Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry Letters 17 (2007) 5013–5018
Bioorganic & Medicinal Chemistry Letters

Synthesis and antibacterial activity of C11, C12-cyclic urea analogues of ketolides

Takushi Kaneko,* William McMillen† and Meghan Keaney Lynch‡

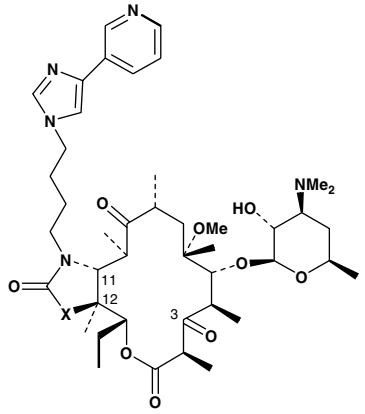
Pfizer Global Research and Development, Eastern Point Road, Groton, CT 06340, USA

Received 31 May 2007; revised 5 July 2007; accepted 9 July 2007
Available online 31 July 2007

Abstract—C11, C12-cyclic urea analogues of ketolides were designed and synthesized by use of a novel ketene acetal intermediate. This intermediate enabled introduction of an amino group at C12 stereospecifically and in high yield. The resulting cyclic urea ketolides appear to have in vitro activity similar to that of telithromycin which contains a C11, C12 cyclic carbamate moiety. Some of the C2 fluorinated compounds have improved potency against *erm*-containing *Streptococcus pyogenes*.
© 2007 Elsevier Ltd. All rights reserved.

Macrolide antibiotics represented by erythromycin A have been in use for more than half a century. More recently, however, due to the success of erythromycin A and its second-generation analogues such as clarithromycin and azithromycin, some pathogens developed resistance to macrolide antibiotics. There are two major mechanisms of resistance, one involving modification of the macrolide target, the ribosome (*erm* (B) encoded), and increased efflux of macrolide (*mef*-encoded).[1] To overcome this resistance, a new series of macrolide antibiotics called ketolides was developed. Their structures are characterized by the presence of a ketone group at C3, a cyclic carbamate group at C11 and C12, and a heterocycle tethered at the cyclic carbamate nitrogen.[1] Telithromycin (**1**) is the first and only ketolide antibiotic approved and marketed to date.[2] In the USA it is approved for the treatment of community acquired pneumonia.[3] Although there have been many ketolide analogues prepared since the original disclosure of telithromycin, almost all of them contain a cyclic carbamate moiety at C11 and C12 which is dictated by the substitution pattern of their starting material, clarithromycin (**3**). We contemplated a series of compounds in which a cyclic urea moiety was incorporated in place of the cyclic carbamate group (e.g., **2**).

We hypothesized that such compounds might have antibacterial activity, pharmacokinetic, and safety properties different from telithromycin since they possess an additional hydrogen bond donor and an additional site for modifications (see Fig. 1).

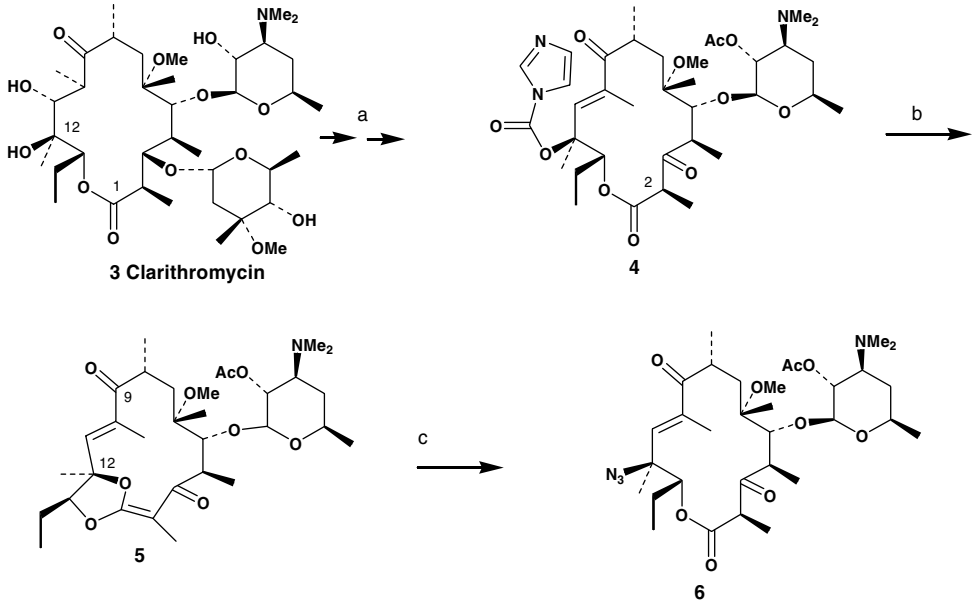


1 X=O Telithromycin
2 X=NH

Figure 1. Telithromycin and a target ketolide.

