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Research paper

Novel cajaninstilbene acid derivatives as antibacterial agents

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ABSTRACT

Discovery of novel antibacterial agents with new structural scaffolds that combat drug-resistant pathogens is an urgent task. Cajaninstilbene acid, which is isolated from pigeonpea leaves, has shown antibacterial activity. In this study, a series of cajaninstilbene acid derivatives were designed and synthesized. The antibacterial activities of these compounds against gram-negative and gram-positive bacteria, as well as nine strains of methicillin-resistant staphylococcus aureus (MRSA) bacteria are evaluated , and the related structure-activity relationships are discussed. Assays suggest that some of the synthetic cajaninstilbene acid derivatives exhibit potent antibacterial activity against gram-positive bacterial strains and MRSA. Among these compounds, **5b**, **5c**, **5j** and **5k** show better antibacterial activity than the positive control compounds. The results of MTT assays illustrate the low cytotoxicity of the active compounds.

1. Introduction

With the expansion of the use and abuse of antibiotics, increasing numbers of drug-resistant strains have emerged in the clinic [1]. One of the prototypical “superbugs” caused by antibiotic use and overuse is methicillin-resistant *Staphylococcus aureus* (MRSA) [2], against which almost all antibiotics are ineffective. As a consequence, novel antibacterial agents with new structural scaffolds are urgently needed to overcome the growing problem of drug resistance. Natural products are an important source of new drugs, and searching for novel antibacterial agents from natural products and their derivatives is an important approach to the discovery of antibacterial agents that can overcome drug resistance.

It has been reported that cajaninstilbene acid (**CSA**, Fig. 1), isolated from pigeonpea leaves [3], shows antibacterial activity against gram-positive bacteria. The minimal inhibitory concentrations (MIC) of **CSA** for *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Bacillus subtilis* are 13, 25, and 25 μg/mL respectively. Its antibacterial activity against *Staphylococcus aureus* is equal to that of the erythromycin positive group, through it is lower than that of penicillin or chloramphenicol [4]. As a natural active compound extracted from edible beans, **CSA** is only mildly toxic [5], so it and its derivatives may have good potential as drugs. **CSA** may have promising activity, but there is still a large gap between its antibacterial effect and that of several existing drugs such as penicillin, norfloxacin and linezolid. In this study, a series of **CSA** derivatives were designed and synthesized in a search for compounds with improved antibacterial activity, and their antibacterial activity against gram-negative, gram-positive, and MRSA bacteria were evaluated, and the structure-activity relationships (SAR) were elucidated and discussed. Among these compounds, several new compounds with low toxicity and promising antibacterial activity were identified.

2. Chemistry

In an effort to develop novel antibacterial agents, a variety of **CSA** derivatives have been designed and synthesized. As shown in Fig. 1, the drug design strategies include: (a) removal of the isoprenyl group of **CSA**, to obtain compounds **3a**–**3k**, **6a**, **6c** and **6f**; (b) esterification of the carboxyl group, to synthesize **4a**–**4k**; (c) cleavage of the cinnamenyl group, giving compound **10**; and (d) introduction of substituents into the phenyl ring B, to obtain **CSA** derivatives **5b**–**5k**.

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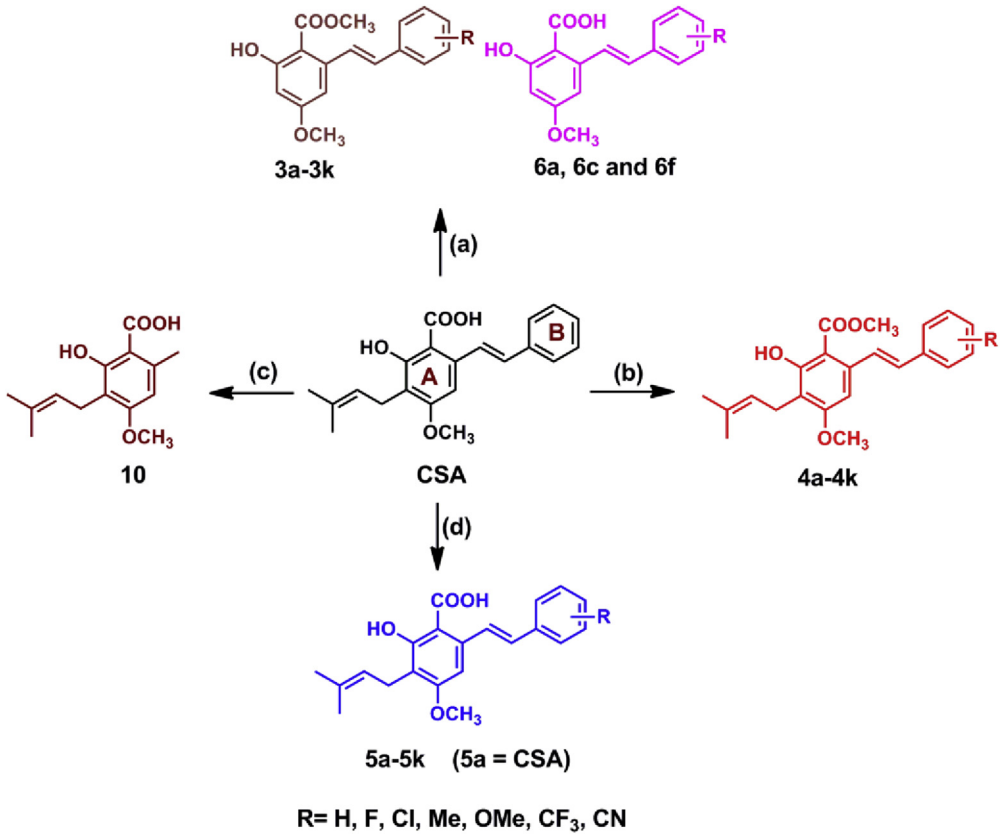


