European Journal of Medicinal Chemistry 45 (2010) 3636–3644

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

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

Original article

Synthesis and antibacterial activity of 3-*O*-carbamoyl derivatives of 6,11-di-*O*-methylerythromycin A: A novel class of acylides

Zhongyuan Wu [a], Yong Lu [a], Ming Luo [a], Xianran He [a], Yuling Xiao [a], Jin Yang [a], Yuanhu Pan [b], Guofu Qiu [a], Hao Guo [a], Hao Hu [a], Dingshan Zhou [a], Xianming Hu [a,*]

[a] *State Key Laboratory of Virology, College of Pharmacy, Laojiashan, Wuhan University, Wuhan 430072, China*
[b] *Huazhong Agricultural University, Wuhan 430070, China*

ARTICLE INFO

Article history:
Received 10 March 2010
Received in revised form
3 May 2010
Accepted 5 May 2010
Available online 12 May 2010

Keywords:
Synthesis
Antibacterial activity
3-*O*-Carbamoyl derivatives
Acylide

ABSTRACT

A novel series of acylides, 3-*O*-carbamoyl derivatives of 6,11-di-*O*-methylerythromycin A, were synthesized and evaluated for their antibacterial activity. These compounds have significant antibacterial activity against Gram-positive pathogens, including erythromycin-resistant but methicillin-susceptible *Staphylococcus aureus*, erythromycin-resistant and methicillin-resistant *S. aureus*, erythromycin-resistant *Streptococcus pneumoniae*, and Gram-negative pathogens, such as *Haemophilus influenzae*. Among the derivatives tested, compounds **4p**, **4r**, **4w**, **4x** and **4z** were found to have potent activity against most susceptible and resistant bacteria. Compound **4p** exhibited excellent antibacterial activity in comparison to the others.

1. Introduction

The rapid development of antibiotic resistance among the major respiratory pathogens has created a serious problem for the effective management of respiratory tract infections [1–6]. There is a great medical need for new antibiotics to address the problem of antibiotic resistance. Under these circumstances, a substantial amount work has been carried out on novel macrolides. These investigations have led to the discovery of the 3-acylides. Acylides, the C-3 acylated analogs of erythromycin A, were first reported in 1997 by Asaka et al. [7,8].

The C-3 cladinose group was long considered to be crucial for the antibacterial activity of erythromycin A. However, recent structural studies have revealed that the C3 substituent of macrolides and ketolides contributes little to the binding interaction with the bacterial ribosome, and appears to occupy a region of considerable steric bulk tolerance. In addition, researchers have shown that macrolides in which the cladinose sugar is replaced by a C3-*O*-acyl group are active against many bacterial respiratory pathogens, including erythromycin-resistant strains [9–11]. The study of high-resolution X-ray co-crystal structures has shown that the 3-position group of macrolides is located near G2505 and C2610, and the cladinose group of erythromycin or clarithromycin is located at and fits with the cavity formed by G2505, C2610 and C2611 in domain V of the erythromycin binding site [12–14]. The C-3 cladinose sugar attached to the 14-membered ring macrolides is believed to be responsible for the inducibility of macrolide resistance. This moiety also appears to be responsible for efflux resistance. Removal of the cladinose can also improve activity against efflux [15]. Both FMA 199 and FMA 481 (Fig. 1) appear to have well-balanced *in vitro* activity against *Streptococcus pneumoniae* [16]. TEA 0777 (Fig. 2) shows significant potent activity against erythromycin-susceptible Gram-positive pathogens and macrolides-lincosamides-streptogramin B (MLS_B) resistant *Staphylococcus aureus* and efflux-resistant *S. pneumoniae* [17]. FMA 0122 (Fig. 2) is active against *Haemophilus influenzae*. However, TEA 0929 (Fig. 2), which shows potent antibacterial activity against almost all of the main causative pathogens of community-acquired pneumonia tested, exhibits excellent *in vivo* efficacy [11]. These results indicate that acylides have potential as next-generation macrolide antibiotics.

The new macrolide derivatives such as FMA 199, FMA 481 (Fig. 1), TEA 0929, CP-544372 (Fig. 2), telithromycin (Fig. 3) [18] and cethromycin (Fig. 3) [19] are carbamate macrolide derivatives modified by introduction of various carbamate groups. The compound CP-544372 also demonstrates good *in vitro* and *in vivo*

* Corresponding author. College of Pharmacy, Wuhan University, Wuhan 430072, China. Tel.: +86 27 68759887; fax: +86 27 68759850.
E-mail address: xmhu@whu.edu.cn (X. Hu).

0223-5234/$ – see front matter © 2010 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2010.05.009

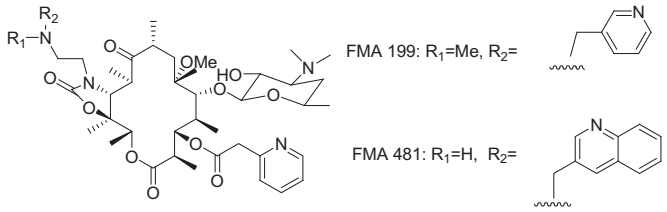

Fig. 1. Structures of FMA 199 and FMA 481.

activity against macrolide-susceptible and -resistant organisms [13–17]. Compounds **CAM-4j** and **CAM-4k** (Fig. 4) appeared potent activity against erythromycin-susceptible *S. aureus*, *Streptococcus pyogenes* and *S. pneumoniae*. Compounds **CAM-4d**, **CAM-4h** and **CAM-4i** (Fig. 4) showed potent activity against erythromycin-resistant *S. pneumoniae* encoded by the *mef* gene and compounds **CAM-4h** and **CAM-4i** displayed greatly improved activity against erythromycin-resistant *S. pneumoniae* encoded by the *erm* gene. Compound **AZM-7c** (Fig. 4) exhibited improved activity against erythromycin-resistant *S. pneumoniae* encoded by the *erm* and *mef* genes [20]. Also, 6,11-di-*O*-methylerythromycin A (Fig. 5) exhibits excellent *in vitro* and *in vivo* antibacterial activity against Gram-positive bacteria and *Mycoplasma pneumoniae* [21]. The structural modification of existing antibiotics, therefore, remains one of the most effective approaches for overcoming bacterial resistance.

