Bioorganic & Medicinal Chemistry 26 (2018) 3573–3579

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Facilely accessible quinoline derivatives as potent antibacterial agents

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ARTICLE INFO

Keywords:
Quinoline
Antibacterial
Gram-positive
Clostridium difficile
In vivo

ABSTRACT

Quinoline compounds have been extensively explored as anti-malaria and anti-cancer agents for decades and show profound functional bioactivities, however, the studies of these compounds in other medicinal fields have lagged dramatically. In this study, we report the development of a series of facilely accessible quinoline derivatives that display potent antibacterial activity against a panel of multidrug-resistant Gram-positive bacterial strains, especially *C. difficile*. We also demonstrated that these molecules are effective in vivo against *C. difficile*. These results revealed that these types of quinoline compounds could serve as prototypes for the development of an appealing class of antibiotic agents used to combat Gram-positive drug-resistant bacterial strains, including *C. difficile*.

1. Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus epidermidis* (MRSE), Vancomycin-Resistant *Enterococci faecalis* (VRE), and *Clostridium difficile* (*C. difficile*) are Gram-positive bacteria that cause severe concerns to public health. The superbug MRSA is among the most common of several difficult-to-treat infections,[1] leading to high morbidity and mortality in the United States.[2,3] MRSE is also known as an opportunistic pathogen of humans and causes various diseases that could also be life-threatening.[4] As one of the predominant enterococcal species, VRE has been recognized as a common cause of endocarditis as well as the second most common cause of wound and nosocomial urinary tract infections in the United States, mainly due to the ability to acquire resistance to the majority of currently available antibiotics.[5] More recently, studies showed that *C. difficile* is the most common cause of hospital-associated diarrhea and could induce other related complications,[6–8] which lead to 29,000 deaths in the United States in 2011.[7] *C. difficile* has been implicated as the leading cause of gastroenteritis-associated death and is emerging as a major enteric pathogen worldwide.[9–11] These Gram-positive bacterial infections have led to incredible expenditures and mortality in the United States and other countries.[12] To tackle infections from these antibiotic-resistant Gram-positive pathogens, persistent efforts have been made among the scientific community,[13–18] however, novel antibiotics that inhibit highly lethal Gram-positive bacterial infections are still urgently needed.

The quinolones (Fig. 1a), such as ciprofloxacin, levofloxacin, lomefloxacin etc. have been one of the largest families of synthetic antibiotic drugs clinically,[19,20] however, extensive use has resulted in the development of resistance to these antibiotics.[21] With similar core structures, quinazolines (Fig. 1b) have also shown potential as an antibacterial with anti-MRSA activity, as demonstrated by several research groups.[22–24] In contrast, the quinolines, with slight difference in the core scaffold compared with quinolones and quinazolines, have been mainly reported to have antimalarial activity (e.g., chloroquine, mefloquine, primaquine, amodiaquine, etc.), as well as analgesic, anti-inflammatory, and antineoplastic activities.[25] The antibacterial study of quinoline compounds have significantly lagged behind quinolones and quinazolines in terms of antibacterial studies. There is limited literature that documents quinoline activity against *Mycobacterium tuberculosis*,[26–29] whose cell wall has characteristics of both Gram-positive and Gram-negative bacteria.[30] These compounds potentially target the proton pump of adenosine triphosphate (ATP) synthase.[26] To the best of our knowledge, quinoline derivatives have been rarely reported to be active against Gram-positive MRSA,[31] MRSE, VRE, and *C. difficile*. We envisioned that quinoline compounds might be active against other bacterial strains, although the exact antibacterial target remains unclear. Herein, we synthesized a focused library of quinoline compounds,

