Highlights on quinolonic compounds with changes on the basic structure as promising molecules to new drugs

Compostos quinolônicos com alterações na estrutura básica como moléculas promissoras para novos fármacos

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Ana Carolyne Sombra Nery
PhD student in Chemistry by Instituto Militar de Engenharia
Institution: Instituto Militar de Engenharia
Address: Praça General Tibúrcio, 80, Praia Vermelha, Urca, Rio de Janeiro - RJ
E-mail: ana_nery@id.uff.br

Kátia Regina de Souza
PhD in Sciences by Universidade Federal do Rio de Janeiro
Institution: Instituto Militar de Engenharia
Address: Praça General Tibúrcio, 80, Praia Vermelha, Urca, Rio de Janeiro - RJ
E-mail: katia.souza@ime.eb.br

Jorge Luiz de Oliveira Domingos
PhD in Sciences by Universidade Federal do Rio de Janeiro
Institution: Universidade do Estado do Rio de Janeiro
Address: Rua São Francisco Xavier, 524, Maracanã, Rio de Janeiro - RJ
E-mail: jlo.domingos@gmail.com

ABSTRACT
The introduction of quinolonic antimicrobials on the market caused a revolution in antibacterial therapy. 4-quinolone skeleton became the target of many studies of structure-activity relationship establishing the parameters considered optimal for the development of new quinolonic antibiotics. These parameters limited the development of new compounds, so it is possible finding compounds with changes in the same position with similar substituents. The purpose of this article is to identify quinolonic compounds which do not fit into one or more criteria determined as ideal in the structure-activity relationship studies for quinolonic antibiotics and exemplify that it is possible to develop of even more active compounds making changes in previously unalterable positions.

Keywords: quinolone, antibacterial, structure-activity relationship.

RESUMO
A introdução dos antimicrobianos quinolônicos no mercado causou uma revolução na terapia antibacteriana. O esqueleto da 4-quinolona tornou-se o alvo de muitos estudos de relação estrutura-atividade, estabelecendo os parâmetros considerados ideais para o desenvolvimento de novos antibióticos quinolônicos. Esses parâmetros limitaram o desenvolvimento de novos compostos, de modo que é possível encontrar compostos com alterações na mesma posição com substituintes semelhantes. O objetivo deste artigo é identificar compostos quinolônicos que não se enquadram em um ou mais critérios determinados como ideais nos estudos de relação

estrutura-atividade para antibióticos quinolônicos e exemplificar que é possível desenvolver compostos ainda mais ativos fazendo alterações em posições anteriormente inalteráveis.

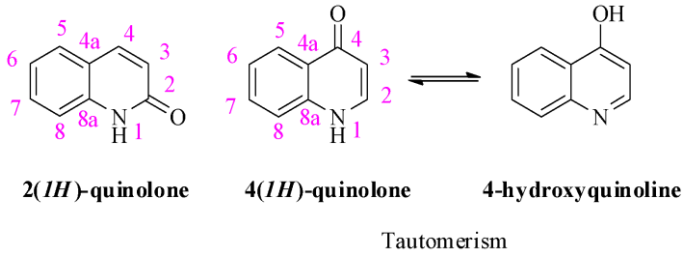
Palavras-chave: quinolona, antibacteriano, relação estrutura-atividade.

1 INTRODUCTION

Quinolones are an important core in medicinal chemistry and drug discovery with pharmaceutical interest (HORTA *et al*., 2018; HONG, SHIN & LIM, 2020), it is possible find about 45,000 references of which 5,000 are review when the keyword quinolone was used for research in Scifinder®, being the first review of the year 1967. These data show how this thematic was explored during the years, they showed the antibacterial activity of quinolones focused on quinolonic antibiotics and in their structure-activity relationship, so the objective of this review is present what currently have about quinolones with antibacterial activity but the focus are structures that not fit in the parameters established as ideal for quinolonics antibiotics.

Quinolones are characterized as aromatic bicycles that have a nitrogen atom and a carbonyl group in the same ring as exhibit at Figure 1. The carbonyl group can occupy position 2 or 4 giving two isomers 2(*1H*)-quinolone or 4(*1H*)-quinolone which are interconverted through keto-enolic tautomerism (Figure 1) (BREHMER, 2002).

Figure 1. General structure of quinolones.

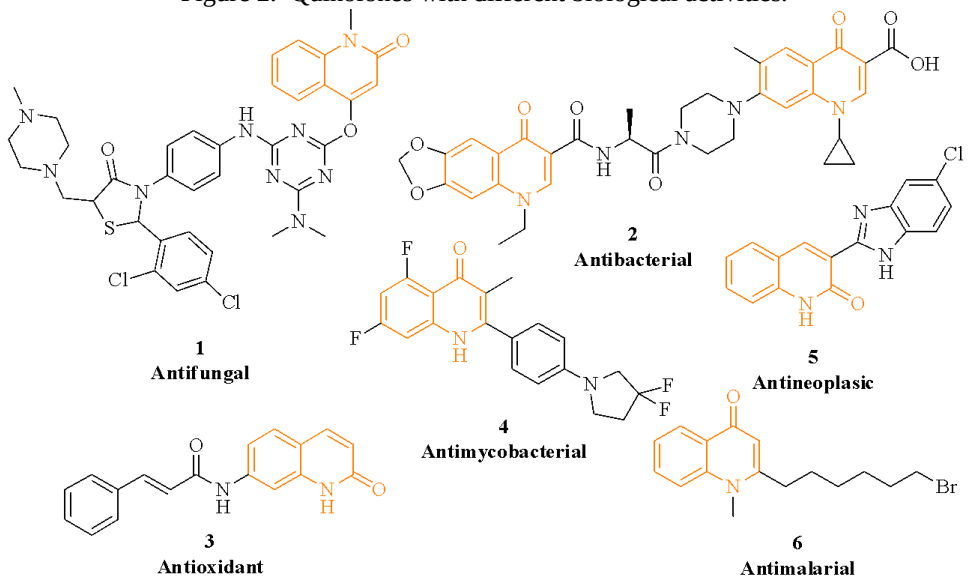


Source: BREHMER, 2002.