On the basis of the above details, we obtained some new derivatives of 6,11-di-*O*-methylerythromycin A by substituting L-cladinose with various carbamate groups. Herein, we describe the synthesis and biological properties of a novel class of acylides, 3-*O*-carbamoyl derivatives of 6,11-di-*O*-methylerythromycin A, which showed significant antibacterial activity against Gram-positive pathogens and *H. influenzae*.

2. Chemistry

3-*O*-Carbamoyl derivatives of 6,11-di-*O*-methylerythromycin A were synthesized as follows (Scheme 1). 6,11-di-*O*-methylerythromycin A was treated with diluted acid to accomplish cleavage of cladinose producing compound **1**. Desosamine sugar remains intact under these conditions. In order to perform chemical transformations on the hydroxyl group at position 3, 2′-hydroxyl group, which is the most reactive one, must be suitably protected. Hydroxyl groups at position 12 is much less reactive. Consequently, reaction of macrolides **1** with acetic anhydride in acetone at room temperature selectively gave 2′-acetate **2** as a sole product, which can be later easily deprotected by methanolysis.

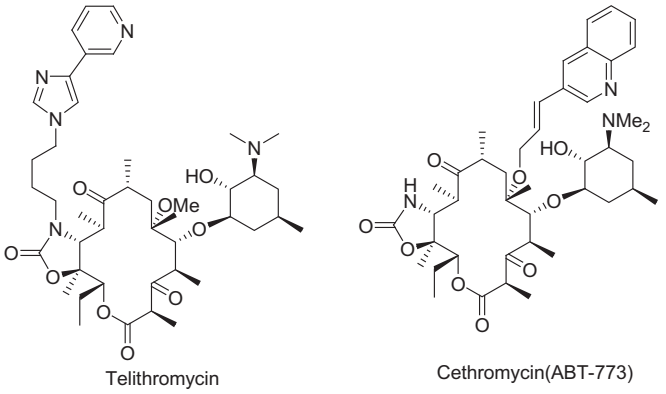

Fig. 3. Structures of Telithromycin and Cethromycin.

By using the method of Baker et al. [18,22,23], **2** was treated with excess 1,1-carbonyldiimidazole (CDI) and sodium hydride in DMF at 0 °C for 1 h, 2′-*O*-acetyl-3-*O*-acylimidazolyl-5-*O*-desosaminyl-6, 11-di-*O*-methylerythronolide A (**3**) was obtained in a yield of 76%. The structure of **3** was confirmed by ^{13}C NMR spectrum in which two carbon peaks of carbonate and carbamate could be found at δ 169.7 and δ 148.6. Compounds **4a-z** were prepared by reacting compound **3** with corresponding amines and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), followed by deprotection of the acetate group with methanol (Scheme 1). The structures of **4a-z** were determined by ^{13}C NMR, ^{1}H NMR, MS and IR spectra.

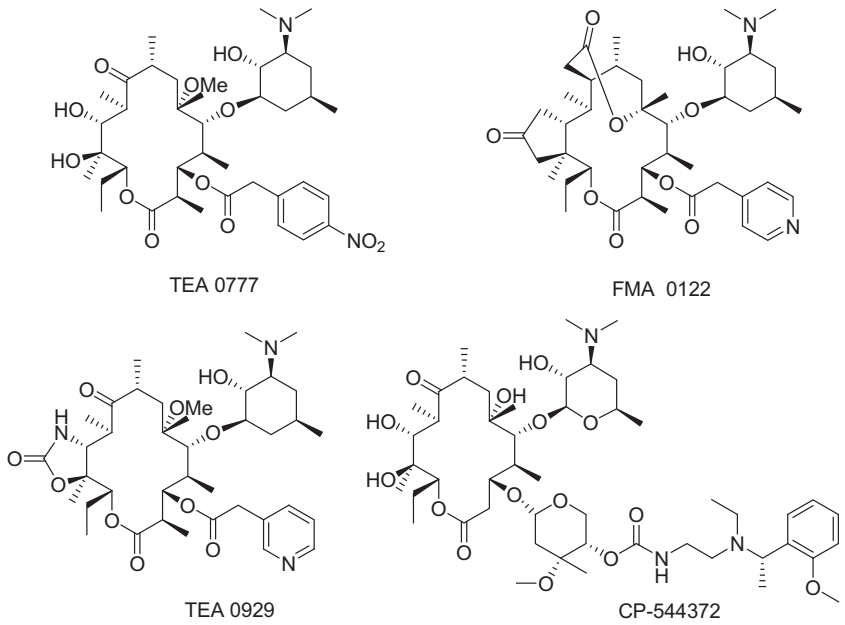

Fig. 2. Structures of TEA 0777, FMA 0122, TEA 0929 and CP-544372.