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Research paper

The synthesis and antistaphylococcal activity of 9, 13-disubstituted berberine derivatives

Jing Wang [a, 1], Teng Yang [b, c, 1], Huang Chen [d], Yun-Nan Xu [a], Li-Fang Yu [a], Ting Liu [a], Jie Tang [a, e], Zhengfang Yi [d], Cai-Guang Yang [c], Wei Xue [b, **], Fan Yang [a, *]

[a] Shanghai Engineering Research Center of Molecular Therapeutics and New Drug Development, SCME, East China Normal University, Shanghai 200062, China
[b] Center for Research and Development of Fine Chemicals of Guizhou University, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Guiyang 550225, China
[c] State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, China
[d] Shanghai Key Laboratory of Regulatory Biology, Institute of Biomedical Sciences and School of Life Sciences, East China Normal University, Shanghai, 200241, China
[e] Shanghai Key Laboratory of Green Chemistry and Chemical Processes, SCME, East China Normal University, Shanghai 200062, China

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ABSTRACT

A series of novel 9, 13-disubstituted berberine derivatives have been synthesized and evaluated for the antibacterial activities against *Staphylococcus aureus*, including Newman strain and multidrug-resistant strains (NRS-1, NRS-70, NRS-100, NRS-108, and NRS-271). Compound **20** shows the most potent activity against the growth of Newman strain, with a MIC value of 0.78 μg/mL, which is comparable with the positive control vancomycin. In addition, compound **20**, **21**, and **33** are highly antistaphylococcal active against five strains of multidrug-resistant *S. aureus*, with MIC values of 0.78–1.56 μg/mL. Of note, theses antibacterial active compounds have no obvious toxicity to the viability of human fibroblast (HAF) cells at the MIC concentration.

1. Introduction

Staphylococcus aureus is a Gram-positive bacterium that causes many infections of ecological niches within the human body, leading to a wide range of diseases [1]. Methicillin-resistant *S. aureus* (MRSA) is a nosocomial and communal menace that is resistant to most antibacterial drugs and antiseptics [2]. MRSA accounts for 60–70% of *S. aureus* infections in hospitals and causes the highest number of invasive infections among all antibiotic-resistant bacteria [3–6]. It is estimated that by 2050, worldwide drug-resistant infections will cause an additional 10 million deaths annually [2]. Therefore the demand for the development of new antimicrobial agents with novel chemical scaffolds and biological mechanisms is necessary [7,8].

Natural products have been a rich resource for drug discovery [9]. Berberine (Scheme 1) is an isoquinoline alkaloid extracted from *Coptis chinensis* (Huang-Lian, a common herb in traditional Chinese medicine), and has been traditionally used as a nonprescription drug with a confirmed safety to treat diarrhea and gastrointestinal disorders for decades in China [10,11]. Recent studies show that berberine has various biological activities such as antimalarial [12], antileishmanial [13], anticancer [14–17], anti-alzheimer's disease [18,19], antiviral [20,21], cholesterol lowering effect [22], hypoglycemic effect [23], G-quadruplex binding ligands [24], and particularly antibacterial activity [25–28]. The lipophilic substituents at C-9 position of berberine could enhance the antimicrobial activities and broaden antimicrobial spectrum significantly. Zhou et al. showed the synthesis of 9-O-substituted berberine derivatives with antimicrobial activity by introducing various heterocycles such as triazole, metronidazole, and benzimidazole in C-9 position of berberine. Berberine-triazole **A**, berberine-metronidazole **B**, and berberine-benzimidazole **C** exhibited excellent activity against Gram-negative bacteria and fungus (Fig. 1) [29–31]. Su et al. revealed the antibacterial activity of 9-phenoxyalkyl berberine derivatives, for example, compound **D** (Fig. 1) strongly inhibited the proliferation of Gram-positive bacteria [32]. In addition, 9-*N*-

* Corresponding author.
** Corresponding author.
E-mail addresses: wxue@gzu.edu.cn (W. Xue), fyang@chem.ecnu.edu.cn (F. Yang).
[1] These authors contributed equally to this work.