The quinolonic moiety is a pharmacophoric group and it is used for the development of new substances. It is possible find on the literature a wide variety of biological activities (DHIMAN *et al*., 2019), such as: anticancer (RELITTI *et al*., 2020; GAO *et al*., 2019; ZHAO & YU 2018; CHEN *et al*., 2004), antifungal (KHAMKHENSHORNGPHANUCH *et al*., 2020; ZANG, 2019; EL-DESOKY *et al*., 2018), antioxidant (CHENG *et al*., 2016; JAYASHREE *et al*., 2010; CHUNG & WOO, 2001), antimalarial (BETECK *et al*., 2019; FAN *et al*., 2018; WUBE *et al*., 2014), antibacterial (LI & CLARK, 2020; KOIDE *et al*., 2019; KRISHNA & SARVESWARI, 2019; VALADBEIGI & GHODSI, 2017; PANDA *et al*., 2015; KERNS *et al*.,

2003) and antimycobacterial (BETECK *et al*., 2020; BETECK *et al*., 2019; HONG *et al*., 2017; PUCCI *et al*., 2010) (Figure 2).

Figure 2. Quinolones with different biological activities.

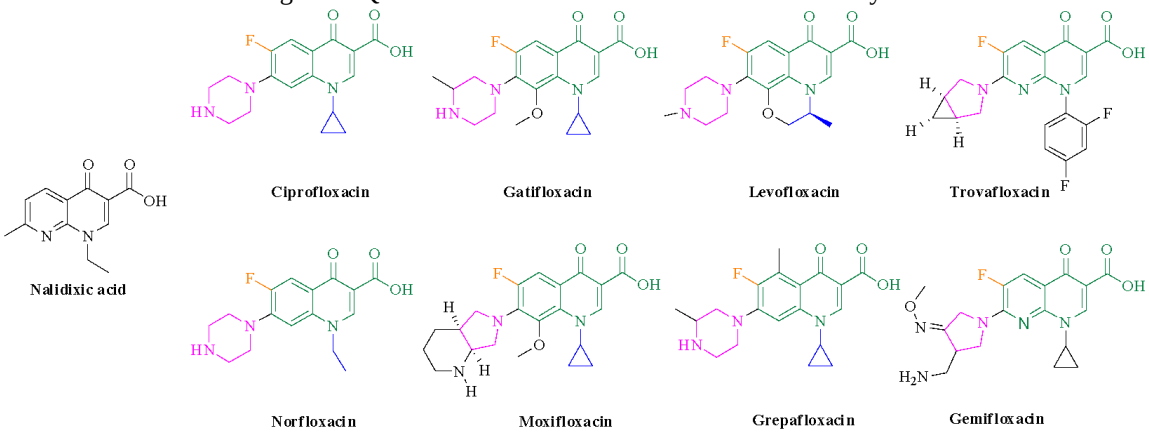


Source: Adapted from antifungal: ZANG, 2019; antibacterial: PANDA *et al*., 2015; antioxidant: JAYASHREE *et al*., 2010.; antimycobacterial:PUCCI *et al*., 2010; antineoplasic: GAO *et al*., 2019 antimalarial: WUBE *et al*., 2014.

2 DEVELOPMENT

The history of quinolonic compounds as antibacterials begins in 1962 with the discovery of nalidixic acid, which was a precursor to different bioactive quinolonic derivatives. These compounds with the quinolonic core as a central skeleton showed excellent antibacterial activity and the entrance of these on the market caused a big impact on antibacterial therapy. So 4-quinolonic structure has become an essential part of many antibiotics used in the clinic (Figure 3) (EMAMI, SHAFIEE & FOROUMADI, 2005; RIOS *et al*., 2020).

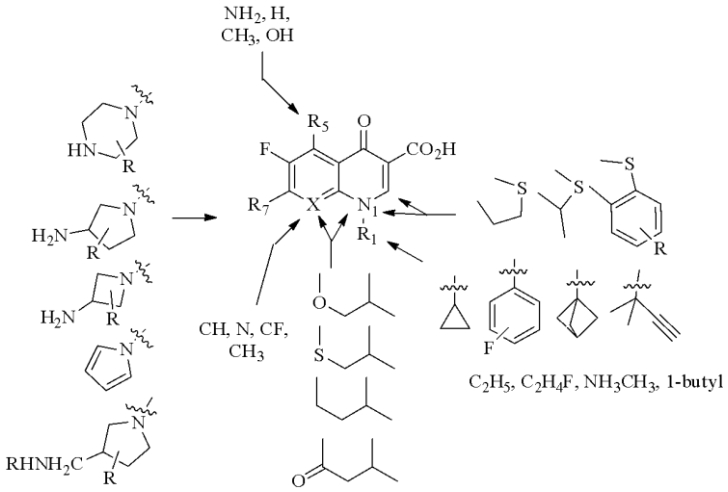
Figure 3. Quinolonic derivatives with antibacterial activity.