Keywords: Ketolide; Macrolide; Cyclic urea; Ketene acetal; Telithromycin; *Streptococcus pneumoniae*; *Streptococcus pyogenes*; *Haemophillus influenzae*.
* Corresponding author. Tel.: +1 203 457 9368; e-mail: takushikaneko@gmail.com
† Present address: Lilly Research Laboratory, Indianapolis, IN 46245, USA.
‡ Present address: Boston University, School of Public Health, Boston, MA 02118, USA.

0960-894X/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2007.07.041



Scheme 1. Reagents and conditions: (a) See Ref. 5; (b) DBU, CH_3CN, 80 °C, 67%; (c) TMS-N_3, $SnCl_4$, CH_2Cl_2, −78 °C to rt, 69%.

The major challenge was how to incorporate a nitrogen atom at C12. This was achieved by utilizing unique ketene acetal intermediate **5** as disclosed in our earlier manuscript (Scheme 1).[4] Thus, well-established intermediate **4** in the ketolide chemistry[5] was treated with DBU to generate ketene acetal (**5**) in 67% yield. This was a product of an internal alkylation of the C2 enolate through the oxygen atom. Its formation was believed to be manifested by the proximity of functional groups within the macrocyclic ring. After establishing its structure, it was envisioned that a nucleophile might add at C12 if the ketene acetal moiety was activated by a Lewis acid. Indeed, treatment of this intermediate with TMS-azide in the presence of tin chloride generated azide **6** in 69% yield. It was shown by X-ray crystallography that the C12 azide group had the same orientation as the C12 hydroxy group in clarithromycin probably as a result of the cage structure of **5**.[4]

The synthesis of cyclic urea analogues was then established as shown in Scheme 2. Thus, the azide group was reduced with zinc and acetic acid and the resulting C12 amine was immediately treated with phosgene to generate isocyanate **8** in a high yield. It was then allowed to react with a side-chain amine ($R–NH_2$). In contrast with the carbamate case, the product isolated from this reaction was uncyclized urea **9**. Cyclization was successfully carried out by treating it with a catalytic amount of KOH in hot toluene. The stereochemistry at C10 was determined as the same as that of telithromycin since the C10 proton appeared as a singlet at δ3.11 ppm in NMR.[6] The acetyl group at the C2′ position of desosamine was then removed by treatment with methanol to give **11**. It had been reported that fluorination at C2 sometimes increases the in vitro potency of the resulting ketolides.[7] For this purpose, the acetyl protected intermediate (**10**) was further treated with potassium hexamethyldisalazide (KHMDS) and Selectfluor™ to introduce a fluorine atom stereospecifically.[8] Alkylation of the urea nitrogen was also carried out by treating the fluorinated intermediate (**12**) with one equivalent of KHMDS and alkyl halide. The acetyl group was removed as before to give compound **15**. The compounds prepared by this route are listed in Tables 1 and 2 which incorporate slightly different strains of pathogens for in vitro screening. All MIC (minimum inhibitory concentration) determinations were carried out using NCCLS guidelines.[9] In Tables 1 and 2, average MIC's are given in μg/mL. *Staphylococcus aureus* 0052, 1146, *Streptococcus pyogenes* 203, and *Streptococcus pneumoniae* 1016 are erythromycin-susceptible strains, whereas *S. aureus* 1117, *S. pyogenes* 1079, *S. pneumoniae* 1095, and 1175 are erythromycin-resistant strains by the mechanisms indicated in the parentheses.

From Tables 1 and 2, it appears that most of the compounds are active against macrolide-sensitive *S. aureus*, *S. pyogenes*, *S. pneumoniae*, macrolide-resistant *erm*-containing *S. pneumoniae*, and *Haemophillus influenzae*. Against *mef*-containing *S. pneumoniae* fluorinated analogues are quite potent, whereas unfluorinated analogues are not. Some of the fluorinated cyclic urea derivatives have improved potency against *erm*-containing *S. pyogenes* compared with telithromycin. It is considered desirable to have activity against *erm*-containing *S. pyogenes* as this is the causative pathogen of strep throat. If the newly introduced nitrogen atom is methylated as in **15a**, **15f**, and **15g**, similar profiles to the unmethylated analogues are maintained. Substitution of this nitrogen, however, with a group larger than a methyl group appears to be detrimental for the activity against *erm*-containing *S. pyogenes*. Like telithromycin, these compounds are active against macrolide-sensitive *S. aureus* but not against *erm*-containing *S. aureus*.

Download English Version:

https://daneshyari.com/en/article/1377511

Download Persian Version:

https://daneshyari.com/article/1377511

Daneshyari.com