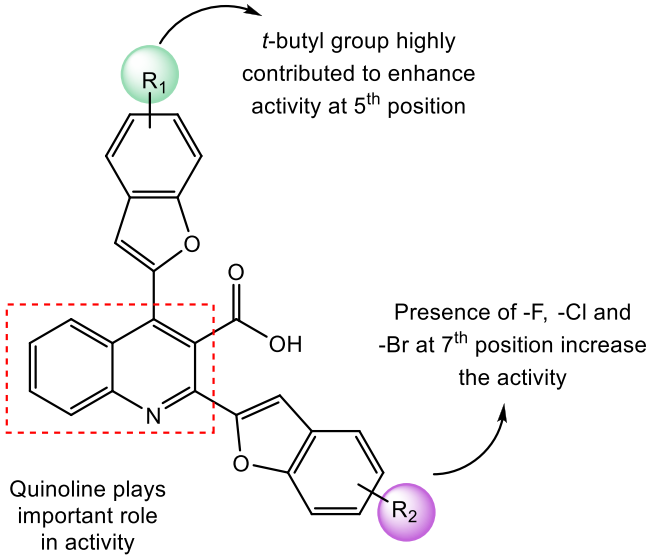
Compound	R_1	R_2	Antibacterial activity (MIC: µg/ml)		
			MRSA	MRSE	VRE
(26)a	4-CF_3	4-CF_3	0.75	3.0	0.75
(26)b	4-CH_3	4-CH_3	12.0	ND	ND
(26)c	4-CF_3	3-CF_3	3.0	6.0	3.0
Daptomycin			0.5	0.5	1.0

2.19. Styryl quinoline derivatives

Styryl quinoline derivatives were designed by Kamal et al. and screened for bacterial action against several strains, Fig. 24. The SAR study revealed that compounds **(27)a** and **(27)b** were found to be equipotent as ciprofloxacin against *M. luteus, K. planticola* and *S. aureus* with an 0.9 µg/ml MIC value. The presence of NO_2 in place of R_1 has promising effects on the antibacterial action.Similarly, OCF_3 and 3,4,5-trimethoxy groups on styryl benzene is necessary for the bacterial activity.While NO_2 present at R_3 diminished the activity, Table 22 [3].

2.20. Benzofuran substituting quinoline derivatives

Yang Li's research group has developed a series of furan substituted quinoline derivatives and evaluated them for the bacterial strains, Fig. 25. The SAR study prompted that presence of the *t*–butyl group has a great impact on the activity. Among them, fluoro substituted hybrids have shown better activity against bacterial pathogens. The presence of halogen (-F, Cl and -Br) at 7th position of benzofuran ring improved the antibacterial potency. Compound **(28)b** showed good activity against *S. aureus* with 31.25 µg/ml MIC.



(28)

Fig. 25. Graphical SAR of benzofuran substituted quinoline as an antibacterial agent.

Table 22
Potent antibacterial styryl quinoline hybrids.

Compound	R_1	R_2	R_3	R_4	Antibacterial activity (MIC: µg/ml)		
					M. luteus	*S. aureus*	*K. planticola*
(27)a	NO_2	H	OCF_3	H	0.9	1.9	0.9
(27)b	NO_2	OCH_3	OCH_3	OCH_3	1.9	0.9	31.2
(27)c	H	H	NO_2	H	>125	>125	>125
Ciprofloxacin					0.9	0.9	0.9

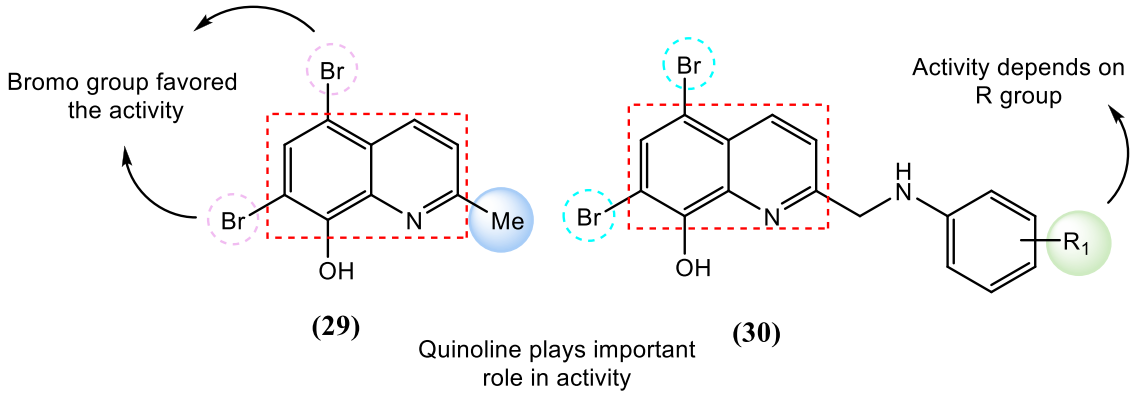


Fig. 26. Graphical SAR of halogenated quinoline as an antibacterial agent.