Source: Adapted from EMAMI, SHAFIEE & FOROUMADI, 2005

However, with the structure-activity relationship studies guided the development of new quinolonic derivatives, and some positions have had few changes because was described that changes in these positions gave origin to structures with less activity. The positions 1, 2, 5, 7 e 8 normally can bear more modifications as shown in Figure 4 (CHU & FERNANDES, 1991; PINTILIE, 2012).

Figure 4. Substitution patterns described in the literature for the quinolone core



Source: Adapted from CHU & FERNANDES, 1991; PINTILIE, 2012 and PHAM, ZIORA & BLASKOVICH, 2019.

The structure-activity relationship gave some information about the molecules and their interaction with the target, was described that a substitution pattern in the nitrogen atom of the quinolonic ring is necessary for antibacterial activity, which is greatly influenced by the spatial volume of the substituent. Studies have shown the best substituent for this position is cyclopropyl, due to its spatial volume and maintenance of the planarity of the molecule which will allow the correct hydrophobic interactions with the DNA (EMAMI, SHAFIEE & FOROUMADI, 2005; PINTILIE, 2012). The hydrogen atom bonded to C-2 is maintained, since its replacement showed a decrease in activity, a fact associated with the proximity to DNA-gyrase and Topoisomerase IV binding site (EMAMI, SHAFIEE & FOROUMADI, 2005; PINTILIE, 2012; PETERSON, 2001).

In quinolonic antibiotics the C-3, C-4 and C-6 presents a carboxyl group, carbonyl group and a fluorine atom, respectively. Usually, these substituents are maintained because they are considered essential for biological activity (EMAMI, SHAFIEE & FOROUMADI, 2005; PINTILIE, 2012). It was reported that replacement of the fluorine atom at C-6 resulted in less efficient compounds, besides their action was associated with better inhibition of DNA-gyrase

and increased cell penetration of 6-fluoroquinolones (EMAMI, SHAFIEE & FOROUMADI, 2005).

According to Wang *et al*. (2019), the change in C-3 of the quinolonic core can be positive, carboxyl (C-3) and carbonyl group (C-4) are responsible for binding to the active site of bacterial enzymes DNA-gyrase and Topoisomerase IV through the formation of a complex mediated by metal, usually magnesium, and water. It is reported the excessive and irrational use of these antibiotics make a weakened link, triggering an error-prone signal, generating specific mutations in these enzymes and the emergence of resistant strains (CHENG *et al*., 2016). Therefore, changes in these positions would be an interesting strategy searching active molecules against resistant strains (WANG *et al*., 2019; CHENG *et al*., 2016)

The substituent at position 5 controls the potency and affinity for gram-positive bacteria (EMAMI, SHAFIEE & FOROUMADI, 2005; CHU & FERNANDES, 1991). Peterson (2001) reported that substituents in this position is capable to modify the planar structure of the compound and affect directly the activity, for example, substituents with modesty size like amino, methyl and hydroxyl group give compounds with better activity against gram-positive bacteria (PETERSON, 2001).

Some properties are associated with substituent bonded at C-7. Usually, 5- or 6- atoms of nitrogen ring is used, for example, piperazine and pyrrolidines, the introduction of these basics groups in this position favors the pharmacokinetics of the compounds (EMAMI, SHAFIEE & FOROUMADI, 2005; PINTILIE, 2012). The bioavailability can be modified because the solubility of the compound, pyrrolidines is associated with lower water solubility when compared with piperazines, so alkylation of this ring help to improve this physical property (EMAMI, SHAFIEE & FOROUMADI, 2005). The spectrum of antibacterial action can be changed according to the ring used in this position, for example, piperazine ring, like ciprofloxacin and levofloxacin has major activity against Gram-negative bacteria (*E. coli* and *K. pneumoniae*) whereas pyrrolidine ring, as trovafloxacin have major activity for Gram-positive bacteria (*S. aureus* and *S. pyogenes*) (Table I) (DOMAGALA, 1994; PETERSON, 2001).

Table 1. Comparison of 7-piperazine and 7-pyrrolidine quinolones and the activity against Gram-positive and negative bacteria.

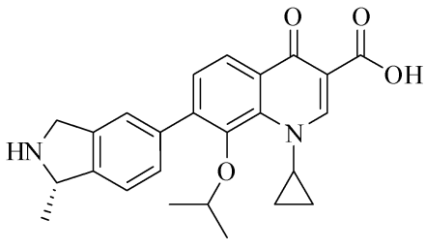
Drugs	MIC_{50} (µg/ml)			
	S. aureus	*S. pyogenes*	*E. coli*	*K. pneumoniae*
Ciprofloxacin	0.12-0.5	0.5-1	0.004-0.03	0.016-0.25
Levofloxacin	0.12-0.25	0.25-1	0.016-0.06	0.03-0.25
Trovafloxacin	0.016-0.06	0.03-0.12	0.03-0.03	0.06-0.5

Source: Adapted from FUNG-TOMC *et al*., 2000.