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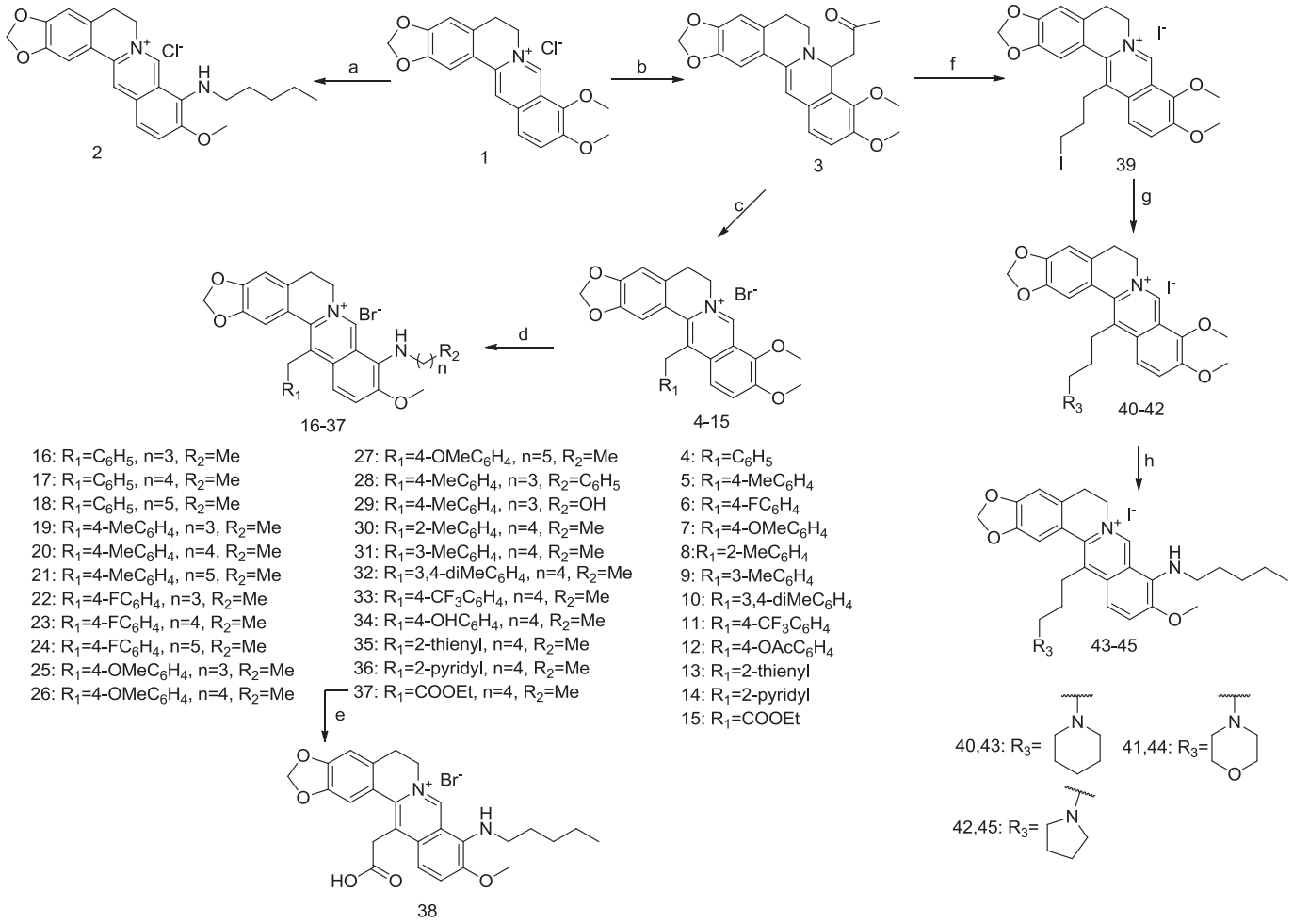

Scheme 1. Reagents and conditions (a) *n*-pentyl amine, EtOH, reflux, 8 h, 72%; (b) 5 N NaOH, acetone, rt, 1 h; (c) various bromides, NaI, CH_3CN, 80 °C, 4 h, 65%–77% (over two steps); (d) various amine, EtOH, reflux, 8–15 h, 60%–85%; (e) NaOH, MeOH, reflux, 1 h, 71%; (f) 1,3-diiodopropane, CH_3CN, 80 °C, 6 h, 50% (over two steps); (g) various amines, EtOH, reflux, 4 h; (h) *n*-pentyl amine, EtOH, reflux, 8 h, 33–42% (over two steps).

substituted berberine derivatives could serve as antioxidant, G-quadruplex binding ligands, inhibitors of acetylcholinesterase, and butyrylcholinesterase [33,34]. Several derivatives of 9-*N*-substituted berberine exhibited better antioxidant activity than 9-O-substituted berberine derivatives [33]. However, antibacterial activity of 9-*N*-substituted berberine has been poorly explored. Moreover, 13-substituted berberine derivatives have been shown a variety of bioactivities [35–38]. Kim et al. investigated the antifungal activities of 13-(substituted benzyl) berberine and showed that 13-(4-isopropyl benzyl) berberine **E** (Fig. 1) exerted the most potent antifungal activities against *Candida species* [35]. Berberine derivative **F** (Fig. 1) reported by Ball et al. showed even better antibacterial activity than berberine against *S. aureus* strain that overexpresses NorA protein [36]. To our knowledge, berberine derivatives bearing structural modification on both C-9 and C-13 positions have been rarely reported, however. In order to search for new chemical classes of potential antibacterial agents, we designed and synthesized a series of 9, 13-disubstituted berberine derivatives. The *in vitro* antibacterial activities against *S. aureus* Newman and five multidrug-resistant strains were evaluated.

2. Chemistry

All berberine derivatives were synthesized from commercially available berberine (**1**) as the starting material as described in Scheme 1. Compound **2** was obtained by treatment of berberine with *n*-pentylamine in refluxing EtOH. Compounds **4**–**15** were synthesized from a key intermediate **3** that was prepared by condensation of berberine with acetone. Treatment of **3** with various bromides and sodium iodide (NaI) in CH_3CN yielded 13-substituted berberine derivatives **4**–**15** respectively. The berberine derivatives **16**–**37** were made by reaction of compounds **4**–**15** with primary amines under refluxing EtOH. Compound **38** was synthesized by hydrolysis of **37** in the presence of 30% aqueous NaOH in MeOH at 80 °C. The intermediates **40**–**42** were obtained according to the published procedure [38]. Refluxing of compounds **40**–**42** with *n*-pentylamine in EtOH afforded berberine derivatives **43**–**45** respectively.

3. Result and discussion

3.1. Antibacterial activity

These novel berberine derivatives were first evaluated for the *in vitro* antibacterial activity (MIC; the minimum concentration of the compound that produced completely bacterial growth inhibition) against *S. aureus* Newman strain. The antibacterial activities of **16**, **17**, **20**, **21**, **23**, **26**, and **30**–**34** were shown in Table 1 and berberine, totarol, vancomycin were used as positive controls. The antibacterial activities of all synthesized compounds were shown in