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

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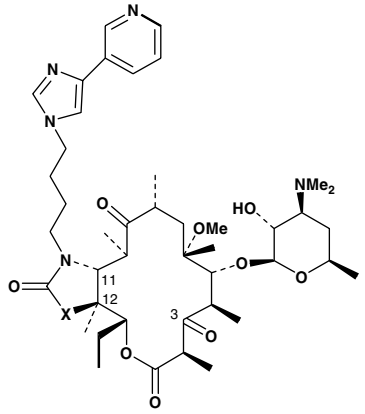
Abstract—C11, C12-cyclic urea analogues of ketolides were designed and synthesized by use of a novel ketene acetal intermediate. This intermediate enabled introduction of an amino group at C12 stereospecifically and in high yield. The resulting cyclic urea ketolides appear to have in vitro activity similar 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*.

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*.
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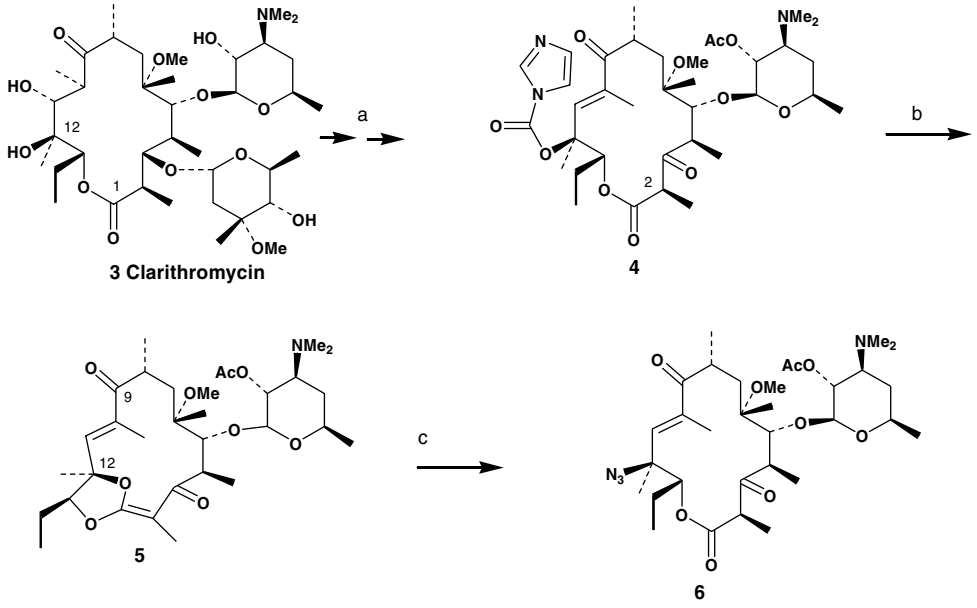
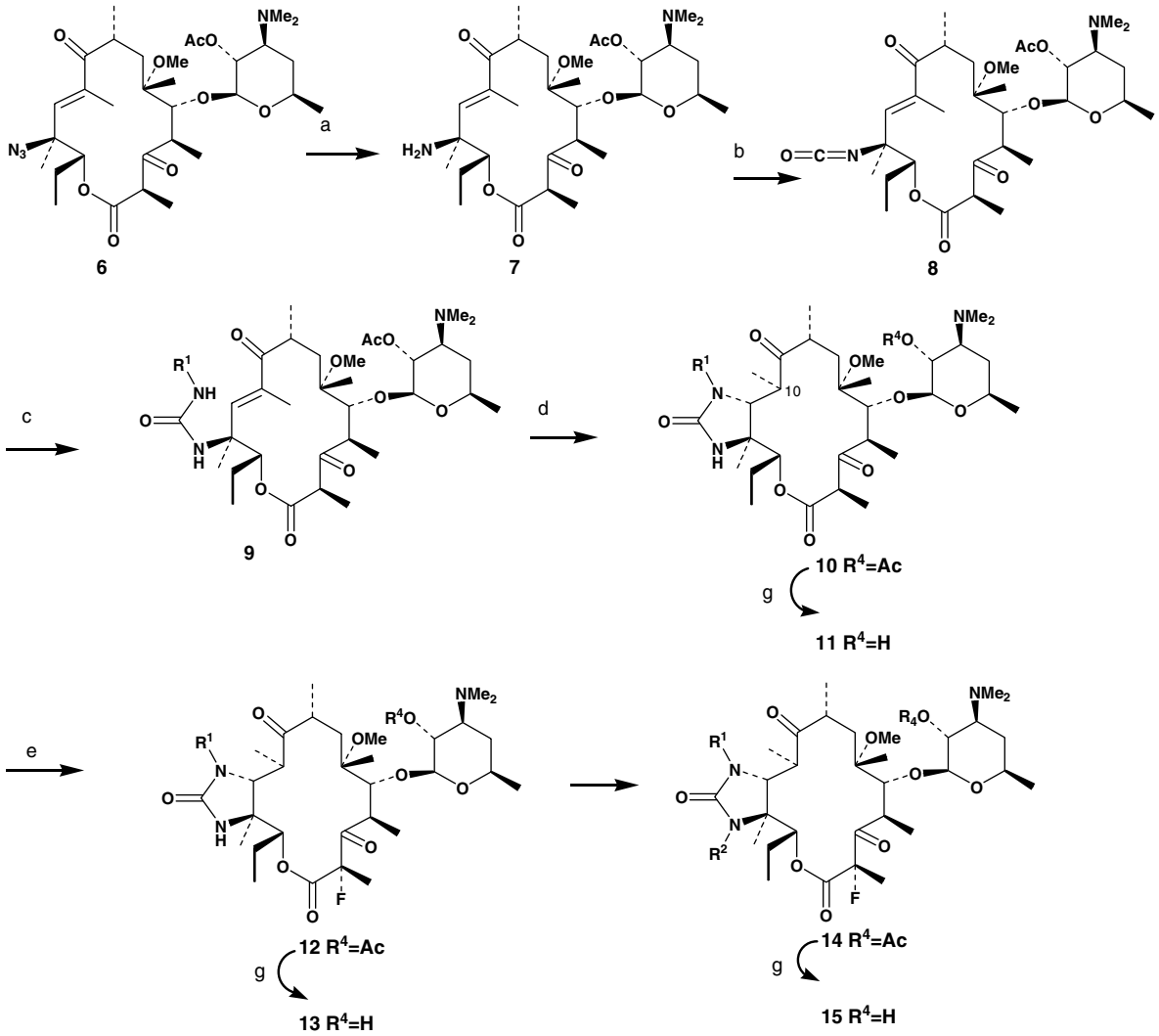