As in position 5, the substituents in C-8 can modify the molecular configuration of the structure, therefore depending on the change in this position the affinity with the target are affect (PETERSON, 2001). This position is considered important for the pharmacokinetics of the compound and also influence the spectrum of antibacterial activity. It is possible to observe better activity against Gram-positive bacteria when the substituents are fluorine, chlorine, methyl and methoxy, such as described for Pham, Ziora & Blaskovich (2019) where we can compare gatifloxacin (8-H - MIC_{90}= 0.256 mg/L) and grepafloxaxin (8-MeO - MIC_{90}= 0.12 mg/L) against *Staphylococcus aureus* (PHAM, ZIORA & BLASKOVICH, 2019). There is also an improvement in potency against anaerobic bacteria when the carbon is replaced for nitrogen, Pham, Ziora & Blaskovich (2019) reported that gemifloxacin with nitrogen at position 8 exhibited MIC_{90}= 0.03 mg/L while moxifloxacin with carbon in this position showed MIC_{90}= 0.06 mg/L (EMAMI, SHAFIEE & FOROUMADI, 2005; PHAM, ZIORA & BLASKOVICH, 2019).

When searching structures containing the quinolone moiety, most of the compounds maintain the characteristics described above, however can be found, in lower proportion, molecules that have changes in positions previously considered unalterable, that exhibit significant antibacterial activity. This is the case of garenoxacin (Figure 5), an antibiotic used in the treatment of Gram-positive and Gram-negative bacterial infections. This medicament does not have fluoride in position 6, considered a des-fluoroquinolone, and does not have a nitrogen ring directly linked to C-7. Garenoxacin has a mechanism of action similar to other quinolones, promoting inhibition of the DNA-gyrase and Topoisomerase IV complex (ZHANEL *et al*., 2006).

Figure 5. Chemical structure of garenoxacin.



Garenoxacin

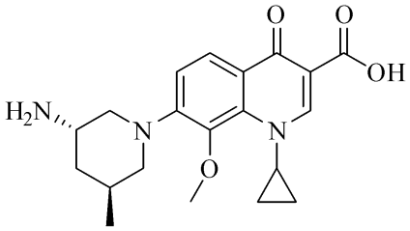
Source: Adapted from ZHANEL *et al*., 2006.

When compared garenoxacin to ciprofloxacin, garenoxacin exhibits increase activity to MIC_{90}= 0.5 μg/ml for MIC_{90}= 0.03 μg/ml against *Staphylococcus* sp., also to strains resistant to methicillin (FUNG-TOMC *et al*., 2000). Broadest spectrum of activity against anaerobic

bacteria, Fung-Tomc *et al*. (2000) reported that garenoxacin showed activity against different strains of anaerobic bacteria tested, except one peptostreptococcal strains at 4 μg/ml, and still improves adverse effects - for example joint toxicity, that is associated with the absence of fluoride in position 6 (KIRBY *et al*., 2002; ZHANEL *et al*., 2006).

Like the previous example, nemonoxacin (Figure 6) is a des-fluoroquinolone which has the same mechanism of action. It is possible to verify a wide spectrum of action for both Gram-negative and positive bacteria, including resistant strains, such as *Staphylococcus* sp. – resistant to methicillin, that presented MIC_{50}= 0.25 mg/L compare to levofloxacin MIC_{50}= 2 mg/L (ADAM *et al*., 2009; CHANG, HSU & ZHANG, 2020). Nemonoxacin also exhibits *in vitro* activity against unusual pathogens such as *Chlamydophila pneumoniae* that showed MIC_{50}= 0.06 μg/L compare to MIC_{50}= 0.5 μg/L of levofloxacin (CHANG, HSU & ZHANG, 2020; CHOTIKANATIS, KOHLHOFF & HAMMERSCHLAG, 2014).

Figure 6. Chemical structure of nemonoxacin.



Nemonoxacin

Source: Adapted from ADAM *et al*., 2009.

This drug also plays an important role in the treatment of Community Acquired Pneumonia (CAP), because it has good clinical and microbiological efficacy compared to levofloxacin and moxifloxacin, the references drugs for the treatment of CAP. Unlike levofloxacin (LEV) and moxifloxacin (MOX), nemonofloxacin (NEM) has low activity against *Mycobacterium tuberculosis*. When 43 isolates of *M. tuberculosis* were tested against these agents at concentration range 0.03 mg/L to 32 mg/L, the sensibility of the isolates of *M. tuberculosis* occur in lowest MICs for LEV and MOX (0.25 mg/L) than NEM (2 mg/L), the MICS were at least 8 times lowest (Table 2). This is advantageous as its use would not harm or delay the diagnosis of tuberculosis, which happens with the reference drugs mentioned above (CHANG *et al*., 2019; TAN *et al*., 2009).

Table 2. Relation between activity in isolates od M. tuberculosis and quinolones

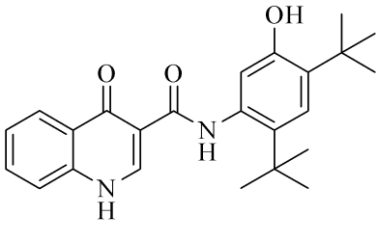
Drugs	MICs (mg/L)												
	<0.03	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32
Levofloxacin	-	-	-	-	8	27	8	-	-	-	-	-	-
Moxifloxacin	-	-	-	-	22	15	6	-	-	-	-	-	-
Nemonofloxacin	-	-	-	-	-	-	-	1	12	25	5	-	-

Source: Adapted from TAN *et al*., 2009.