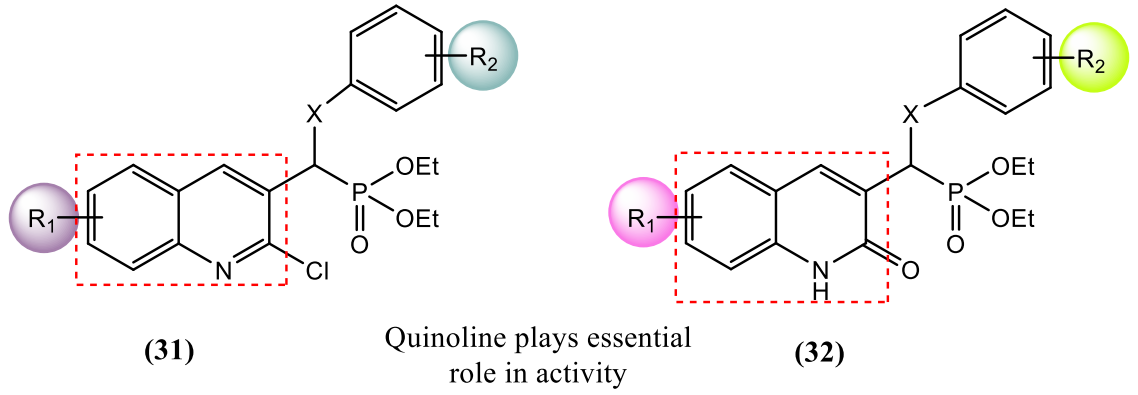


Fig. 27. Graphical SAR of sulfamidophosphonate and sulfonamidophosphate quinolone as an antibacterial agent.

Table 23
Potent antibacterial benzofuran substituted quinoline hybrids.

Compound	R_1	Antibacterial activity (MIC: µg/ml)
		S. aureus
(28)a	*t*–butyl 7-Br	125
(28)b	*t*–butyl 7-F	31.25
(28)c	5–OCH_3	125
(28)d	3-CH_3 5-Br	125
Ciprofloxacin		15.625

The *t*–butyl group replaced by H, diminished the antibacterial activity, Table 23 [75].

2.21. Halogenated quinoline derivatives

Halogenated quinoline derivatives were designed and developed by Akash and co-workers and evaluated for their antibacterial activity, Fig. 26. The SAR study showed that the unsubstituted broxyquinoline (12.5 µg/ml MIC) shows moderate activity compared to 2-methyl broxyquinoline (0.78 µg/ml MIC) against *S. aureus* and *S. epidermidis*. 2-methyl broxyquinoline **(29)** showed noticeable activity against MRSA, MRSE and VRE, which was profoundly active than reference.w. *Para* bromo substituted **(30)a** and unsubstituted phenyl ring **(30)d** showed marvelous activity against MRSE as compared to all drugs. EDG and EWG present in the compound diminished the activity, Table 24 [76].

2.22. Sulfamidophosphonate and sulfonamidophosphate quinolone derivatives

All sulfamidophosphonate and sulfonamidophosphate quinoline derivatives were synthesized by Bazine et al. and screened for their antibacterial activity against *E. coli, S. aureus* and *P. aeruginosa* strains with MIC of 0.125–512 µg/ml, Fig. 27. The SAR study demonstrated that sulfonamidophosphate quinoline derivatives have more potent activity than sulfamidophosphonate. Sulfamide ring with *ortho*-methoxy, *para*-bromo, *para*-fluoro, and *para*-methyl substituents had a stronger bacterial potency against all the pathogens. Compound **(31)a** and **(32)a** found to be the most prominent activity against all the pathogens, Table 25 [77].

Table 24
Potent antibacterial halogenated quinoline hybrids.

Compound	R_1	MRSA(MIC)	MRSE(MIC)	VRE(MIC)
(29)	–	0.78	0.39	2.35
(30)a	4-Br	3.13	0.15	0.78
(30)b	3,5-Di Br 4-Me	18.8	9.38	75
(30)c	3,5-Di Cl	1.56	0.30	0.39
(30)d	H	0.78	0.15	0.78
Vancomycin		0.59	0.78	>100
Daptomycin		4.69	12.5	–
Linezolid		3.13	3.13	3.13

Table 25
Potent antibacterial sulfamidophosphonate and sulfonamidophosphate quinolone hybrids.

Compound	R_1	R_2	X	Antibacterial activity (MIC: µg/ml)		
				E. coli	*S. aureus*	*P .aeruginosa*
(31)a	8-CH_3	4-Br	SO_2NH_2	0.125	0.25	0.5
(31)b	6- CH_3	4- CH_3	$SO_2N_2H_3$	128	256	–
(32)a	8- CH_3	2–OCH_3	SO_2NH_2	0.125	0.125	0.25
(32)b	8- CH_3	4- CH_3	$SO_2N_2H_3$	4	8	32

Table 26
Potent antibacterial acetohydrazide quinoline hybrids.

