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Bioorganic & Medicinal Chemistry Letters 16 (2006) 6231–6235

Bioorganic & Medicinal Chemistry Letters

Synthesis and antibacterial activity of C6-carbazate ketolides

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Received 22 August 2006; revised 5 September 2006; accepted 7 September 2006
Available online 25 September 2006

Abstract—A novel series of ketolides containing heteroaryl groups that are linked to the erythronolide ring via a C6-carbazate functionality has been successfully synthesized. Careful modulation of the heteroaryl groups, the length and degree of saturation of the C6-carbazate linker, and the substituents present on each of the carbazate nitrogens led to compounds with potent activity against key bacterial respiratory pathogens. The best analogs of this series had in vitro and in vivo (sc dosing) profiles that were comparable to telithromycin.

The well-known macrolide antibiotic erythromycin A (**1**) was first used in the clinic for the treatment of upper respiratory tract infections in 1953.[1] Since then, erythromycin and second generation macrolides, such as clarithromycin (**2**) and azithromycin, have been extensively used for the treatment of upper and lower respiratory tract infections caused by Gram-positive bacteria.[2] However, during the past two decades there has been an emergence of bacteria that are resistant to these known macrolide antibiotics.[3]

In an effort to overcome bacterial resistance a novel class of macrolides known as ketolides was reported in the mid 1990s.[4] Ketolides are semi-synthetic derivatives of erythromycin A that possess a characteristic C3-ketone in place of the L-cladinose sugar residue and in most cases contain a C11,C12-cyclic carbamate functionality. The introduction of the C3-ketone functionality is instrumental in circumventing efflux (*mef*) resistance and in preventing the induction of macrolide-lincosamide-streptogramin B (MLS_b; *erm*) resistance.[5] Extensive ketolide structure–activity relationship (SAR) studies also demonstrated that binding affinity for the bacterial ribosome can be improved by attaching a heteroaryl-alkyl side chain to the erythronolide core, which forms an additional binding contact with domain II of 23S rRNA.[5,6] The side chain may be attached to the macrocyclic ring through the C11,C12-cyclic carbamate, as in telithromycin (**3**), or the C6-oxygen, as in cethromycin (**4**), with similar results. These encouraging findings have led to considerable research efforts devoted to the discovery of novel ketolide antibiotics within the pharmaceutical industry.[7] The recent worldwide marketing approval of the first ketolide Ketek® (telithromycin) from Sanofi-Aventis highlights the clinical potential of ketolides.

We recently reported a series of ketolides in which various heteroaryl side chains were attached to the erythronolide ring via a C6-carbamate moiety.[8,9] This series of carbamate ketolides showed in vitro and in vivo antibacterial profiles that were comparable to telithromycin. As a result of our continuing medicinal chemistry efforts in this area, we have identified a novel series of ketolides in which the heteroaryl group is attached to the macrocycle via a C6-carbazate functionality. The synthesis, in vitro and in vivo activities of this novel C6-carbazate ketolide series are disclosed herein.[8a,10]

This novel series of C6-carbazate ketolides (Table 1) was prepared via synthetic routes shown in Schemes 1 and 2. A key intermediate for this chemistry was primary carbamate **5** (Scheme 1), which was synthesized from commercially available erythromycin via a 9-step reaction sequence described previously.[8] Trifluoroacetic acid catalyzed condensation of 2-formyl-4,4-dimethoxy-butyronitrile with the primary carbamate of intermediate **5** gave cyanopyrrole **6**.[11] Displacement of the cyanopyrrole with hydrazine then cleanly gave primary carbazate

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Keywords: Ketolide; Macrolide; Carbazate; Macrolide-resistant bacteria.

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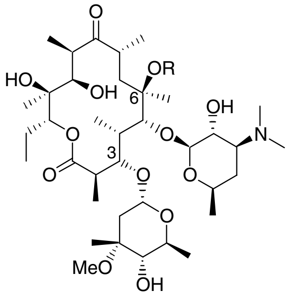
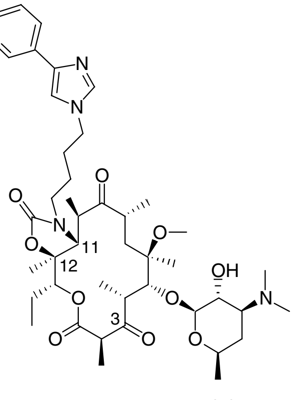
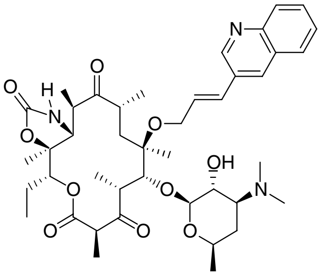
doi:10.1016/j.bmcl.2006.09.036



R = H Erythromycin A (**1**)
R = CH$_3$ Clarithromycin (**2**)



Telithromycin (**3**)



Cethromycin (**4**)

7. Various heteroaryl side chains were appended to the terminal nitrogen of the C-6 carbazate via reductive amination with a suitable aldehyde[12] in the presence of sodium cyanoborohydride to give **8a**–**8d**. A second reductive amination with 37% aqueous formaldehyde or acetaldehyde in the presence of sodium cyanoborohydride gave the dialkylated C-6 carbazates **9a**–**9j**.

