Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry Letters 17 (2007) 3900–3904
Bioorganic & Medicinal Chemistry Letters

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

Bin Zhu,* Brett A. Marinelli, Darren Abbanat, Barbara D. Foleno, Karen Bush and Mark J. Macielag

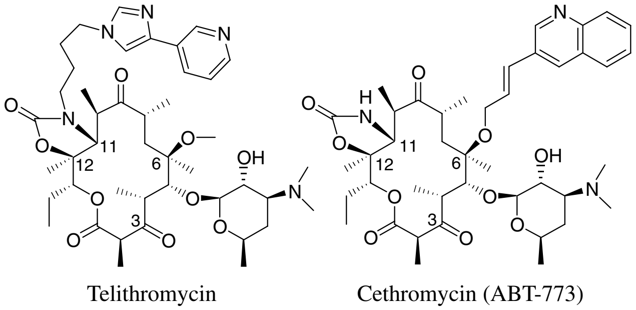
Research & Early Development, Johnson & Johnson Pharmaceutical Research & Development, L.L.C., 8 Clarke Drive, Cranbury, NJ 08512, USA

Received 20 March 2007; revised 26 April 2007; accepted 30 April 2007
Available online 3 May 2007

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]



Telithromycin Cethromycin (ABT-773)

Figure 1.

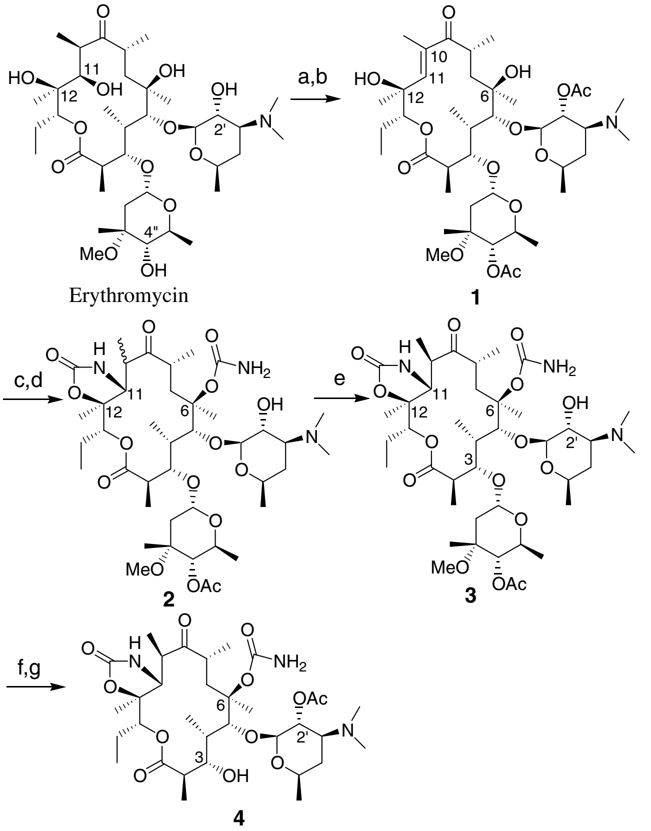
Keywords: Erythromycin A; Macrolide; Ketolide; Antibacterial.

* Corresponding author. Tel.: +1 609 409 3472; fax: +1 609 655 6930; e-mail: bzhu@prdus.jnj.com

0960-894X/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2007.04.104

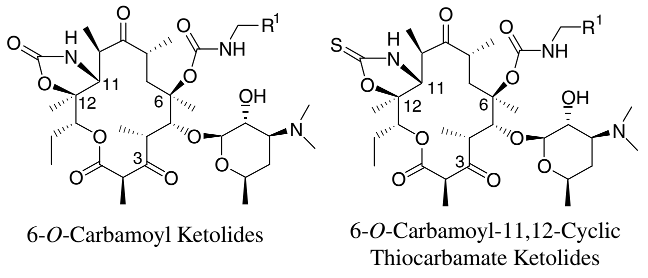
We have recently identified a series of ketolides in which the heteroaryl side chain is attached to the macrolide core via a C6-carbamate linkage.[8] To broaden our investigation of this 6-*O*-carbamoyl series and explore the structure–activity relationships in the C11/C12 region, we synthesized 6-*O*-carbamoyl 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$_3$N, MeOH/H$_2$O), 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$_2$O, Et$_3$N, cat. DMAP, CH$_2$Cl$_2$; (b) NaN(TMS)$_2$, THF, 0 °C; (c) Cl$_3$CC(O)NCO, CH$_2$Cl$_2$, 0 °C; (d) Et$_3$N, MeOH, H$_2$O, reflux; (e) KO^{t}Bu, THF, 0 °C; (f) Ac$_2$O, Et$_3$N, CH$_2$Cl$_2$; (g) aq HCl, EtOH. rt, 35% for seven steps.