Compound	R_1	ZOI (mM)			
		E.coli	*P.aeruginosa*	*S.aureus*	*S.pyogenes*
(33)a	2,4-F	21	20	18	20
(33)b	3,4-F	20	19	18	19
(33)c	4-F	17	17	13	15
(33)d	3,4- OCH_3	11	10	7	11
Ampicillin		19	18	16	18

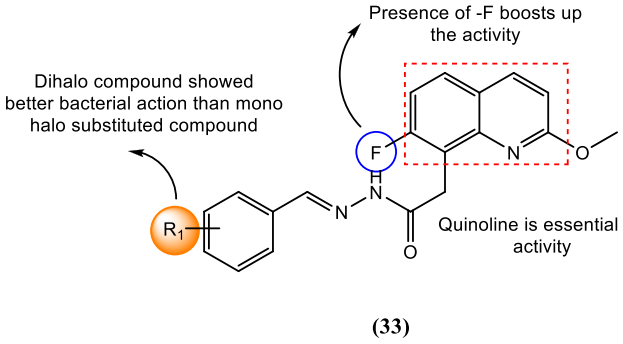


Fig. 28. Graphical SAR of acetohydrazide quinoline as an antibacterial agent.

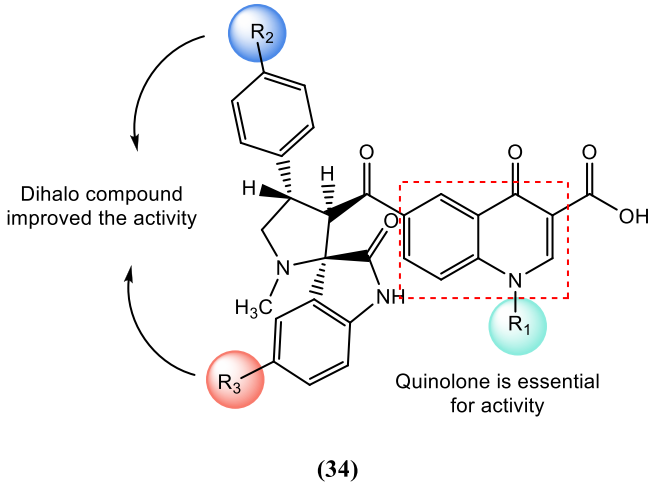


Fig. 29. Graphical SAR of spirooxindole-pyrrolidine quinolone as an antibacterial agent.

2.23. Acetohydrazide quinoline derivatives

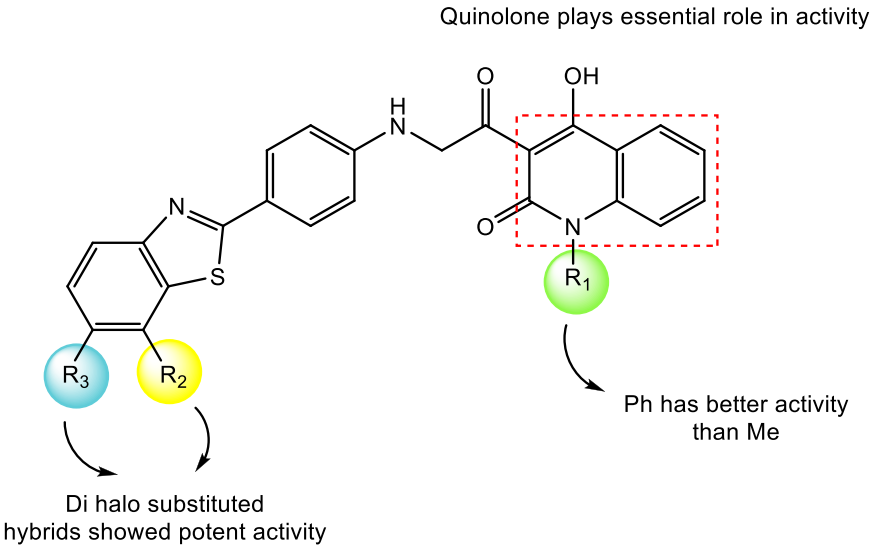
Acetohydrazide quinoline derivatives were designed and synthesized by Sridhar et al. and tested for their antibacterial activity with ZOI from 7 to 21 mm at a fixed concentration of 250 μg/mL separately for each bacterial strain., Fig. 28. The SAR study showed that compounds with 2,4-F and 3,4-F at R_1 in quinoline scaffolds would be an effective antibacterial agent with maximum ZOI compared to the standard drug ampicillin. F, OCF_3 and CF_3-containing compounds also showed good activity and EDG containing compounds showed moderate activity, Table 26 [78]. Acetohydrazidequinolines were docked with DNA gyrase A (PDB ID: 1ZI0) and gyrase B protein (PDB ID: 2ZJT). **(33)b** was observed to have −91.6 kcal/mol binding energy.

2.24. Spirooxindole-pyrrolidine quinolone derivatives

Because of their countless healing potential, Arasakumar and his research group designed spirooxindole-pyrrolidine substituted quinolone derivatives by 1,3-dipolar cycloaddition reaction and further screened for their antibacterial activity with MIC of 12.5–100 µg/ml, Fig. 29. The SAR study revealed that halogen at R_1 and R_2 has a great impact on antibacterial action. The dihalo-substituted compound showed better activity than the monohalo-substituted compound, while the unsubstituted compound reduces

Table 27
Potent antibacterial spirooxindole-pyrrolidine quinolone hybrids.