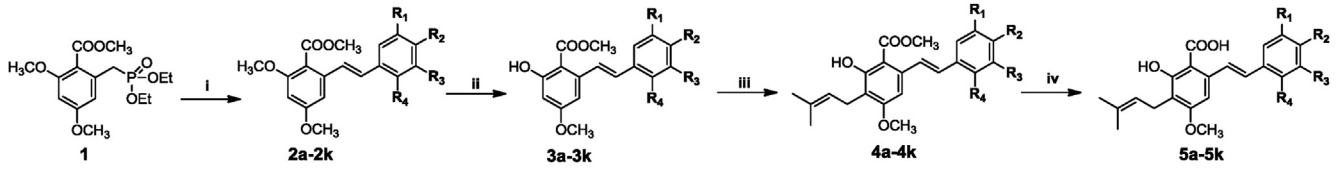
Fig. 1. Design of novel cajaninstilbene acid (**CSA**) derivatives.

The synthetic routes to the compounds in Fig. 1 are depicted in Schemes 1–3. Intermediate **1** was prepared according to a published method [6]. Compounds **2a**–**2k** were synthesized by reacting **1** with different benzaldehydes under the conditions of the Horner–Wadsworth–Emmons reaction [7]. During this reaction, the *E*-configuration products can be isolated in high yield and high selectivity when a catalytic amount of 15-crown-5 (the cyclic pentamer of ethylene oxide) is used [8]. Compounds **3a**–**3k** were obtained from selective demethylation of the 2-OMe group of **2a**–**2k**. Compounds **3a**–**3k** were then treated with prenyl bromide and NaH to give **4a**–**4k**. The yield of **4a**–**4k** depends on the amount of NaH and prenyl bromide and the optimum ratio (1.2 equiv) was determined in a number of experiments [9]. Finally, cajaninstilbene acid and its derivatives **5a**–**5k** were obtained by hydrolysis of the ester group of **4a**–**4k** (Scheme 1). Another series (**6a**, **6c** and **6f**) was conveniently prepared by hydrolysis of **3a**, **3c** and **3f** (Scheme 2). In addition, as shown in Scheme 3, intermediate **8** was prepared from **7** by oxidative aromatization using iodine in methanol [10]. Compound **10** was synthesized by coupling the isoprenyl group and ester hydrolysis.

3. Results and discussion

3.1. Evaluation of antibacterial activity

The antibacterial activities of all synthesized compounds were



2a, 3a, 4a, 5a(CA): R_1=H, R_2=H, R_3=H, R_4=H

2b, 3b, 4b, 5b: R_1=H, R_2=H, R_3=H, R_4=F

2c, 3c, 4c, 5c: R_1=H, R_2=H, R_3=F, R_4=H

2d, 3d, 4d, 5d: R_1=H, R_2=F, R_3=H, R_4=H

2e, 3e, 4e, 5e: R_1=H, R_2=Cl, R_3=H, R_4=H

2f, 3f, 4f, 5f: R_1=H, R_2=CH_3O, R_3=H, R_4=H

2g, 3g, 4g, 5g: R_1=H, R_2=CH_3, R_3=H, R_4=H

2h, 3h, 4h, 5h: R_1=R_2=R_3=CH_3O, R_4=H

2i, 3i, 4i, 5i: R_1=H, R_2=H, R_3=CN, R_4=H

2j, 3j, 4j, 5j: R_1=H, R_2=CF_3, R_3=H, R_4=H

2k, 3k, 4k, 5k: R_1=H, R_2=F, R_3=H, R_4=F

Scheme 1. General synthetic route of cajaninstilbene acid derivatives **3a**–**3k**, **4a**–**4k** and **5a**–**5k**. Reagents and conditions: (i) aromatic aldehyde, 15-crown-5, NaH, THF, −2 °C, 2 h; (ii) BCl_3, CH_2Cl_2, −30 °C, 2 h; (iii) prenyl bromide, NaH, 78 °C, 2 h; (iv) KOH, EtOH, H_2O, 70 °C, 2 h.