Compound **4** was treated with di-*tert*-butyl dicarbonate (Boc$_2$O) 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$_3$N, CH$_2$Cl$_2$) 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$_3$N. 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).



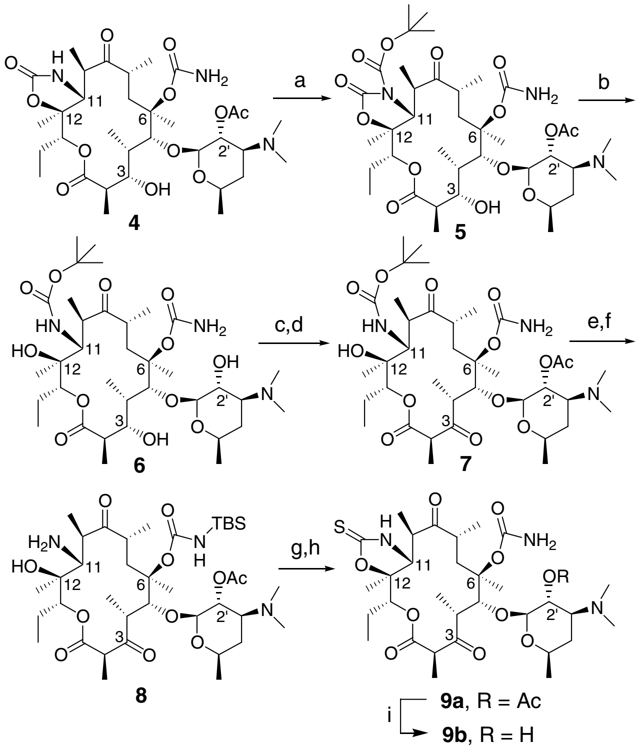
6-*O*-Carbamoyl Ketolides

6-*O*-Carbamoyl-11,12-Cyclic Thiocarbamate Ketolides

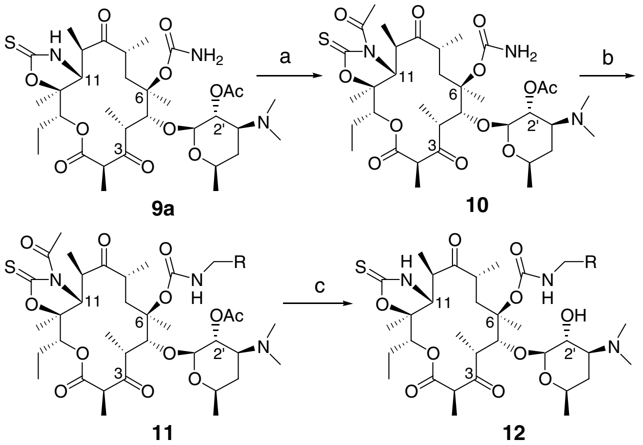
Figure 2.

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$_3$SiH, CF$_3$CO$_2$H, CH$_3$CN, 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



Scheme 2. Reagents and conditions: (a) Boc_2O, DMAP, THF, rt, 2 h, 64%; (b) aq LiOH, THF/MeOH, rt, 82%; (c) Ac_2O, Et_3N, CH_2Cl_2; (d) Dess–Martin periodinane, CH_2Cl_2, 70% for two steps; (e) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 30 min, 79%; (f) KF, THF, 10 min, 50%; (g) CS_2, Et_3N, THF, reflux, 92%; (h) $Bu_4N^+F^-$, THF, 0 °C, 30 min, 28%; (i) MeOH, rt, 24 h.



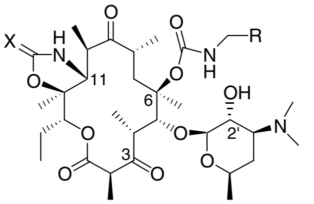
Scheme 3. Reagents and conditions: (a) Ac_2O, Et_3N, DMAP, CH_2Cl_2; (b) RCHO, Et_3SiH, CF_3CO_2H, CH_3CN, 65 °C, 51–59% yield for two steps; (c) K_2CO_3, MeOH, 15–75% yield.

