



Short Communication

ESKAPE Pathogens: Structure-Activity Relationships of 2,4-Diarylquinolines

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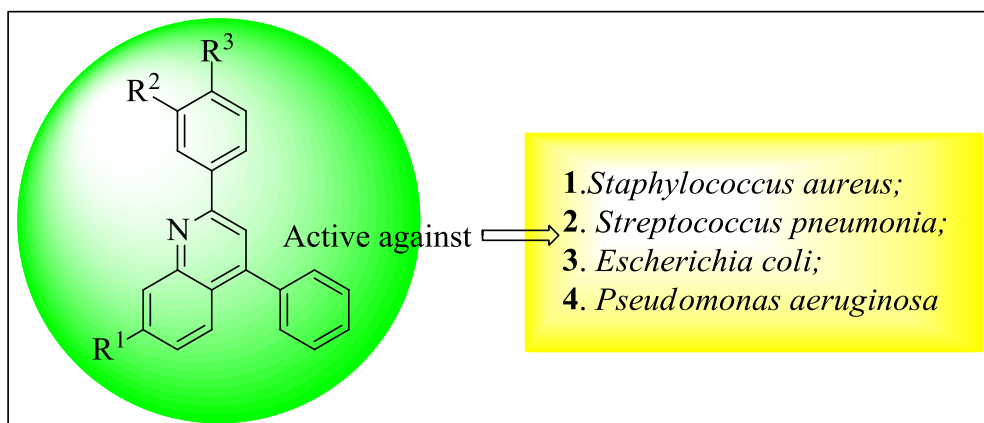
Minimum inhibitory concentration

Zone of inhibition

ABSTRACT

Drug resistance by persisters is a global issue that requires urgent attention. Quinolines and quinolones have proven to be important cores in several bioactive organic chemotypes, based on this, the antimicrobial activity of six derivatives of 2,4-diarylquinolines was evaluated using the disc diffusion method at 5-20 $\mu\text{M}/\text{mL}$. The bioactivity evaluation was conducted on four bacteria examples, two of which are ESKAPE bacteria (*Staphylococcus aureus*, *Streptococcus pneumoniae*, *Escherichia coli* and *Pseudomonas aeruginosa*). The results indicated promising minimum inhibitory concentrations (5 and 10 $\mu\text{M}/\text{mL}$ in some cases) and encouraging zones of inhibition against the 4 germs while interesting and reasonable structure-activity relationships were established at the end of the study.

GRAPHICAL ABSTRACT



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Introduction

The attainability of Millennium Development Goals (MDGs) and Sustainable Development Goals (SDGs) is threatened by antimicrobial resistance, antibiotic persistence and tolerance by bacteria [1]. Antimicrobial resistance, antibiotic persistence and tolerance by persisters have been implicated as the cause of treatment failure in patients receiving antibiotics [2].

Enterococcus faecium, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp are represented by the acronym ESKAPE. These pathogens have shown resistance to current antibiotics [3]. ESKAPE germs possess resistance traits caused by mechanical protection as a result of their ability to synthesis biofilm among other attributes [4]. Therefore, there is a need for continual search and development of novel

antibiotics while taking other measures such as combination of antibiotics with adjuvants, photodynamic and photochemical therapies [3].

Quinoline and quinolone scaffolds are broad spectrum cores in terms of bioactivities while some of the current antibiotics have quinoline/quinolone cores [5-7]. For example, Ciprofloxacin **1** (Figure 1), a quinolone, is a quinolin-4(1H) core and its bioactivity against bacteria relies on the inhibition of DNA gyrase and topoisomerase IV [8]. Clioquinol **2** (Figure 1) on the other hand has a quinoline core, it is a dihalogenated 8-hydroxyquinoline. It has antiseptic activity, a useful drug against drug-resistant *Candida* and it acts by inhibiting the development of hyphal which in turn block the formation of biofilm [9, 10]. Recently, the activity of 2,4-diarylquinoline derivatives **3** (Figure 1) against *Trypanosoma brucei brucei* was reported [11].