The synthesis of carbazate ketolides **11** and **12** is shown in Scheme 2. Methyl hydrazine displacement of the cyanopyrrole of ketolide **6** gave carbazate ketolides **10a** and **10b** as an inseparable isomeric mixture. Treatment with 4-pyrazinyl benzeneacetaldehyde in the presence of sodium cyanoborohydride in methanol gave a 1:1 ratio of **11** and **9f**. HPLC separation of this mixture provided pure **11**. The carbazate β-nitrogen of **11** could be further alkylated with 37% aqueous formaldehyde in the presence of sodium cyanoborohydride to give **12**. As had been previously reported for the C6-carbamate ketolides, all carbazate analogs (**8a**–**8d**, **9a**–**9j**, **11**, and **12**) contained minor amounts (<10%) of the C2-(*S*)-epimer and were tested in subsequent assays as their epimeric mixtures.

Broth microdilution minimum inhibitory concentrations (MICs; lowest concentration of compound inhibiting visible growth) of these carbazate ketolides were determined against a panel of erythromycin-susceptible and erythromycin-resistant bacterial strains. All MIC determinations were performed according to CLSI (formerly NCCLS) guidelines.[13] 2-fold differences are considered to be within the error of this method. Table 1 shows MIC data for six select strains. Two of these strains, *Staphylococcus aureus* (Smith) OC4172 and *Streptococcus pneumoniae* OC9132, are erythromycin-susceptible. *Staphylococcus haemolyticus* OC3882 is inducibly resistant to erythromycin due to the presence of a ribosomal methylase [*erm*(C)]. *Streptococcus pneumoniae* OC4051 and *Streptococcus pneumoniae* OC4421 are erythromycin-resistant due to ribosomal methylation [*erm*(B)] and efflux [*mef*(A)], respectively. The Gram-negative respiratory pathogen *Haemophilus influenzae* ATCC49766 is telithromycin-susceptible. To determine the effect of serum proteins on in vitro activity, MIC values for *S. aureus* (Smith) OC4172 were also measured in the presence of 50% mouse serum.

The unsubstituted parent carbazate ketolide **7** was less active than erythromycin against the macrolide-susceptible *S. aureus* and *S. pneumoniae* strains tested. While **7** showed slight improvements in activity against the *erm*(C)-containing *S. haemolyticus* and *erm*(B)-containing *S. pneumoniae* strains compared to erythromycin, no change in activity against *H. influenzae* was seen. Most notably, even though ketolides have been shown to be less susceptible to *mef*-mediated efflux,[5] the MIC value of carbazate **7** was 16-fold higher against the *mef*(A)-containing *S. pneumoniae* strain than the erythromycin-susceptible strain.

The introduction of a heterobiaryl-alkyl side chain led to a dramatic decrease in the MIC values against both the macrolide-susceptible and macrolide-resistant strains, particularly for the *erm*(B)- and *mef*(A)-containing *S. pneumoniae* strains. To determine the optimum length of the carbon spacer between the C-6 carbazate unit and the heteroaryl moiety, a series of N-methylated 4-(2-pyrimidinyl)phenyl compounds (**9a**, **9b**, **9d**, and **9e**) containing carbon spacers of varied chain lengths and degree of saturation were prepared. The nature of the linker had a small but noticeable effect on the antibacterial activity, with the ethyl linker in **9b** giving the best overall profile against the panel of macrolide-susceptible and macrolide-resistant bacterial strains. Compounds containing the shorter methyl linker (**9a**) or the longer propenyl (**9d**) and propyl (**9e**) linkers were 2- to 8-fold less active against the *erm*(B)- and *mef*(A)-containing *S. pneumoniae* strains than the compound containing the ethyl linker (**9b**). Taking into consideration the extra nitrogen atom present in the side chain of the carbazate ketolides compared to the previously reported carbamate series,[8c] the ethyl spacer of the carbazate side chain places the heterobiaryl moiety approximately equidistant from the macrocyclic ring as the propenyl linker in the carbamate ketolides, which was found to be the optimal spacer in that series.

In general, methylation of the carbazate β-nitrogen was well tolerated (cf. **8a**, **9b**, and **8b**, **9f**). A notable exception to this trend was the 3-quinolylethyl analog where a significant elevation in the MICs for *H. influenzae* and the *erm*(C)-containing *S. haemolyticus* was observed upon methylation of the β-nitrogen (cf. **8c** and **9g**). Ethylation of the β-nitrogen (**9c**) or methylation of the α-carbazate nitrogen (**11**) led to a 2- to 16-fold increase in MIC values compared to the corresponding non-methylated/ethylated congeners. Alkylation of both carbazate nitrogens (**12**) also had a detrimental effect on antibacterial activity.