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Synthesis and antibacterial activity of 3-keto-6-*O*-carbamoyl-11,12-cyclic thiocarbamate erythromycin A derivatives

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Abstract—A series of 3-keto-6-*O*-carbamoyl-11,12-cyclic thiocarbamate erythromycin A derivatives has been synthesized. The best compounds in this series possess potent in vitro antibacterial activity against erythromycin-susceptible and erythromycin-resistant bacteria.

Erythromycin A and its derivatives such as clarithromycin and azithromycin are well-established macrolide antibiotics that have been widely used to treat respiratory tract bacterial infections.[1] However, in recent years there have been reports of failed therapy due to bacterial resistance to these macrolide antibiotics.[2] The macrolide antibiotics act against bacteria by selectively binding to the bacterial ribosome and inhibiting protein synthesis.[3] The most widespread mechanisms of bacterial resistance in the important respiratory pathogen, *Streptococcus pneumoniae*, involve the *erm*(B) methyltransferase, which methylates a specific adenine residue in the macrolide binding site of the bacterial ribosome, and the *mef*(A) efflux pump.[4]

Because of the perceived safety of the early macrolide antibiotics, and the increased resistance to these agents, especially in *S. pneumoniae*, compounds like the ketolids with the ability to treat macrolide-resistant pneumococci are particularly attractive. The ketolides are a new class of erythromycin A derivatives, in which the natural C3-cladinose sugar is replaced by a keto group.[5] The two most advanced ketolides reported to date are telithromycin[6], approved in markets worldwide including Europe (2001) and the United States (2004), and cethromycin[7], currently in phase III clinical trials (Fig. 1). The distinguishing molecular features of both compounds are the C3-ketone, a C11,C12-cyclic carbamate, and a heteroaryl side chain, each of which contributes to the improved activity against erythromycin-susceptible and erythromycin-resistant pneumococci. The C3-ketone plays a key role in circumventing efflux-mediated resistance (*mef*) and in preventing the induction of macrolide–lincosamide–streptogramin B (MLS_B, *erm*) resistance.[7] It has been reported that the C11,C12-cyclic carbamate improves activity against both erythromycin-susceptible and MLS_B-resistant organisms,[7] and that the heteroaryl group of the side chain enhances the binding affinity of ketolides for both macrolide-susceptible and macrolide-resistant bacterial ribosomes.[4]

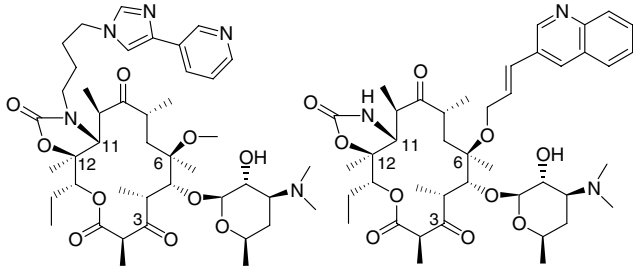

Figure 1.

Keywords: Erythromycin A; Macrolide; Ketolide; Antibacterial.
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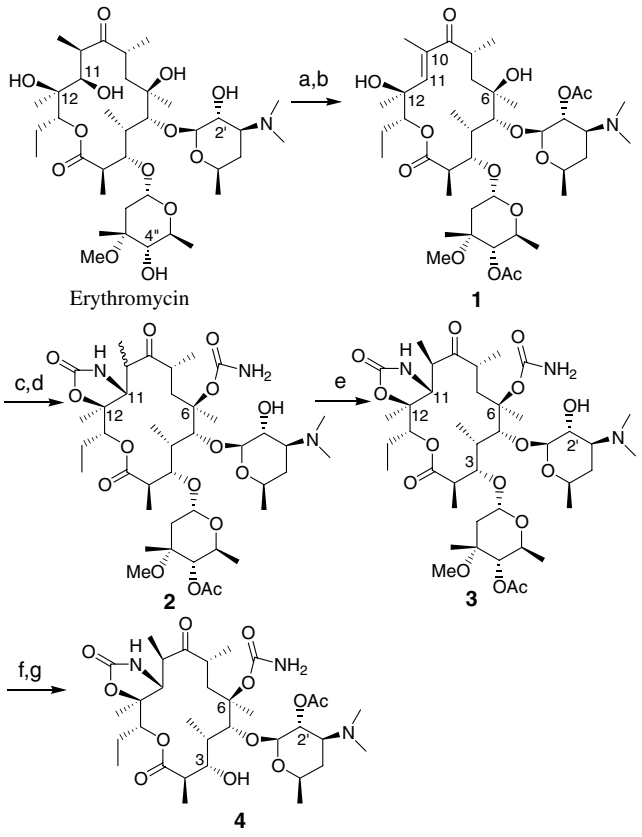
We have recently identified a series of ketolides in which the heteroaryl side chain is attached to the macrolide core via a C6-carbamate linkage.[8] To broaden our investigation of this 6-*O*-carbamoyl series and explore the structure–activity relationships in the C11/C12 region, we synthesized 6-*O*-carbamoyl ketolides with a C11,C12-cyclic thiocarbamate (Fig. 2). Herein, we report the chemistry and antibacterial activity of this novel series of 6-*O*-carbamoyl-11,12-cyclic thiocarbamate ketolides.