Another compound that does not fit the requirements established in the structure-activity relationship studies is ivacaftor (Figure 7). It was approved in 2012 by the Food and Drug Administration (FDA) for cystic fibrosis treatments in individuals with specific mutations in the gene that encodes the transmembrane protein - which regulates ionic transport (CFTR protein) (THAKARE *et al*., 2017; MILLAR *et al.*, 2018). This drug act as an enhancer of the CFTR protein facilitating the transport of chloride ions, favoring the probability of opening the protein channel on the cell surface (MILLAR *et al*., 2018; SOUZA *et al*., 2022).

The reports of infections by common pathogens decreased after the use of ivacaftor in treatments of cystic fibrosis, as the *Pseudomonas aeruginosa* (VOLKOVA *et al*., 2020). Considering the similar central skeleton of ivacaftor with quinolonic antibiotics, some studies have been conducted evaluating the activity of this compound (REZNIKOV *et al*., 2014; THAKARE *et al*., 2017).

Figure 7. Chemical structure of ivacaftor.



Ivacaftor

Source: Adapted from THAKARE *et al*., 2017.

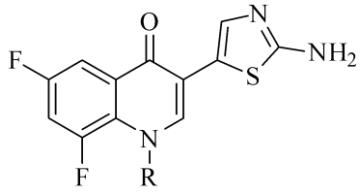
Different of all others quinolone antibiotics, ivacaftor has substitution only in position 3, where the carboxyl is replaced by an amide diverging from everything previously established as ideal, and still presents excellent results. To investigate and evaluate the ivacaftor antibacterial properties different assays was used, such as bioluminescence, colony forming unit (CFU) and minimal inhibitory concentration (MIC).

On bioluminescence assay was observed a dose-dependent and reduction of bioluminescence similar to vancomycin, that suggest a reduction on the viability of the bacteria. Ivacaftor showed MIC= 8 mg/L against strains of *Staphylococcus aureus*, including resistant

strains (REZNIKOV *et al*., 2014). Such results put ivacaftor in evidence as a drug in repositioning process for the treatment of *Staphylococcus aureus* infections (THAKARE et al., 2017).

Another function that was reported in the place of carboxylic acid is the 2-aminothiazole, some researchers described this moiety like an important structural fragment, being possible to find a lot of drugs with antibacterial activity that present this core in the structure, such as ceftadizime and cefuzonam. In this context, Cheng *et al*. (2016) and Cui, Addla & Zhou (2016) developed molecules with changes in the function present at C-3 of the quinolonic ring. In both molecules, carboxyl portion was replaced by 2-aminothiazole group, generating a series of antibacterial derivatives type 7 and 8 (Table 3 and 4), respectively.

Table 3. Chemical structure of compounds type 7 and MICs values.

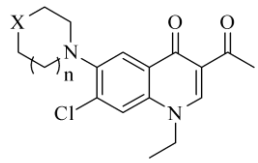
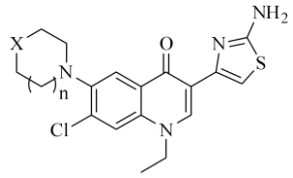
	R		MIC (μg/mL)	
			S. dysenteriae	*B. typhi*
 7	a	$CH_2CH_2CH_3$	4	16
	b	$CH_2(CH_2)_3CH_3$	16	64
	c	$CH_2(CH_2)_5CH_3$	32	64
	d	$CH_2(CH_2)_8CH_3$	64	256
	e	$CH_2(CH_2)_{10}CH_3$	128	64
	f	$CH_2C{=}CH$	8	1
Chloromycin			16	32
Norfloxacin			16	4

Source: Adapted from CHENG *et al*., 2016.

Among compounds of type 7, compound **7f** (Table 3) showed the better antibacterial activity (MIC= 1.0 μg/mL) against *Bacillus typhi* compared to chloromycin (32 μg/mL) and norfloxacin (8 μg/mL), so for *B. typhi*, it was 32 times more potent than chloromycin and 4 times more potent than norfloxacin (CHENG *et al*., 2016). Another good result of this compound was the activity against strains of *Shigella dysenteriae* that show lowest MIC (8 μg/mL) than the references drugs (16 μg/mL).

Just like Cheng *et al*. (2016), Cui, Addla & Zhou (2016) and Zhang *et al*. (2023) synthesized compounds with 2-aminothiazole at C-3. Cui, Addla & Zhou (2016) tested some compounds before the inclusion of 2-aminothiazole what is interesting to evaluate the real benefit of this change (Table 4).

Table 4. Chemical structure of compounds 8 and 9 with their MICs values.

		R	MIC (μg/mL)					
			MRSA	*Sa*	*Pa*	*Ec*	*Bp*	*Et*
 **8**	a	n =1, X=CH_2	128.0	37.3	42.7	13.3	170.7	NA
	b	n = 0, X= CH_2	16.0	18.7	9.3	26.7	64.0	18.7
	c	n = 1, X=O	128.0	NA	42.7	NA	13.3	37.3
 **9**	a	n =1, X= CH_2	24.6	61.2	34.4	117. 8	34.4	17.2
	b	n = 0, X= CH_2	0.8	0.6	0.5	0.8	1.0	2.0
	c	n = 1, X=O	255.3	0.8	170.2	127.7	NA	95.7
	d	n = 1, X=N-Boc	32.0	127.7	8.0	10.7	32.0	NA
	e	n = 1, X= NH	NA	8.0	10.7	128.0	6.4	8.0
Chloromycin			21.3	16.0	32.0	13.8	32.0	26.6
Norfloxacin			10.7	0.8	1.7	4.3	13.3	5.3

MRSA: *Methicillin-Resistant Staphylococcus aureus* N315; Sa: *Staphylococcus aureus* ATCC 25923; Pa: *Pseudomonas aeruginosa* ATCC 9027, Ec: *Escherichia coli* ATCC 25922; Bp: *Bacillus proteus* ATCC 13315; Et: *Eberthella typhosa* ATCC 14028. NA: no activity.
Source: Adapted from CUI, ADDLA & ZHOU, 2016.

