European Journal of Medicinal Chemistry 51 (2012) 145–153

Contents lists available at SciVerse ScienceDirect

European Journal of Medicinal Chemistry

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

Original article

Thieno[2,3-*d*]pyrimidinedione derivatives as antibacterial agents

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ARTICLE INFO

Article history:
Received 22 November 2011
Received in revised form
10 February 2012
Accepted 16 February 2012
Available online 25 February 2012

Keywords:
Thieno[2,3-*d*]pyrimidinediones
Antibacterial
MRSA
Antibiotic-resistant bacteria
Heterocycle synthesis

ABSTRACT

Several thieno[2,3-*d*]pyrimidinediones have been synthesized and examined for antibacterial activity against a range of Gram-positive and Gram-negative pathogens. Two compounds displayed potent activity (2–16 mg/L) against multi-drug resistant Gram-positive organisms, including methicillin resistant, vancomycin-intermediate, vancomycin-resistant *Staphylococcus aureus* (MRSA, VISA, VRSA) and vancomycin-resistant enterococci (VRE). Only one of these agents possessed moderate activity (16–32 mg/L) against Gram-negative strains. An examination of the cytotoxicity of these agents revealed that they displayed low toxicity (40–50 mg/L) against mammalian cells and very low hemolytic activity (2–7%). Taken together, these studies suggest that thieno[2,3-*d*]pyrimidinediones are interesting scaffolds for the development of novel Gram-positive antibacterial agents.

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1. Introduction

The increasing prevalence of pathogenic bacteria that are resistant to currently available antibiotics represents an alarming threat to public health. The most commonly encountered antibiotic-resistant bacteria, methicillin-resistant *Staphylococcus aureus* (MRSA), has had a major impact on infections in both the hospital and community setting [1,2]. While vancomycin continues to be the standard treatment option for antibiotic-resistant infections, the isolation of vancomycin-resistant *Staphylococcus* (VRSA) and *Enterococci* (VRE) foreshadows a day in which the utilization of vancomycin may become limited [3]. Unfortunately, as antibiotic-resistant organisms have become more commonplace, the pipeline for the discovery of new antimicrobial agents has decreased [4]. Thus, there is a pressing need for new antimicrobial agents that are capable of treating resistant bacterial strains.

Thienopyrimidines are interesting heterocyclic compounds and a number of derivatives of these compounds display therapeutic activity as antimicrobial [5–7], antiviral [8,9], antiinflammatory [10] antidiabetic [11] and anticancer [12,13] agents [14–16]. Despite the breadth of biological activities displayed by these agents, the antibacterial activity of this class of compounds has been underexplored. El-Sherbeny and colleagues examined the antimicrobial and antiviral activity of cyclopenteno and cyclohexeno [*b*]thieno[2,3-*d*]-3,4-dihydropyrimidine-4-one derivatives (Fig. 1a) [8]. These agents displayed reasonable activity (MIC values 6.25–25 mg/L) against both Gram-positive and Gram-negative bacteria; however, these agents were significantly more potent against herpes simplex virus [8]. Furanyl-thieno[2,3-*d*]pyrimidin-4-ones (Fig. 1b) were examined by Bahekar et al. for their antibacterial activity [7]. These agents displayed MIC values in the range of 4–100 mg/L against a collection of Gram-positive and Gram-negative microbes. Interestingly, these compounds also displayed antimycobaterial activity [7]. The antibacterial activity of thieno[2,3-*d*]pyrimidindiones (Fig. 1c) has not been reported in the literature; however, these compounds have been examined for antiviral activity [15].

Recently, during a study on thieno[2,3-*d*]pyrimidinones, we discovered a set of compounds that possessed antibacterial activity (Fig. 1d). These agents are structurally unrelated to any clinically used antibiotic and display discreet structural overlap with thieno[2,3-*d*]pyrimidines that have been reported in the literature. In this report, we discuss the synthesis of thieno[2,3-*d*]pyrimidinediones and their antibacterial and cytotoxic activities.

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doi:10.1016/j.ejmech.2012.02.035

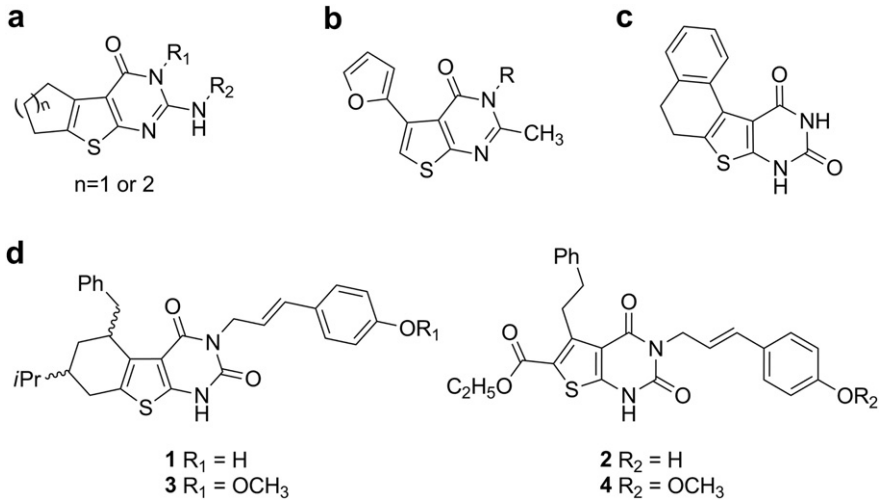


Fig. 1. Thieno[2,3-*d*]pyrimidineone derivatives.