Compound	R_1	R_2	R_3	Antibacterial activity (MIC: µg/ml)		
				S. aureus	*B. subtilis*	*E. coli*
(34)a	H	F	Br	12.5	12.5	25
(34)b	Benzyl	Cl	Br	25	25	12.5
(34)c	Benzyl	OCH_3	NO_2	25	25	12.5
(34)d	H	F	NO_2	50	50	25
Ciprofloxacin				12.5	12.5	12.5



(35)

Fig. 30. Graphical SAR of benzothiazolyl quinolone as an antibacterial agent.

Table 28
Potent antibacterial benzothiazolyl quinolone hybrids.

Compound	R_1	R_2	R_3	Antibacterial activity (MIC: µg/ml)	
				E. coli	*P. aeruginosia*
(35)a	CH_3	F	Cl	0.5	2.0
(35)b	CH_3	Cl	Cl	0.5	0.5
(35)c	Ph	F	Cl	0.5	2.0
(35)d	Ph	Cl	H	2.0	2.0
(35)e	Ph	Cl	Cl	0.5	1.0
Ampicillin				0.5	0.5

the bacterial activity. Compound **(34)a** was recognized as a potent antibacterial agent counter to *S. aureus* and *B. subtilis* pathogen with 12.5 µg/ml MIC value, Table 27 [79].

2.25. Benzothiazolyl quinolone derivatives

Benzothiazolylquinolone derivatives were synthesized by Girish et al. and evaluated for their antibacterial activity with 0.5–128 µg/ml MIC, Fig. 30. The SAR study indicated that dihalo hybrids showed a greater impact on activity than monohalo hybrids. The equipotent antibacterial action of hybrid **(35)b** is observed with respect to the standard 0.5 µg/ml MIC against *E. coli* and *P. aeruginosia*, Table 28 [80]. In docking of Benzothiazolylquinolones with epidermal growth factor receptor (PDB ID: 1M17), compound **(35)e** displayed maximum hydrogen bond interactions with the surrounding amino acid residues of the active sites. The oxygen atom (4–hydroxyl group of 2-quinolone ring) exhibited three hydrogen bonding interactions with key amino acids such as Thr830, Asp831 and Asp831. The nitrogen atom on the 2-phenyl ring displayed two hydrogen bonding interactions with the OH group of Thr830 and Thr766 residues.

2.26. Biquinolone-isoniazid quinolone derivatives

Biquinolone-isoniazid hybrids were designed by Hardik and coworkers and screened for their antibacterial activity with 62.5–500 µg/ml MIC Fig. 31. The SAR study demonstrated that EWG or EDG at R_1, H or CH_3 at R_2 and different lipophilic group at R_3 play a vital role to enhance the antibacterial activity. It was seen that H or EDG at R_1 enhances the activity as compared to EWG. Substitution of Cl with OCH_3 auspicious for improved activity. Replacement of H with CH_3 at R_1 enhances and at R_2 reduces the antibacterial activity. Compound **(36)a** revealed that substituent at R_1 affects the antibacterial action showed excellent potency with 25 µg/ml MIC against *S. typhi* which is equipotent as ciprofloxacin, Table 29 [81].

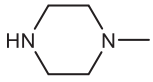
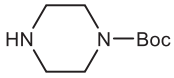
2.27. N-acyl substituting quinolone derivatives

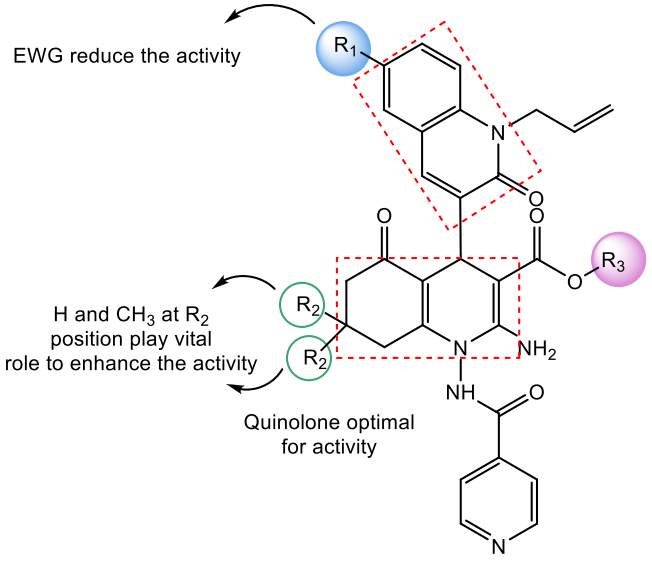
N-acyl-substituted quinolone derivatives were synthesized by Liu et al. and assessed for their antibacterial activity with MIC 8–256 µg/ml Fig. 32. The SAR study showed that the presence of aliphatic amine has better activity than the aromatic amine. Dipropylamine **(37)a** and diethylamine **(37)b** showed potent activity with 8.0 µg/ml MIC value against *S. aureus* and *E. coli* respectively. Compound with dibenzyl group had a lower potency than benzyl compound. Cyclic amine showed better activity than acyclic amine. **(37)c** and **(37)d** also showed good activity against Gram-negative bacteria, Table 30 [82].

Table 29
Potent antibacterial biquinolone-isoniazid quinolone hybrids.