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https://doi.org/10.1016/j.bmc.2018.05.031
Received 11 April 2018; Received in revised form 14 May 2018; Accepted 21 May 2018
Available online 22 May 2018
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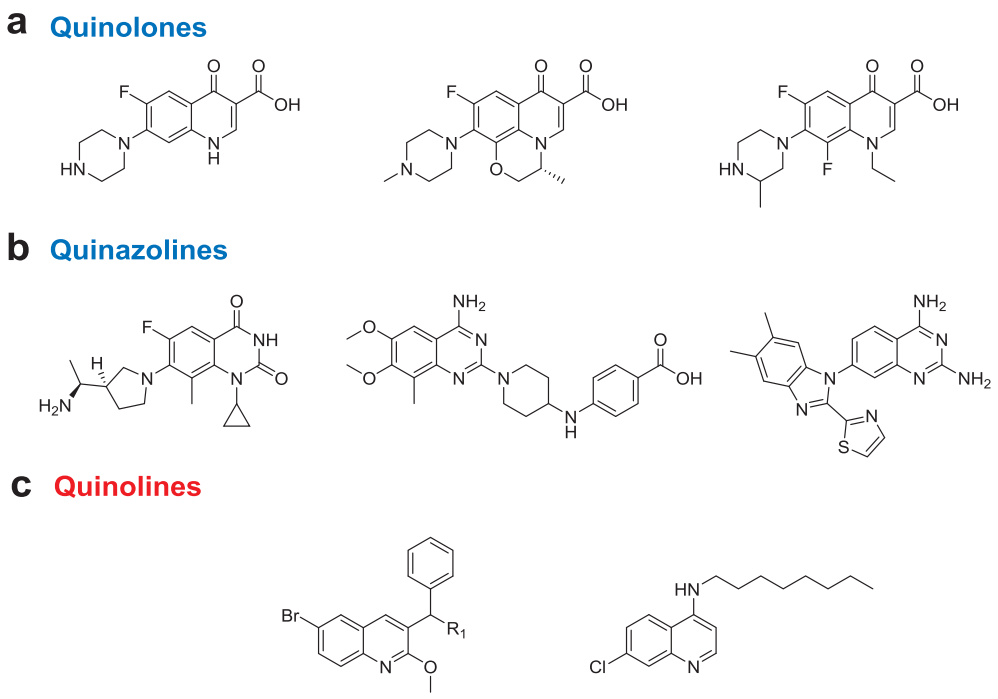
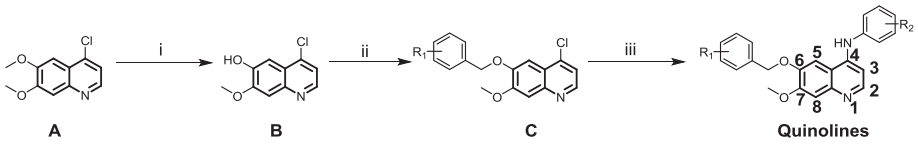


Fig. 1. Examples of quinolones, quinazolines, and quinolines with reported antibacterial activity.



Scheme 1. Synthesis of quinoline derivatives. Reagents and conditions: (i) L-methionine, methanesulfonic acid, 120 °C, yield 57.4%; (ii) benzyl bromide, DMF, K_2CO_3, 60 °C, yield 84.1–91.6%; (iii) substituted aniline, HCl (cat.), *n*-butanol, 120 °C, yield 71.6–93.2%.

and explored their activity against a panel of Gram-positive bacteria.

2. Results and discussion

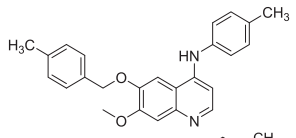
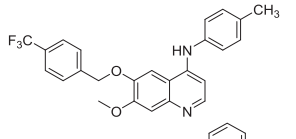
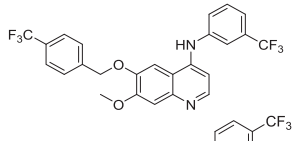
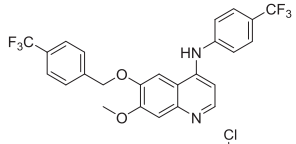
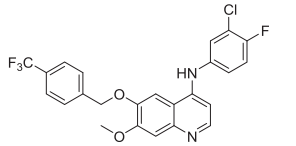
2.1. Synthesis of quinoline compounds

The quinoline library was synthesized through a three-step reaction by using commercially available starting materials. As briefly shown in Scheme 1, commercially available 4-chloro 6,7-dimethoxyquinoline (**A**) was treated with methanesulfonic acid in the presence of L-methionine to selectively remove 6-methoxy group.[32] The afforded mono-hydroxy intermediate **B** was reacted with benzyl bromide to give the ether **C**, which could be used without any further purification. Amine substitution occurred at position-4 in the presence of catalytic concentrated HCl to give the 4-amino-6-ether-substitued quinoline. Recrystallization from ethyl acetate/dichloromethane gave the final compounds without further column purification. Throughout this synthetic sequence, only **B** needed to be purified by column chromatography, hence large scale of molecules could be easily obtained for further investigations in the future.

2.2. Potency of compounds against MRSA, MRSE, and VRE

Two areas of substitution were assessed, including N^4-substitution and O^6-substitution (O^7-substitution was not preferred here because the intermediate **B** is much easier accessed). Eight compounds were synthesized and tested against three clinically relevant, multidrug resistant Gram-positive bacterial pathogens, namely MRSA, MRSE, and VRE. The last-resort antibiotic, daptomycin,[33] was employed as a control. As shown in Table 1, firstly, when R_1 and R_2 were both kept as *para*-methyl group, only weak activities were detected for compound **1**, with minimum inhibitory concentration (MIC) of 12 μg/mL against MRSA.

Table 1
The structure of quinoline compounds **1–5** and their antibacterial activity against MRSA, MRSE, and VRE.

Cpd	Structure	MIC (μg/mL)		
		MRSA	MRSE	VRE
1		12	ND[a]	ND
2		3.0	3.0	3.0
3		3.0	6.0	3.0
4		0.75	3.0	0.75
5		1.5	3.0	1.5
	Daptomycin	0.5	0.5	1.0

[a] ND, not determined because compounds are not active.