European Journal of Medicinal Chemistry 195 (2020) 112276

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Research paper

Synthesis of novel monocarbonyl curcuminoids, evaluation of their efficacy against MRSA, including *ex vivo* infection model and their mechanistic studies

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ARTICLE INFO

Article history:
Received 30 December 2019
Received in revised form
27 February 2020
Accepted 24 March 2020
Available online 3 April 2020

Keywords:
Curcumin
Curcuminoids
S. aureus
MRSA
Antibacterial

ABSTRACT

In continuation of our effort to improve the physiological stability and the antibacterial activity of curcuminoids against drug-resistant bacteria, a series of novel monocarbonyl curcuminoids were synthesized and screened for antibacterial activity against *S. aureus* and *E. coli* strains. These curcuminoids showed potent antibacterial activity against both methicillin-sensitive and methicillin-resistant strains of *S. aureus* with MIC values 2–8 and 4–16 μg/mL, respectively. They also exhibited moderate potency against *E. coli* strains. The four most active curcuminoids (**7d**, **7i**, **7m**, and **7p**) were on further investigation found to be very stable under physiological conditions, non-hemolytic, and non-toxic toward mammalian cells up to 150 μg/mL concentration. Mechanistic studies revealed that these curcuminoids displayed potent bactericidal activity by targeting cell membranes. Further, in an *ex vivo* mammalian co-culture infection model study, remarkably, the curcuminoids **7i** and **7p** were able to clear the internalized bacteria in mammalian cells and the activity was found to be superior to conventional antibiotics such as vancomycin and linezolid. Therefore, the present study affords us water-soluble, stable, non-toxic curcuminoids that may serve as lead molecules for development as antibacterial agents against MRSA infections.

1. Introduction

The rapid emergence of antibiotic resistance in bacteria is a significant global threat to human health [1]. The excessive use or rather misuse of antibiotics has jeopardized the efficacy of long used antibiotics, which resulted in a major deficit of effective treatment [2]. Amidst the emerging resistance problem, WHO has listed Methicillin-resistant *Staphylococcus aureus* (MRSA) as a "high-priority" deadly antibiotic-resistant bacterial pathogen [3]. *Staphylococcus aureus* (*S. aureus*) is one of the most prevalent and common causes of healthcare-associated infections. It is a commensal but opportunistic bacterium that is present in the nasal carriage of every third person in the world [4] and becomes a clinically significant pathogen when there is a breach of defense barrier that allows access to the bloodstream. Thereafter it causes a wide array of infections from common skin infections to severe life-threatening diseases, such as endocarditis [5], osteomyelitis [6], joint infections [7], pneumonia [8], urinary tract infections [9], etc. Over the years, the pervasive use of antibiotics against *S. aureus* led to the emergence of resistant strains; now, it shows resistance to several marketed antibiotics such as penicillin, methicillin, rifampin, fluoroquinolone, vancomycin, etc. and is thus considered as a multi-drug-resistant (MDR) bacteria [10]. Even daptomycin, a drug of last resort, cannot cure nearly one-third of MRSA infections, leaving patients with poor prognosis [11]. This therapeutic crisis has spurred an urgent need for new antibacterial drug molecules that might overcome these alarming drug resistance problems.

In the light of continuously emerging drug resistance and failures in finding new antibiotics, the exploration of natural antibacterial products, particularly secondary metabolites of plants has accelerated recently [12–14]. Curcumin, one such natural compound, isolated from the rhizome of turmeric (*Curcuma longa*)

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https://doi.org/10.1016/j.ejmech.2020.112276
0223-5234/