Compound	R_1	R_2	R_3	Antibacterial activity (MIC: µg/ml)		
				B. subtilis	*E. coli*	*S. typhi*
(36)a	H	CH_3	*i*-pr	500	200	25
(36)b	OCH_3	H	CH_3	50	100	125
(36)c	Cl	H	CH_3	500	250	200
Ciprofloxacin				50	25	25
Chloramphenicol				50	50	50

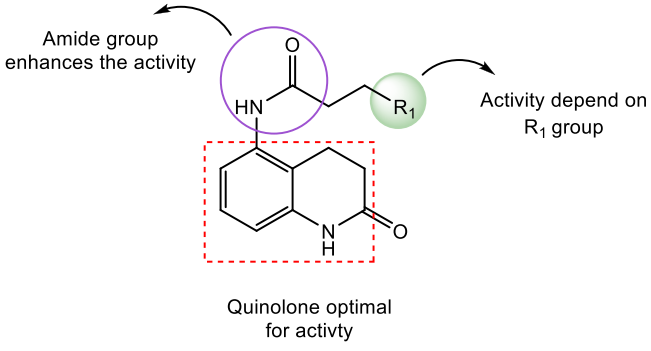
Table 30
Potent antibacterial acyl quinolone hybrids.

Compound	R_1	Antibacterial activity (MIC: µg/ml)			
		S.aureus	*B.subtilis*	*B.proteus*	*E .coli*
(37)a	$-N((CH_2)_2CH_3)_2$	8	64	256	64
(37)b	$-N(CH_2CH_3)_2$	128	32	256	8
(37)c		64	64	16	128
(37)d		64	32	128	16
Streptomycin		32	32	64	16



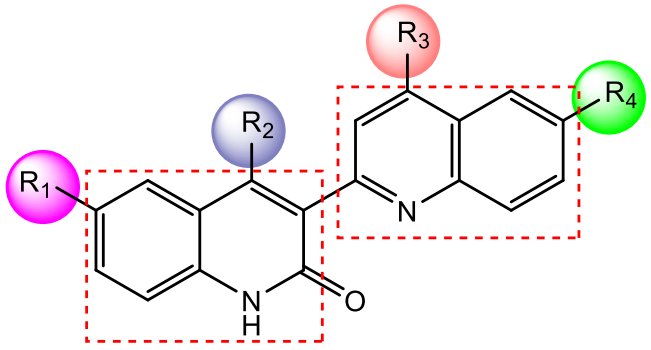
(36)

Fig. 31. Graphical SAR of biquinolone-isoniazid quinolone as an antibacterial agent.



(37)

Fig. 32. Graphical SAR of acyl quinolone as an antibacterial agent.



(38)

Fig. 33. Graphical SAR of quinolinyl quinolone as an antibacterial agent.

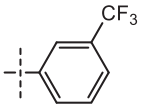
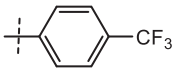
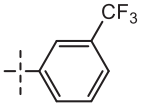
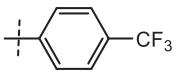
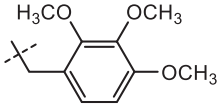
2.28. Quinolinylquinolinone derivatives

Subashini and co-workers developed quinolinylquinolinones by microwave-assisted reaction and evaluated their antibacterial activity. The range of MIC reported from 15.62 to 200 µg/ml, Fig. 33. Compounds **(38)b** and **(38)c** showed noticeable activity against the *E. coli* strain with 15.62 µg/ml MIC. The SAR recommended improvement of antibacterial action with different type of substitution on quinoline ring, so quinoline based derivatives is the hottest subject for the development of new novel antibacterial drug. The presence of chlorine at R_1 diminished the activity against *E.coli*

Table 31
Potent antibacterial quinolinyl quinolinones hybrids.

Compound	R_1	R_2	R_3	R_4	Antibacterial activity (MIC: µg/ml)	
					E. coli	*K.pneumonia*
(38)a	Cl	C_6H_5	H	CH_3	125	15.62
(38)b	H	CH_3	H	CH_3	15.62	31.25
(38)c	H	C_6H_5	H	C_6H_5	15.62	31.25
Ampicillin					31.25	31.25

Table 32
Potent antibacterial thiazole and oxazole-containing quinolone hybrids.

Compound	R_1	X	Antibacterial activity (MIC: µg/ml)			
			S. aureus	*B. cereus*	*P. aeruginosia*	*K. pneumonia*
(39)a		O	62.5	6.25	12.5	25
(39)b		O	25	6.25	12.5	25
(39)c		S	12.5	12.5	12.5	6.25
(39)d		S	6.25	25	6.25	6.25
(39)e		S	3.12	25	50	62.5
Ampicillin			12.5	12.5	25	25
Gentamicin			6.25	6.25	12.5	25