In general, the inclusion of 2-aminothiazole provide molecules with better biological activity when the compounds **8** and **9** were compared, such as **8c** and **9c**, the MIC value against *Methicillin-Resistant Staphylococcus aureus* changed of 128 μg/mL for 0.8 μg/mL with the introduction of 2-aminothiazole, this value is lowest when compared with chloromycin (16 μg/mL) and equal to norfloxacin (0.8 μg/mL) (CUI, ADDLA & ZHOU, 2016).

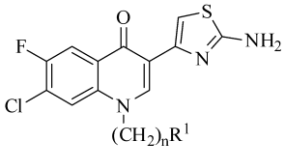
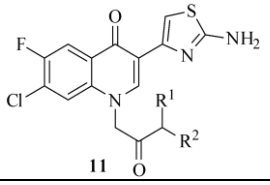
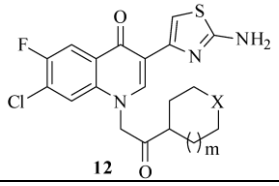
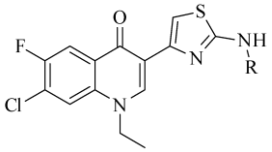
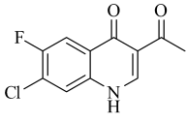
For compounds of type **9**, compound **9b** presented MIC values lower (0.5-2 μg/mL) than chloromycin (13.8-32 μg/mL) and norfloxacin (1.7-13.3 μg/mL) for Gram-negative bacteria - *E. Coli* DH52, *E. typhosa*, *P. aeruginosa* and *B. proteus*. For Gram-positive bacteria, this compound showed MIC values lower than the reference drugs, for example, against *Staphylococcus aureus* sensitive strain showed MIC= 0.6 μg/mL while chloromycin and norfloxacin showed 16 and 0.8 μg/mL, respectively. In case of *Staphylococcus aureus* resistant to methicillin, compound 9**b** exhibit MIC= 0.8 μg/mL it was 13 times more active than norfloxacin (10.7 μg/mL) and 27 times more active than chloromycin (21.3 μg/mL) (CUI, ADDLA & ZHOU, 2016).

Another parameter analyzed in this study was the possible mechanism of action of the molecule **9b**, the most activity compound, for this they used one target of the quinolonic

antibiotic, the enzyme DNA gyrase. The supercoiling activity inhibiton of DNA gyrase was analyzed and the IC_{50} observed was 11.5 μM, this value was better than the standard norfloxacin (18.2 μM) (CUI, ADDLA & ZHOU, 2016).

Zhang *et al.* (2023) described different compounds with 2-aminothiazole moiety at position C-3 and tested their biological activity against several bacteria. Some examples are shown in Table 5.

Table 5. Chemical structure of compounds 10-13 with their MICs (mM) values.

	R		*Sa* 29213	*Ec 25922*	*Pa*
 **10**	a	n=1, R= $CHCH_2$	0.048	0.048	0.048
	b	n=1, R= CHCH	0.192	0.048	0.192
 **11**		R^1= C_6H_{11} R^2= C_6H_{11}	0.015	0.062	0.031
 **12**	a	m=0, X= CH_2	0.039	0.039	0.039
	b	m=1, X= N-Boc	0.061	0.031	0.061
 **13**	a	R= CH_3	0.042	0.168	0.001
	b	R=CH_2CH_3	0.023	0.182	0.006
 **14**			0.534	0.534	1.068
Norfloxacin			0.025	0.050	0.002

Sa: *Staphylococcus aureus* ATCC 29213; Pa: *Pseudomonas aeruginosa*; Ec: *Escherichia coli* ATCC 25922
Source: Adapted from Zhang *et al.*, 2023.

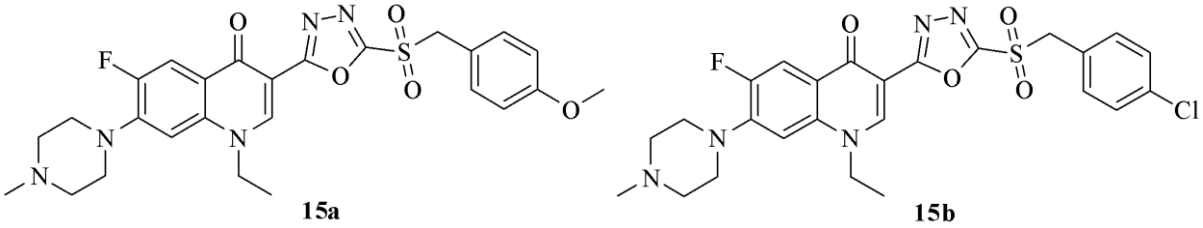
Substances **10-13** were screened through a twofold serial dilution technique in 96-well micro test plates. Compounds **13b** and **11** showed better activity against *Staphylococcus aureus* with MIC value of 0.015 mM and 0.023 mM, respectively, when compared with Norfloxacin (0.025mM). In case of compounds **10a-b** and **12a-b** when tested against *Escherichia coli* showed MICs values smaller (0.031-0.048 mM) than Norfloxacin that exhibit 0.050 mM.