The synthesis of the 6-*O*-carbamoyl-11,12-cyclic thiocarbamate ketolides is outlined in Schemes 1–3. Intermediate **4** was prepared by methods described previously.[8] Briefly, erythromycin A was reacted with acetic anhydride in the presence of triethylamine and 4-dimethylaminopyridine (DMAP) to give 11,2′,4″-triacetylerythromycin A. Subsequent elimination of the C11-*O*-acetyl group using sodium bis(trimethylsilyl)amide led to 10,11-anhydroerythromycin A derivative **1**. Treatment of compound **1** with trichloroacetyl isocyanate, followed by base hydrolysis (Et_3N, MeOH/H_2O), generated the C6- and C12-primary carbamates. Under the reaction conditions, the C12-primary carbamate underwent spontaneous intramolecular Michael addition to form the C11,12-cyclic carbamate. The Michael addition product **2** was obtained as a mixture of C10-methyl epimers, which could be equilibrated to the desired C10-β-epimer **3** by treatment with potassium *tert*-butoxide. The C2′-hydroxyl group of **3** was reprotected, and the C3-cladinose sugar was then selectively removed under acidic conditions (1 N aq HCl, EtOH) to give the 3-descladinosyl derivative **4** (Scheme 1).



Scheme 1. Reagents and conditions: (a) Ac_2O, Et_3N, cat. DMAP, CH_2Cl_2; (b) $NaN(TMS)_2$, THF, 0 °C; (c) $Cl_3CC(O)NCO$, CH_2Cl_2, 0 °C; (d) Et_3N, MeOH, H_2O, reflux; (e) KO′Bu, THF, 0 °C; (f) Ac_2O, Et_3N, CH_2Cl_2; (g) aq HCl, EtOH. rt, 35% for seven steps.

Compound **4** was treated with di-*tert*-butyl dicarbonate (Boc_2O) in the presence of catalytic DMAP to selectively acylate the C11,C12-cyclic carbamate. The resulting compound **5** was hydrolyzed by treatment with aqueous lithium hydroxide solution to give the ring opened product **6**. Reprotection of the C2′-hydroxyl group (acetic anhydride, Et_3N, CH_2Cl_2) followed by Dess–Martin oxidation of the C3-hydroxyl to the corresponding C3-ketone gave compound **7**. The Boc protecting group of the C11-amine was removed by a two-step sequence due to the acid sensitivity of compound **7**. The C11-*N*-*tert*-butyl carbamate was first transformed to a *tert*-butyldimethylsilyl carbamate by reaction of **7** with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) in the presence of 2,6-lutidine. The C6-primary carbamate was also silylated under these conditions. The C11-*N*-*tert*-butyldimethylsilyl carbamate was then removed by brief treatment with potassium fluoride to give the C11-amino, C12-hydroxy ketolide **8**. Formation of the C11,C12-cyclic thiocarbamate was accomplished by reacting **8** with carbon disulfide (CS_2) in the presence of Et_3N. The silyl group of the C6-carbamate was then removed using tetrabutylammonium fluoride to give 6-*O*-carbamoyl-11,12-cyclic thiocarbamate ketolide **9a**, which was converted to compound **9b** by methanolysis of the C2′-acetyl group (Scheme 2).

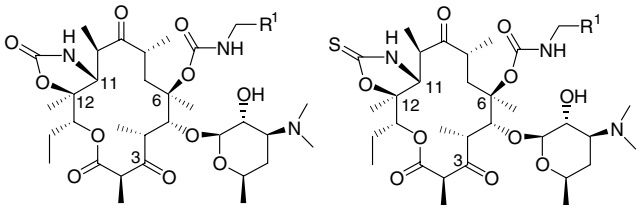


Figure 2.

Our initial attempt to install the aryl side chain at the C6 position by reacting compound **9a** with an aldehyde under reductive alkylation conditions (Et_3SiH, CF_3CO_2H, CH_3CN, 65 °C)[8] was unsuccessful. Fortunately, once the 11,12-cyclic thiocarbamate of **9a** was acetylated as in compound **10**, the installation of the aryl side chain went smoothly to give compound **11**. Removal of the acetyl protecting groups at the C11 and C2′ positions was achieved by the treatment with potassium carbonate in methanol to give the desired product **12** (Scheme 3).

The in vitro antibacterial activity of the 6-*O*-carbamoyl-11,12-cyclic thiocarbamate ketolides was assessed