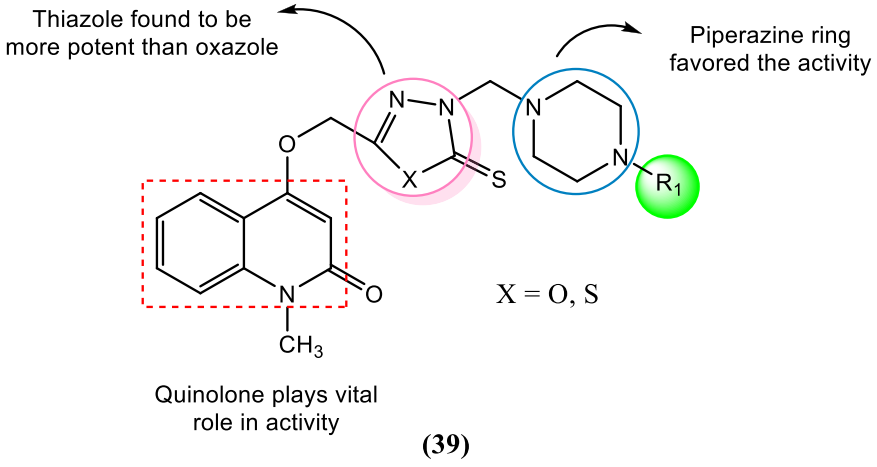


Fig. 34. Graphical SAR of thiazole and oxazole bearing quinolone as an antibacterial agent.

and contrarily enhanced the activity against *K. pneumonia*, Table 31 [83].

2.29. Thiazole and oxazole bearing quinolone derivatives

Thiazole and oxazole bearing quinolone derivatives were synthesized by Rahul et al. and tested for their antibacterial activity revealed to MIC from 3.12 to 200 µg/ml, Fig. 34. The SAR prompted that the thiazole-substituted hybrids were better antibacterial agents than the oxazole substituted hybrids. Compound **(39)e** showed excellent activity with 3.12 µg/ml against *S. aureus* than the standard drug. The presence of -CF_3 group on the piperazine ring is most favourable for the antibacterial movement against pathogens. In the comparison of thiazole and oxazole, thiazole has relatively stronger antibacterial activity than oxazole moiety. *Para* substituted CF_3 quinolone was found to be more active than *meta* substituted CF_3 quinolone, Table 32 [84].

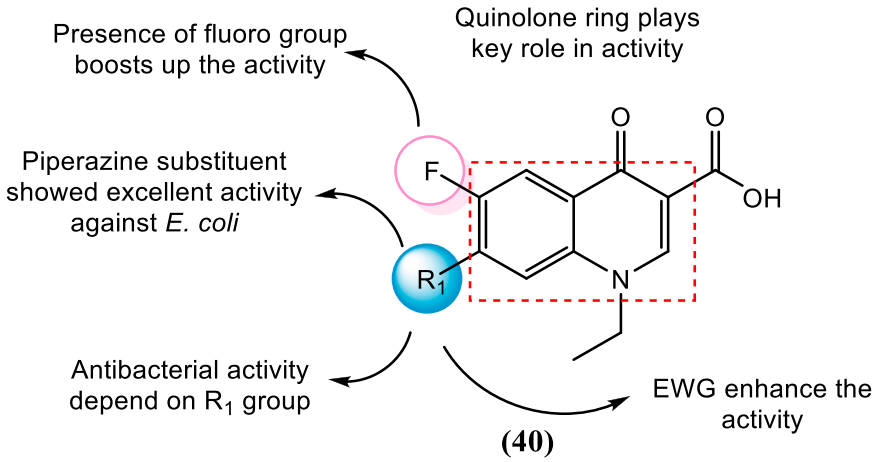


Fig. 35. Graphical SAR of fluoroquinolone as an antibacterial agent.

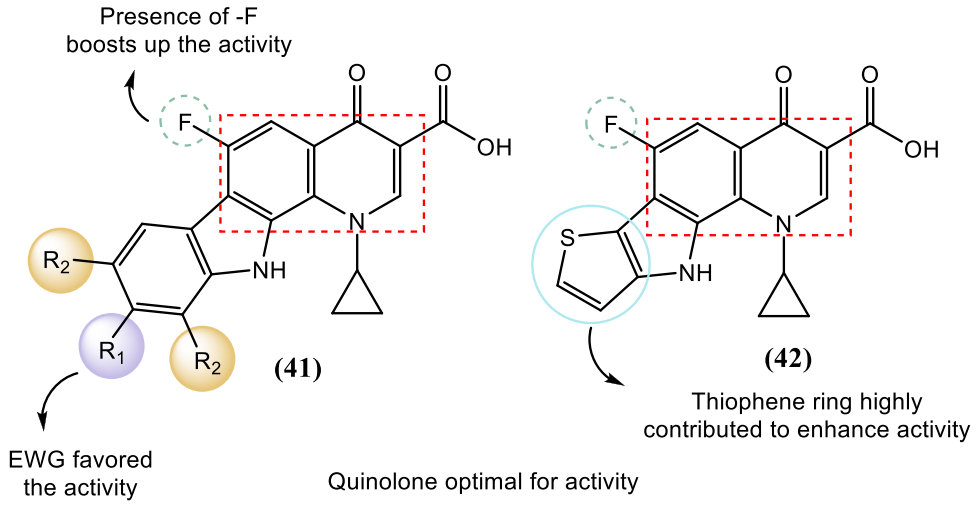


Fig. 36. Graphical SAR of fluoroquinolone as an antibacterial agent.