2. Results and discussion

2.1. Chemistry

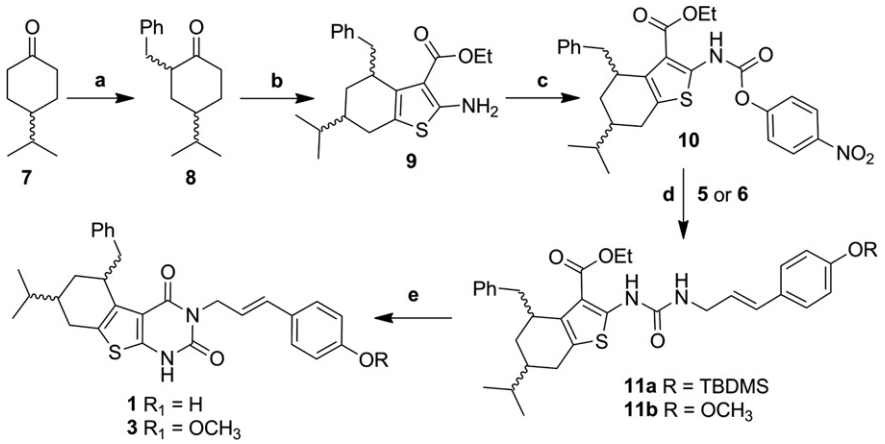
For a project on the development of antiviral therapeutics, we required the synthesis of two constrained (**1** and **3**) and two unconstrained (**2** and **4**) thieno[2,3-*d*]pyrimidine-2,4-dione derivatives (Fig. 1d), neither of which had been described in the literature. A retrosynthetic analysis of these agents suggested that an amino thiophene ester ring would be prepared first using the standard Gewald reaction [17,18]. Once the thiophene was in hand, the pyrimidine ring could be prepared by converting the amine into a urea followed by cyclizing with the ester under basic conditions.

The synthesis of compounds **1**–**4** is shown in schemes 1–3. The synthesis of the constrained derivatives **1** and **3** starts from the commercially available ethyl-2-cyanoacetate and racemic benzylated isopropyl cyclohexanone (**8**, prepared from **7**). These were reacted with sulfur to obtain the amino thiophene ester, **9**, in decent yields. Activation of **9** with *p*-nitrophenyl chloroformate generated the unstable intermediate **10**, which upon reaction with amines **5** or **6** produced urido compounds **11a** and **11b** [19]. Formation of the pyrimidinedione ring was accomplished with refluxing sodium methoxide to provide the final compounds **1** and **3** (Scheme 1) [16]. The unconstrained compounds **2** and **4** were prepared using similar methodology starting from the ethyl 3-oxo-5-phenylpentanoate, **13** (Scheme 2).

The amines, **5** and **6**, were prepared, as shown in the Scheme 3, from commercially available compounds (**17** and **21**) using procedures published for related compounds [20–26]. Amine **5** was prepared from *p*-hydroxycinnamic acid (**17**) by first protecting the phenol as the silyl ether followed by conversion of the acid into the azide (**20**). Selective reduction of the azide to **5** was accomplished using catalytic hydrogenation in the presence of Lindlar's catalyst ($Pd/CaCO_3$). Amine **6** was synthesized from *p*-iodoanisole (**21**) using a Heck reaction with acrylonitrile to generate *E*-cinnamonitrile (**22**). Reduction of the nitrile to the amine was accomplished with $LiAlH_4$.

2.2. In vitro antibacterial activity

The initial examination of compounds **1**–**4** failed to detect antiviral activity. As part of a further investigation of the biological activities of these compounds, we examined the antibacterial activity of compounds **1**–**4** and intermediates **11a**, **11b**, **16a** and **16b** against a panel of five Gram-positive and four Gram-negative bacteria (Table 1). Compounds **1** and **2** demonstrated significant



Scheme 1. a) *n*BuLi, BnBr, THF, −78 °C to r.t.,18 h, 80% b) ethyl 2-cyanoacetate, S_8, morpholine, EtOH, Δ, 24–48 h., 39% c) *p*-nitrophenyl chloroformate, pyridine, CH_2Cl_2, r.t. 6–12 h, 77% d) pyridine, DMAP, THF, r.t. 12–24 h, 69–79% e) NaOMe, MeOH, reflux, 3 h, 76–77%.

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