Norfloxacin demonstrate low MIC value when tested for *Pseudomonas aeruginosa* but the compound **13a** reveal better MIC, 0.002 and 0.001 mM, respectively. We can see when comparing compounds **10-13** to **14** the importance of introduction of 2-aminothiazole, all compounds showed better biological activity with substitution of methyl for 2-aminothiazole.

Allaka *et al.* (2022) also inserted a cycle in position C-3 but it is an oxadiazole moiety, and evaluated the zone of inhibition using three Gram positive bacteria, *Staphylococcus aureus*, *Enterococcus faecalis* and *Streptococcus pneumoniae* strains, and two Gram negative bacteria, *Escherichia coli* and *Klebsiella pneumoniae*.

Among all synthetized compounds it is worth to mention **15a** and **15b** (Figure 8) which exhibit the best results when compared with ciprofloxacin and pefloxacin.

Figure 8. Chemical structure of 15a and 15b.



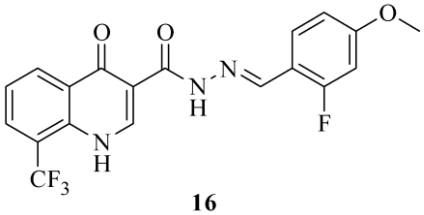
Source: Adapted from Allaka *et al*., 2022.

Against *Staphylococcus aureus* these substances exhibited zone inhibition 42 and 38 mm, respectively, this value is near than ciprofloxacin (44 mm) and better when compared with pefloxacin (35 mm). Another good result is zone inhibition of **15a** against *Enterococcus faecalis* (36 mm) while pefloxacin showed 32 mm, and **15b** against *Escherichia coli* with 34 mm of zone inhibition while pefloxacin and ciprofloxacin are 30 mm and 35 mm, respectively. Zone Inhibition of compound **15a** is equal of pefloxacin (31 mm) and nearly of ciprofloxacin (34 mm) when we talk about *Escherichia coli.*

These results show the importance of diversify the substituents of C-3 and put some cycles in evidence to improve the biological activity of quinolone core.

Other group that can be found at C-3 is a carbo-hydrazone, this group was described as pharmacophoric group and showed antitubercular activity (SINHA *et al*., 2015; ABDELRAHMAN *et al*., 2017), so Thomas *et al*. (2011) and Abdelrahman *et al*. (2017) also explored changes in this moiety and it is possible to found good to excellent activity in their compounds, such the structure **16** (Figure 9) synthesized by Thomas *et al*.

Figure 9. Chemical structure of compound 16.

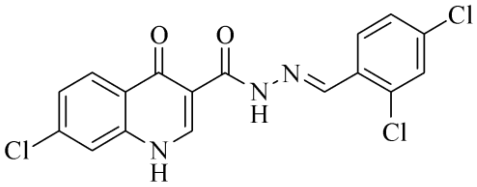


16

Source: Adapted from THOMAS *et al*., 2011.

Compound **16** exhibit lower MIC against *Staphylococcus aureus* (0.8 µg/mL) when compared to reference drug ciprofloxacin (1 µg/mL), and equal MIC (0.4 µg/mL) for *Streptococcus pneumoniae* and *Pseudomonas aeruginosa*. Like the study before, Abdelrahman *et al*. (2017) also obtained a compound **(17)** with antibacterial activity against *Streptococcus pneumoniae* comparable to reference drug ampicillin (MIC= 0.98 µg/mL), and better activity against *Escherichia coli* with MIC= 0.49 µg/mL while ciprofloxacin exhibit MIC = 0.98 µg/mL.

Figure 10. Chemical structure of compound 17.

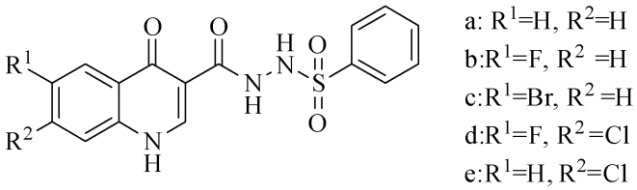


17

Source: Adapted from ABDELRAHMAN *et al*., 2017.

Like these authors, Saxena *et al*. (2022) promoted changes in the position C-3 including a benzene sulfonamide group using hydrazine as linker (Figure 11). Compounds **18a-e** were screened for antibacterial activity using agar diffusion method and norfloxacin and ciprofloxacin as standard.

Figure 11. Chemical structure of compounds 18.



a: R^1=H, R^2=H
b:R^1=F, R^2 =H
c:R^1=Br, R^2 =H
d:R^1=F, R^2 =Cl
e:R^1=H, R^2=Cl

18a-e

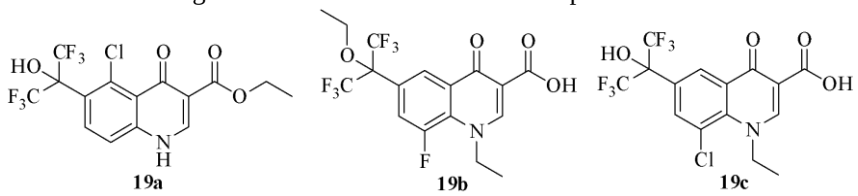
Source: Adapted from Saxena *et al*., 2022.