2.30. Fluoroquinolone derivatives

A progression of 7-substituted fluoroquinolone derivatives developed by Leyva-Ramos et al. and surveyed for their in vitro antibacterial action against *P. aeruginosa, E. coli* and *S. aureus* pathogens, Fig. 35. Fluoroquinolone derivatives revealed moderate to surprising antibacterial activity. The SAR study prompted that the piperazine-substituted **(40)a** hybrid has significant bacterial activity with 0.012 μg/ml against the *E. coli* strain. The presence of halogen or EWG at R_1 increases the antibacterial action. Acetyl piperazine had a better potency than piperazine moiety at R_1 the position of the fluoroquinolone molecule. While in the case of halogen (-F and -Cl), chlorine substituted compound showed better antibacterial action. Pyrimidine and triazole-containing compound showed poor bacterial inhibition than other compounds. Chlorine-bearing compound **(40)c** showed potent antibacterial activity than the standard against *S. aureus,* Table 33 [85,86].

Salah's research group designed a series of fluoroquinolone derivatives and studied their in vitro antibacterial activity and revealed the value of MIC extending from 0.003 to 100 μg/ml, Fig. 36. Compound **(42)** displayed promising activity against *B. subtilis, S. aureus* and *S. epidermidis* pathogens with 0.003 μg/ml, 0.03 μg/ml and 0.03 μg/ml respectively, better or comparable to all reference drugs. The SAR study demonstrated that the phenyl group replaced by thiophene played a crucial role in enhancing antibacterial activity. The presence of fluorine on the benzene ring of benzimidazole enhances the antibacterial activity. Benzimidazole substituted fluoroquinolone compound had a better inhibition than thienopyrrole substituted fluoroquinolone compound compared to standard drugs. Methyl and methoxy–bearing derivatives had a lower potency against bacterial strain than fluorine-bearing fluoroquinolone, Table 34 [87].

2.31. Piperazine-bearing fluoroquinolone derivatives

Rahul and his research group designed and developed piperazine-bearing fluoroquinolone derivatives and screened for their antibacterial activity against Gram-positive and Gram-negative bacteria. All fluoroquinolone derivatives were less active than ciprofloxacin against almost all the pathogens with 6.25–100 μg/ml MIC, Fig. 37. The SAR revealed that the *para*-substituted CF_3 group containing quinoline was more effective than a *meta*-substituted hybrid and a fluoro-containing hybrid. Fluoro-bearing quinoline showed excellent activity against bacterial pathogens with 6.25 μg/ml. CF_3 substituted at R_2 auspicious for antibacterial activity against Gram-positive bacteria, Table 35 [88].

Łukasz Szczupak et al. synthesized a series of fluoroquinolone derivatives and inspected their antibacterial activity. Their MIC ranges from 0.0001 to 50 μg/ml. Bacterial topoisomerase inhibitory activity of ciprofloxacin and generation of reactive oxygen species caused by the organometallic moiety are two modes of action which help to kill the bacteria. The outcome result revealed that

Table 33
Potent antibacterial 7-substituted-6-fluoroquinolone hybrids.

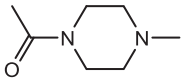
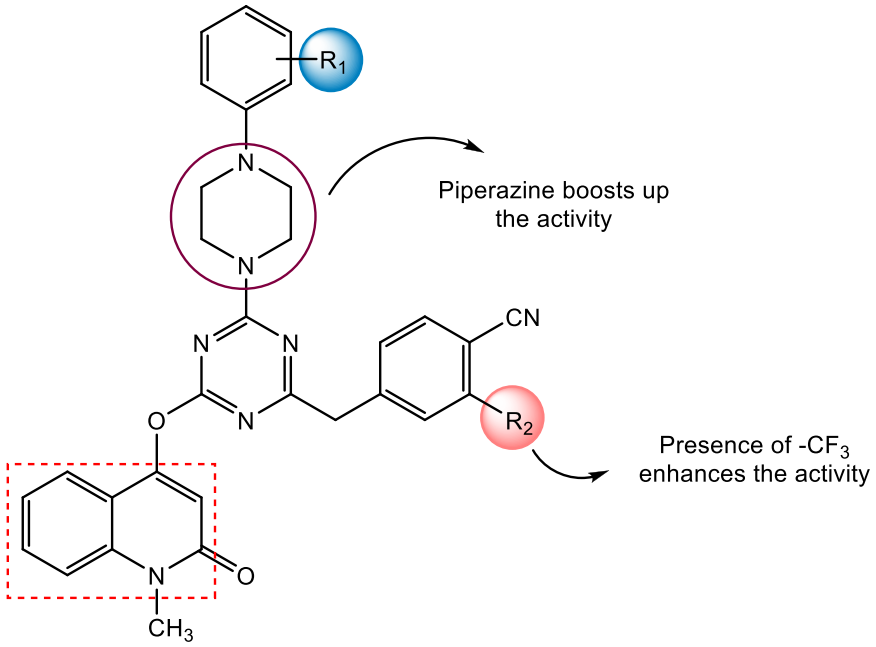
Compound	R_1	Antibacterial activity (MIC: µg/ml)		
		P. aeruginosa	*E. coli*	*S. aureus*
(41)a		>500	0.012	10.72
(41)b	F	138.5	24.64	369.1
(41)c	Cl	116.5	0.355	0.535
Norfloxacin		0.2	0.25	0.8

Table 34
Potent antibacterial fluoroquinolone hybrids.