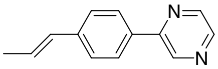
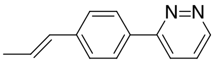
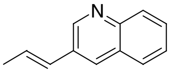
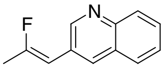
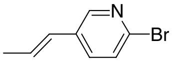
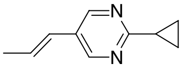
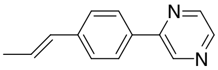
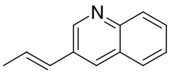
against both erythromycin-susceptible and erythromycin-resistant bacteria, with particular emphasis on respiratory pathogens. Data for selected compounds are presented in Table 1 as the minimal inhibitory concentration (MIC; lowest concentration of compound inhibiting visible growth)[9] against an abbreviated panel of five bacterial strains, including macrolide-susceptible *Staphylococcus aureus* (Smith) OC4172, macrolide-susceptible *S. pneumoniae* OC9132, macrolide-resistant *S. pneumoniae* OC4051 with the *erm*(B) ribosomal methylase gene, macrolide-resistant *S. pneumoniae* OC4438 containing the *mef*(A) efflux pump, and *Haemophilus influenzae* OC4882, a Gram-negative respiratory pathogen.

The unsubstituted parent compound **9b** was less active (higher MIC values) than erythromycin A against erythromycin-susceptible *S. aureus* and *S. pneumoniae* strains, but it was at least fourfold more potent than erythromycin A against *mef*(A)- and *erm*(B)-containing *S. pneumoniae*. In designing 11,12-cyclic thiocarbamate ketolides based on the **9b** template, we took a cue from our earlier studies of the 11,12-cyclic carbamate series,[8] in which analogs with a heteroarylpropenyl side chain at the C6 position were highly active against erythromycin-susceptible and erythromycin-resistant strains. As before, attachment of the side chain to the primary carbamate of **9b** improved the activity of the resulting compounds **12** against erythromycin-resistant *S. pneumoniae* strains. A notable exception to this trend was the equivalent activity of compounds **9b**, **12a**, and **12b** against *mef*(A)-containing *S. pneumoniae*, suggesting that in this strain the heteroaryl side chain may not be suitably disposed for productive contact with the bacterial ribosome. In reviewing the data of Table 1, it is evident that compounds with a mono-aryl (compounds **12e** and **12f**) or a fused-aryl side chain (compounds **12c** and **12d**) generally possessed a better overall antibacterial profile than compounds with a biaryl side chain (compounds **12a** and **12b**). This stands in sharp contrast to our previous results in the 11,12-cyclic carbamate series, wherein ketolides with biaryl side chains and fused-aryl side chains are similarly potent. In fact, the 11,12-cyclic thiocarbamate ketolides with a biaryl side chain are considerably less active against the erythromycin-susceptible and erythromycin-resistant *S. pneumoniae* strains than their 11,12-cyclic carbamate counterparts (**12a** vs **13**), whereas the 3-quinolinyl analog **12c** had a similar antibacterial profile as its carbamate congener **14**.[8a] It is also noteworthy in comparing **12c** and **12d** that substitution of fluorine on the double bond of the side chain had little effect on antibacterial activity. In terms of the activity against *H. influenzae*, compound **12e** showed a fourfold improvement of activity over erythromycin A, similar to that of telithromycin.

In conclusion, a series of novel 6-*O*-carbamoyl-11,12-cyclic thiocarbamate ketolides has been prepared. The antibacterial activity of these compounds was evaluated against erythromycin-susceptible and erythromycin-resistant bacterial respiratory pathogens. The best compounds of this series possess in vitro antibacterial activity similar to that of telithromycin. Further studies of this series of ketolide compounds will be reported in the future.