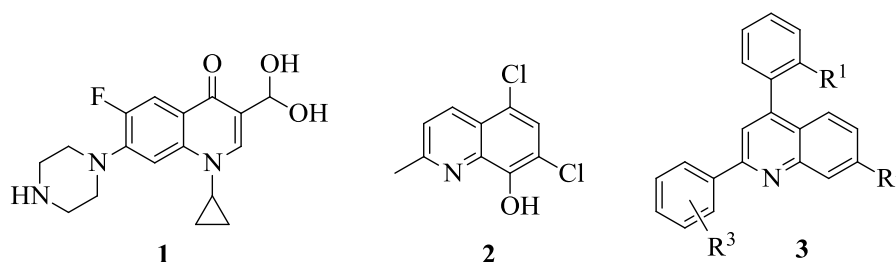


Figure 1. Structural representations of quinolone and quinoline-based antibiotics and 2,4-diarylquinoline

As a contribution to the development of new and efficient antimicrobial chemotypes which may help overcome the problem of antimicrobial resistance, especially in ESKAPE bacteria, this short communication further explores the application of derivatives of 2,4-diarylquinolines (compounds **3**) as antimicrobial agents. The quinoline derivatives used for this study were available from previous study [11] while the unavailable ones were freshly prepared. The molecules were tested against *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Escherichia coli* and *Pseudomonas aeruginosa*. It should be noted that this group of compounds are not cytotoxic

having previously screened them for toxicity against HeLa cells [11].

Experimental

Materials, chemicals and bacterial strains

All the chemicals and solvents were purchased from the Sigma Aldrich and used as supplied.

The four bacteria (*S. aureus*, *S. pneumoniae*, *E. coli* and *P. aeruginosa*) used for this study were provided by the Microbiology laboratory of Lagos State Teaching Hospital (LUTH), Nigeria. The

isolates were inoculated on the Ageller Mueller-Hinton culture medium.

Antibacterial test

Test for susceptibility of bacteria to antibiotics was carried out using the agar disc diffusion assay [12]. This method essentially involves the spread of the 24-h bacterial culture on the surface of the Mueller-Hinton agar plate. Different concentrations of 20, 10, and 5 μM solutions of the molecules under study were prepared by serial dilution. A disc of sterile 6-mm filter paper was saturated with the different concentration of solution of the studied compounds in dimethyl sulfoxide (DMSO) and allowed to diffuse for 1h. The Petri dishes were incubated at 37 $^{\circ}\text{C}$ for 24 h and the diameter of the zone of inhibition was taken. The measured diameter was compared to that of Ofloxacin **4** standard (Figure 2).

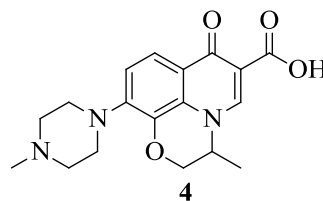
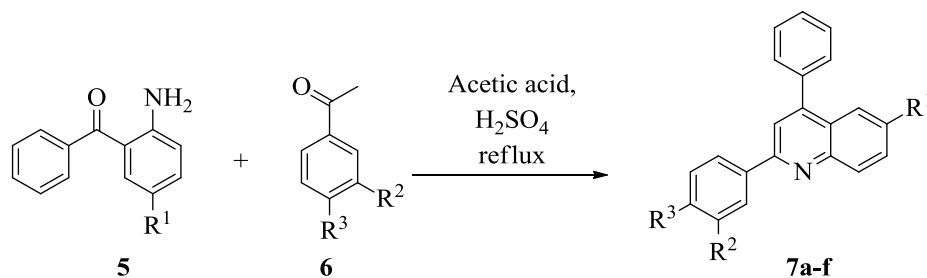


Figure 2. Ofloxacin, a standard antibiotic

Results and Discussion

Chemistry

The 2,4-Diarylquinolines (**7a-f**) were prepared from 2-aminobenzophenones (**5**) and acetophenones (**6**) as described by Oluwafemi *et al* (Scheme 1) [11]. The desired products were obtained in essentially pure form as evidenced by thin layer chromatography (TLC) and nuclear magnetic resonance (NMR) spectroscopy [11].



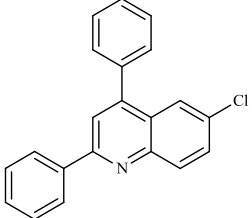
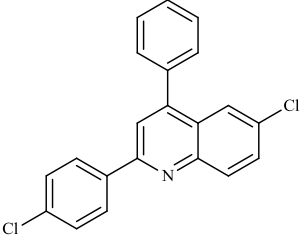
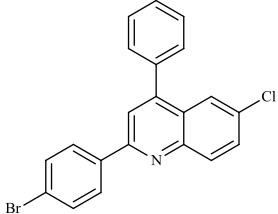
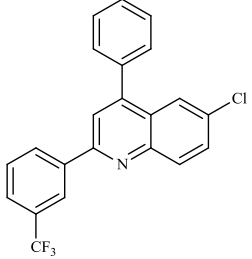
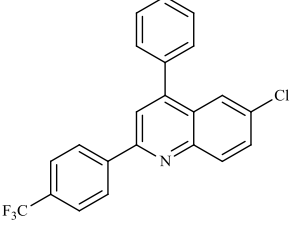
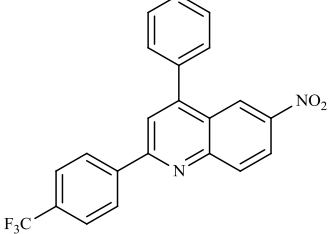
Scheme 1. Synthesis of 2,4-Diarylquinolines

