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Research paper

Natural product inspired library synthesis - Identification of 2,3-diarylbenzofuran and 2,3-dihydrobenzofuran based inhibitors of *Chlamydia trachomatis*

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ABSTRACT

A natural product inspired library was synthesized based on 2,3-diarylbenzofuran and 2,3-diaryl-2,3-dihydrobenzofuran scaffolds. The library of forty-eight compounds was prepared by utilizing Pd-catalyzed one-pot multicomponent reactions and ruthenium-catalyzed intramolecular carbenoid C-H insertions. The compounds were evaluated for antibacterial activity in a panel of test systems including phenotypic, biochemical and image-based screening assays. We identified several potent inhibitors that block intracellular replication of pathogenic *Chlamydia trachomatis* with $IC_{50} \leq 3$ μM. These new *C. trachomatis* inhibitors can serve as starting points for the development of specific treatments that reduces the global burden of *C. trachomatis* infections.

1. Introduction

Natural products have been a valuable source to identify candidates for drug discovery and development [1–3]. Our interest in biologically active natural products originates from the identification of the plant derived resveratrol tetramer, (−)-hopeaphenol (Fig. 1), as an antibacterial agent that blocks the type III secretion system in *Pseudomonas aeruginosa* and *Yersinia pseudotuberculosis* without affecting bacterial growth [4,5]. In addition, we found that (−)-hopeaphenol reduced cell entry of the obligate intracellular sexually transmitted pathogen *Chlamydia trachomatis* [4]. (−)-Hopeaphenol, the first characterized resveratrol oligomer, is based on a 2,3-*trans*-diaryl-2,3-dihydrobenzo[b]furan scaffold. Benzofuran and 2,3-disubstituted benzofuran moieties are widespread in nature and present in a large number of natural products that display numerous biological activities, including antibacterial, antifungal, antiviral, antioxidant, anti-inflammatory and anticancer activities (Fig. 1) [6–10]. For example, 2-substiuted-3H-benzofurans and 3-benzoyl-2-aryl benzofurans were reported as antibacterial against *Mycobacterium tuberculosis* H37Rv and methicillin-resistant *S. aureus* (MRSA) respectively [8].

In the present study, we designed, synthesized, and characterized a natural-product-like screening library based on 2,3-diarylbenzo[b]furan and 2,3-diaryl-2,3-dihydrobenzo[b]furan scaffolds to explore these scaffolds as a source for novel antibacterial compounds. This compound collection was interrogated in a number of phenotypic and biochemical screening assays leading to identification of potent inhibitors that block intracellular replication of the Gram-negative pathogen *C. trachomatis.* To the best of our knowledge there no benzofurans besides (−)-hopeaphenol that have previously been reported to display antibacterial activity against *C. trachomatis*.

C. trachomatis is a clinically important pathogen that causes over 100 million cases of sexually transmitted disease annually [11–13], which may give rise to infertility [14]. Furthermore, trachoma, an

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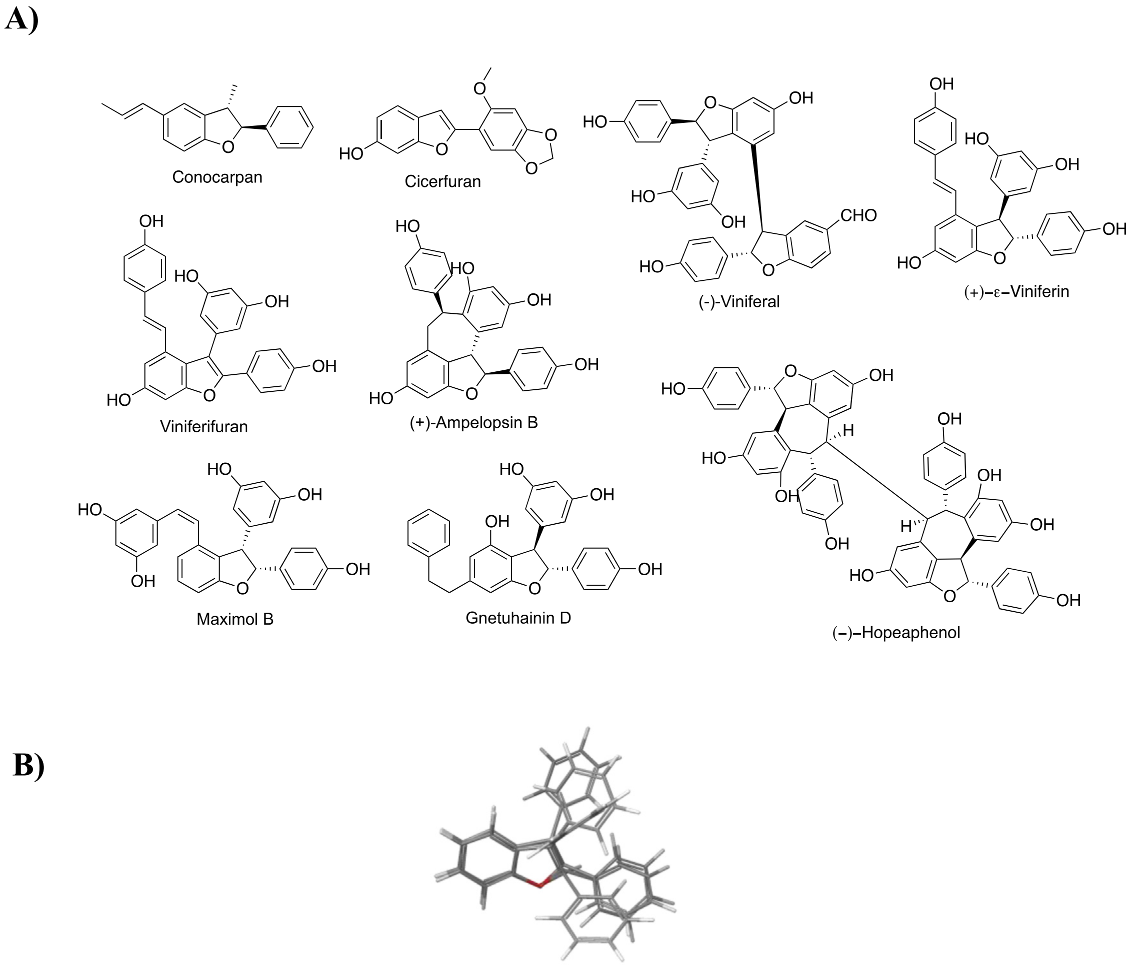