Table 1. In vitro antibacterial activity of 6-*O*-carbamoyl-11,12-cyclic thiocarbamate ketolides



Compound	X	R	MIC (μg/ml)				
			S. aur.[a]	*S. pneum.*[b]	*S. pneum.* [*erm*(B)][c]	*S. pneum.*[*mef*(A)][d]	*H. inf.*[e]
EryA	—	—	0.5	0.06	>16	4	8
Telith	—	—	0.25	0.03	0.06	0.25	2
9b	S	—	4	0.25	4	1	8
12a	S		0.5	0.25	0.25	1	8
12b	S		0.5	0.12	0.5	1	4
12c	S		0.25	⩽0.015	0.03	0.12	4
12d	S		0.5	⩽0.015	0.06	0.12	4
12e	S		0.5	⩽0.015	0.06	0.25	2
12f	S		0.5	0.03	0.06	0.25	4
13[f]	O		0.12	0.03	0.06	0.25[g]	4
14[f]	O		0.25	⩽0.015	0.03	0.12[g]	4

[a] *Staphylococcus aureus* OC4172 (erythromycin-susceptible).

[b] *Streptococcus pneumoniae* OC9132 (erythromycin-susceptible).

[c] *Streptococcus pneumoniae* OC4051 (erythromycin-resistant due to ribosomal methylation).

[d] *Streptococcus pneumoniae* OC4438 (erythromycin-resistant due to efflux).

[e] *Haemophilus influenzae* OC4882.

[f] Ref. 8a.

[g] Unpublished results.

Acknowledgment

The authors wish to thank Ellyn Wira for contributions to in vitro testing.

References and notes

1. Bryskier, A. J.; Butzler, J.-P.; Neu, H. C.; Tulkens, P. M. *Macrolides. Chemistry, Pharmacology and Clinical Uses*; Arnette Blackwell: Paris, 1993.
2. (a) Amsden, G. W. *J. Antimicrob. Chemother.* **1999**, *44*, 1; (b) Lonks, J. R.; Garau, J.; Mederios, A. A. *J. Antimicrob. Chemother.* **2002**, *50*, 87.
3. For recent reviews, see: (a) Zhanel, G. G.; Dueck, M.; Hoban, D. J.; Vercaigne, L. M.; Embil, J. M.; Gin, A. S.; Karlowsky, J. A. *Drugs* **2001**, *61*, 443; (b) Blondeau, J. M.; DeCarolis, E.; Metzler, K. L.; Hansen, G. T. *Expert Opin. Investig. Drugs* **2002**, *11*, 189.
4. Kaneko, T.; McArthur, H.; Sutcliffe, J. *Expert Opin. Ther. Patents* **2000**, *10*, 403.
5. For recent reviews, see: (a) Wu, Y.-J.; Su, W.-G. *Curr. Med. Chem.* **2001**, *8*, 1727; (b) Zhanel, G. G.; Walters,

M.; Noreddin, A.; Vercaigne, L. M.; Wierzbowski, A.; Embil, J. M.; Gin, A. S.; Douthwaite, S.; Hoban, D. J. *Drugs* **2002**, *62*, 1771; (c) Asaka, T.; Manaka, A.; Sugiyama, H. *Curr. Top. Med. Chem.* **2003**, *3*, 961.

6. Denis, A.; Agouridas, C.; Auger, J.-M.; Benedetti, Y.; Bonnefoy, A.; Bretin, F.; Chantot, J.-F.; Dussarat, A.; Fromentin, C.; Gouin D'Ambrieres, S.; Lachaud, S.; Laurin, P.; Le Martret, O.; Loyau, V.; Tessot, N.; Pejac, J.-M.; Perron, S. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3075.
7. Ma, Z.; Clark, R. F.; Brazzale, A.; Wang, S.; Rupp, M. J.; Li, L.; Griesgraber, G.; Zhang, S.; Yong, H.; Phan, L. T.; Nemoto, P. A.; Chu, D. T. W.; Plattner, J. J.; Zhang, X.; Zhong, P.; Cao, Z.; Nilius, A. M.; Shortridge, V. D.; Flamm, R.; Mitten, M.; Meulbroek, J.; Ewing, P.; Alder, J.; Or, Y. S. *J. Med. Chem.* **2001**, *44*, 4137.
8. (a) Henninger, T. C.; Xu, X.; Abbanat, D.; Baum, E. Z.; Foleno, B. D.; Hilliard, J. J.; Bush, K.; Hlasta, D. J.; Macielag, M. J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4495; (b) Xu, X.; Henninger, T.; Abbanat, D.; Bush, K.; Foleno, B.; Hilliard, J.; Macielag, M. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 883.
9. The minimal inhibitory concentrations (MICs) were determined by the broth microdilution method according to Clinical and Laboratory Standards Institute (CLSI, formerly NCCLS) guidelines. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically*, 5th ed.; Approved standard: NCCLS Document M7-A5, 2000.