Compound	R_1	R_2	Antibacterial activity (MIC: µg/ml)		
			B. subtilis	*S. aureus*	*S. epidermidis*
(41)	F	H	0.003	0.07	0.07
(42)	–	–	0.003	0.03	0.03
Ciprofloxacin			0.03	0.3	0.07
Levofloxacin			0.03	0.7	0.15
Moxifloxacin			0.015	0.03	0.07



(44)

Fig. 37. Graphical SAR of fluoroquinolone as an antibacterial agent.

Table 35
Potent antibacterial piperazine substituted fluoroquinolone hybrids.

Compound	R_1	R_2	Antibacterial activity (MIC: µg/ml)		
			S. aureus	*B. cereus*	*P. aeruginosia*
(43)a	4-F	H	100	100	6.25
(43)b	4-CF_3	H	6.25	12.5	12.5
(43)c	4-F	CF_3	100	12.5	6.25
(43)d	4-CF_3	CF_3	6.25	25	6.25
Ciprofloxacin			<3.12	<3.12	<3.12

N-alkyl ruthenocenyl **(46)b** and cymantrenyl **(46)c** conjugates of ciprofloxacin found to be most potent with MIC 0.0001 µM and 0.0006 µM respectively. These analogs could act as a perfectly beginning stage for development of new antibiotic. Compound **(45)** was found to be less active than compound **(46)** [89].

3. Summary and perspectives

Quinoline-based hybrids have a broad range of pharmacological and biological properties. Quinoline plays a crucial role in the

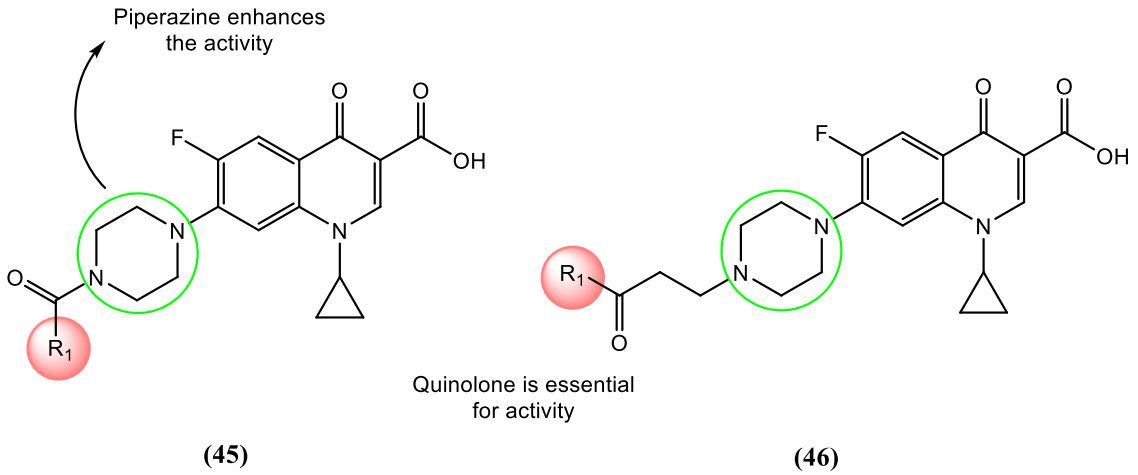
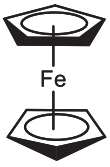
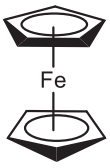
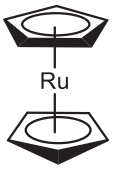
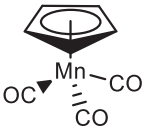


Fig. 38. Graphical SAR of piperazine bearing fluoroquinolone as an antibacterial agent.

Table 36
Potent antibacterial piperazine bearing fluoroquinolone hybrids.

Compound	R_1	Antibacterial activity(MIC: μM)		
		S. aureus	*K. pneumoniae*	*E. coli*
(45)a		6.2	NA	6.2
(46)a		3.1	0.2	0.08
(46)b		0.8	0.05	0.0006
(46)c		0.4	0.001	0.0001
Ciprofloxacin		0.8	0.05	0.01

development of new antibiotics. Some quinoline hybrids are even currently used in the treatment of bacterial infections. In this review, we have discussed quinoline-based hybrids which were designed, synthesized, and evaluated for their antibacterial activity against various types of Gram-positive, Gram-negative bacteria and multidrug-resistant microorganisms. The SAR studies revealed that the antimicrobial activity in heterocyclic class of quinoline molecule depends on the nature of the peripheral substituents and their spatial relationship. Further, the type of moiety and an EWG or EDG substitution on different moieties, plays an essential role in their efficacy against bacterial infections. The SAR provides a better perspective for synthesizing better bioactive quinoline analogs. This review anticipates that quinoline hybrids will play leading roles in the improvement of antibiotics in future.

Declaration of Competing Interest

The authors declare that they have no conflicts of interest.

Data availability

No data was used for the research described in the article.

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