Fig. 1. A) Structures of natural oligomeric resveratrol based on benzofuran and 2,3-diaryl-benzofuran scaffolds including (−)-hopeaphenol [67,68]. **B)** An overlay of energy-minimized conformers of *cis*-2,3-diaryl-2,3-dihydrobenzofuran, *trans*-2,3-diaryl-2,3-dihydrobenzofuran and 2,3-diarylbenzofuran (created in Schrödinger Maestro version 10.5.014).

ocular infection caused by *C. trachomatis*, is responsible for preventable blindness [15]. More specific treatment of *Chlamydia* infections would be beneficial compared to the broad-spectrum antibiotics used today, which have a long-lasting effect on our commensal microbiota and contribute to the development of antibiotic resistance. These new anti-chlamydial compounds constitute starting points for the development of specific treatments that reduces the global burden of *C. trachomatis* infections.

2. Results and discussion

2.1. Synthesis

2.1.1. An overview of benzofurans synthesis

While 2,3-disubstituted benzofurans can be readily prepared [16–22], only few reports describe efficient methods for the synthesis of 2,3-diaryl-2,3-dihydrobenzofurans and they mostly focus on the total synthesis of their parental natural products [23–26]. Wai-Hung et al. applied ruthenium porphyrins and *in situ* generated diazo compounds to synthesize *cis*-2,3-disubstituted-2,3-dihydro-benzofurans *via* carbenoid C-H insertion [23]. However, only one example of a non-substituted 2,3-diaryl-2,3-dihydrobenzofuran was disclosed. In a recent report Soldi et al. [24] elegantly carried out enantioselective synthesis of resveratrol-based natural products containing the 2,3-dihydrobenzofuran scaffold by applying carbenoid C-H insertion with chiral dirhodium catalyst [24,27]. This approach was also applied for the total synthesis of (−)-*E*-δ-viniferin [26].

We have previously completed the total syntheses of (±)-ampelopsin B and (±)-ε-viniferin [28] (Fig. 1), and more recently we reported the total syntheses of other polyphenolic nature products including viniferifuran, a resveratrol-picetannol hybrid and anigopreissin A [29]. To extend the scope of our studies on benzofuran-based natural products, we recently designed and synthesized a library based on 3-carboxy 2-aryl benzofuran and 3-carboxy 2-aryl *trans* 2,3-dihydrobenzofuran scaffolds [30].

2.1.2. Synthesis of 2,3-diarylbenzo[b]furans series

In this study, we thought to synthesize a set of 2,3-diarylbenzo[*b*]furans as precursors to access *cis*- and *trans*-2,3-diaryl-2,3-dihydrobenzofuran *via* catalytic hydrogenation followed by epimerization based on our earlier results (Scheme 1) [31]. The synthesis of 2,3-diarylbenzo[*b*]furan was achieved by utilizing efficient one-pot multicomponent reactions reported by Cacchi [32], Flynn [16,33], and Larock [18]. It starts with Sonogashira coupling