The Minimum Inhibitory Concentration (mg/ml) obtained for molecules **18a-e** to *Staphylococcus aureus*, *Bacillus cereus* and *Pseudomonas aeruginosa* was three to four times

less activity than standards (Table 5). When compare data for *Escherichia coli* (ETEC) they reached good results, compounds **18b-e** showed identical value of MIC to norfloxacin. These studies exemplify the importance to make changes at C-3 and show the relevance to put hydrazine in this context.

Soda *et al*. (2022) changed position C-3 with the introduction of alkyl group making esters in this position, they changed a lot of things said as ideal to bacterial activity as remove the cycle at position C-7, the fluor directly connected at C-6 was replaced for $C(CF_3)_2OH$ or $C(CF_3)_2OEt$ and in some molecules the nitrogen is not substituted. Compounds that exhibit the best results are highlighted in Figure 12.

Figure 12. Chemical structure of compounds 19.

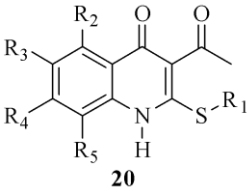


Source: Adapted from Soda *et al*., 2022.

These compounds exhibit excellent activity against *Staphylococcus aureus*, specially **19a** with MIC value less than ciprofloxacin, 0.9 μg/ml and 1.9 μg/ml, respectively. Compounds **19b** and **19c** showed MIC value of 1.9 μg/ml that is equal to the standard (1.9 μg/ml), these data also were found for **19c** against *Pseudomonas aeruginosa*. Soda *et al*. (2022) reported the Minimum Bactericidal Concentration (MBC) of these compounds, in the case of *S. aureus* all results are better than the standard (3.9 μg/ml), 1.8 μg/ml for **19a** and 3.8 μg/ml for **19b-c**, and against *P. aeruginosa* compound **20c** showed MBC value of 3.8 μg/ml also better than standard (3.9 μg/ml).

Xu *et al*. (2018) reported the synthesis of some quinolones containing a sulfur atom in position C-2, they described that nitrogen rings and sulfur atom was identified with a broad spectrum of biological activity. Four compounds are highlighted of the series (Figure 13), these compounds were tested against Gram-positive and negative bacteria and the results are below.

Figure 13. Chemical structure of compounds type 11.



20a R_1:CH_3; R_2:CF_3; R_3:H; R_4:H; R_5:Cl
20b R_1:CH_3; R_2:CF_3; R_3:H; R_4:H; R_5:CF_3
20c R_1: CH_3; R_2:H; R_3: CN; R_4:CF_3; R_5:H
20d R_1: CH_3; R_2:H; R_3:CF_3; R_4:H; R_5:Cl

Source: Adapted from Xu *et al*., 2018.

These structures do not exhibited activity against *Pseudomonas aeruginosa* and *Escherichia coli* (>200 µM) - Gram-negative bacteria, but against *Staphylococcus aureus* and *Bacillus cereus* (Gram-positive) showed MIC values at 0.8 µM and 1.60 µM, respectively, comparable to the standard drug gentamicin in the case of *S. aureus* and tetracycline for *B. cereus* (Table 6).

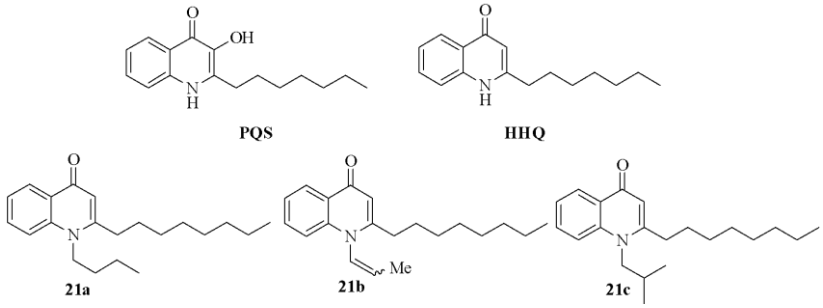
Table 6. MICs (µM) values for molecules type 20.

Compounds	*S. aureus*	*B. cereus*
20a	0.8	1.60
20b	0.8	1.60
20c	0.8	1.60
20d	0.8	1.60
Gentamicin	0.8	1.60
Tetracycline	0.0325	1.60

Source: Adapted from Xu *et al*., 2018.

Changes in position 2 were, recently, also explored because PQS (*Pseudomonas* quinolone signal) and HHQ (2-heptyl-4(1*H*)-quinolone), compounds responsible for the quorum sensing (QS) of *Pseudomonas aeruginosa* (Figure 12), these molecules regulate the expression of genes that code virulence factors in this bacteria (GEDDIS *et al*., 2018; Li & Clark, 2020; RAMOS *et al*., 2020). So, Geddis *et al*. (2018) reported synthetic compounds, we will focus on the compounds **21a**, **21b** and **21c** (Figure 14), and tested the growth of *Staphylococcus aureus* 25923 in the presence of 200 µM of each compound using gentamicin as positive control. They observed a strong effect comparable to the standard when the optical density 600 (OD600) was measured.

Figure 14. Quinolones obtained by Geddis *et al*. and the quinolones responsible for QS.



Source: Adapted from Geddis *et al*., 2018.

3 CONCLUSION

In conclusion, there are already quinolonic compounds with modifications that show advantages as lesser adverse effects and maintenance of antibacterial activity. Furthermore, studies report molecules that exhibited antibacterial activity, *in vitro*, better than the reference drugs even with changes in essential positions for biological activity according to studies of structure-activity relationship. These compounds show how quinolones remain a class of great importance in the development of new compounds and there are still many structural aspects to be explored.

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