Antimicrobial activity

The structure-activity relationships observed for 6-chloro-2,4-diphenylquinoline **7a**; 6-chloro-2-(4-chlorophenyl)-4-phenylquinoline **7b**; 2-(4-bromophenyl)-6-chloro-4-phenylquinoline **7c**; 6-chloro-2-[3-(trifluoromethyl)phenyl]-4-phenylquinoline **7d**; 6-chloro-2-[4-(trifluoromethyl)phenyl]-4-phenylquinoline **7e** and 6-nitro-2-[4-(trifluoromethyl)phenyl]-4-phenylquinoline **7f** after screening against *S. aureus*, *S. pneumonia*, *E. coli* and *P. aeruginosa* is summarised in Table 1. Compound **7a** gave minimum inhibitory concentrations (MIC) of 10

$\mu\text{M}/\text{mL}$ when tested on *S. pneumonia*, *E. coli* and *P. aeruginosa* while 20 $\mu\text{M}/\text{mL}$ was recorded for *S. aureus*. With chlorine as R^1 and R^3 in compound **7b**, the MICs were 20 and 10 $\mu\text{M}/\text{mL}$, respectively for *S. aureus* and *S. pneumonia* while **7b** was not active against *E. coli* and *P. aeruginosa*. Changing R^3 to bromine to have **7c**, there was activity against all the microbes (MICs of 10 $\mu\text{M}/\text{mL}$ against *S. aureus*, *S. pneumonia* and *P. aeruginosa* but a MIC of 20 $\mu\text{M}/\text{mL}$ was recorded for *E. coli*). Compound **7c** was very good against *S. aureus* because 25 mm was obtained as the zone of inhibition.

Table 1. The minimum inhibitory concentration of compounds **7a-f** against *S. aureus*, *S. pneumoniae*, *E. coli* and *P. aeruginosa*

Compound	Structure	MIC ($\mu\text{M}/\text{mL}$)			
		<i>S. aureus</i>	<i>S. pneumoniae</i>	<i>E. coli</i>	<i>P. aeruginosa</i>
7a		20 (15) ^a	10(12) ^a	10(12) ^a	10(9) ^a
7b		20 (15) ^a	10 (17) ^a	–	–
7c		10 (25)^a	10(10)^a	20(23)^a	10(14)^a
7d		10(8) ^a	10(10) ^a	10(16) ^a	5(12) ^a
7e		–	–	–	–
7f		5(15)^a	10(10)^a	20(14)^a	20(19)^a

^a Zone of Inhibition (millimetre)^b MIC for Ofloxacin = 5 $\mu\text{M}/\text{mL}$ with Zone of Inhibition averaging 27 millimeter at all concentrations

On exploring trifluoromethane functionalized 2,4-diarylquinolines (in compounds **7d-f**), It was found that changing R² to trifluoromethane (-CF₃) to obtain **7d**, the compound was active against the four microbes, but on moving the -CF₃ functionality to R³ position (compound **7e**), the bioactivity disappeared. When the R¹ in **7e** was changed to a nitro group (-NO₂) to obtain **7f**, bioactivity was experienced with MICs of 5 μM/mL against *S. aureus* (zone of inhibition = 15 mm), 10 μM/mL against *S. pneumonia* but 20 μM/mL against *E. coli* and *P. aeruginosa* (zone of inhibition = 14 and 19 mm, respectively). The improved bioactivity could be attributed to the presence of the strongly electron withdrawing nitro group as R¹.

Conclusion

In this research study, six 2,4-diarylquinolines were screened for bacteria susceptibility against *S. aureus*, *S. pneumonia*, *E. coli* and *P. aeruginosa* at concentrations of 5-20 μM/mL. Results obtained established the importance of the nitro-, bromo-, chloro- and trifluoromethyl-substituents on the 2,4-diarylquinoline core in relation to bioactivity against microbes. This work also established that 2,4-diarylquinolines, especially the 2-(4-bromophenyl)-6-chloro-4-phenylquinoline **7c** and 6-nitro-2-[4-(trifluoromethyl)phenyl]-4-phenylquinoline **7f** are suitable to be considered for a prospective hit-to-lead expansion in a future pharmacomodulation process as search for better antibiotics against ESKAPE pathogens continues. It should be noted that the mode of inhibitory action/mechanism of antibiotic action of these compounds against *S. aureus*, *S. pneumonia*, *E. coli* and *P. aeruginosa* are not known at the moment.

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Disclosure statement

No potential conflict of interest was reported by the author.

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