Scheme 1. Reagents and conditions: (a) See Ref. 5; (b) DBU, CH_3CN, 80 °C, 67%; (c) TMS-N_3, $SnCl_4$, CH_2Cl_2, −78 °C to rt, 69%.

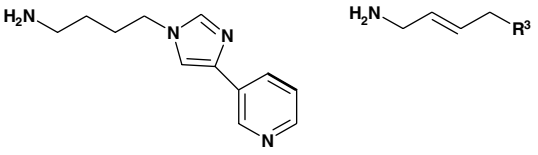
The major challenge was how to incorporate a nitrogen atom at C12. This was achieved by utilizing unique ketene acetal intermediate **5** as disclosed in our earlier manuscript (Scheme 1).[4] Thus, well-established intermediate **4** in the ketolide chemistry[5] was treated with DBU to generate ketene 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*.



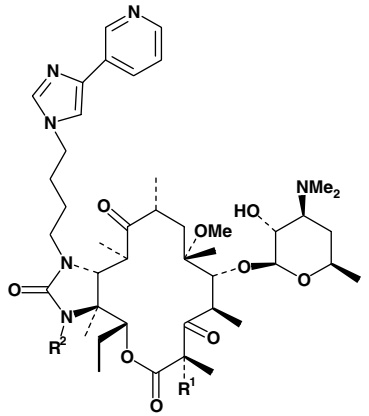
Scheme 2. Reagents and conditions: (a) Zn, HOAc, rt, 30–45 min, 99%; (b) phosgene, Et_3N, THF, 0 °C, 45 min, 86%; (c) R^1–NH_2, CH_3CN, rt, overnight, 40–80%; (d) powdered KOH, toluene, 85–90 °C, 30 min to 1.2 h, 70–99%; (e) KHMDS, Selectfluor™, DMF, −60 °C, 15 min, 90–98%; (f) KHMDS, R^2–I or R^2–Br, DMF, −60 °C to rt, 2 h, 60–70%; (g) MeOH, rt, 6 h, 90–95%. R^1—NH_2=

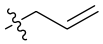
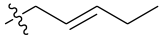
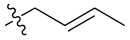


Within the limited heterocycles tested, the unsaturation in the tether imparts little difference into their in vitro potency (**11a** vs **11c**; **13a** vs **13c**; **15a** vs **15g**). Some analogues have activity against *H. influenzae* similar to or slightly better than telithromycin. Compound **15f** appears to have a balanced in vitro profile against macrolide-resistant *S. pneumoniae*, *S. pyogenes*, and *H. influenzae*. Due to changes in the direction of research, no in vivo data were generated on any of these compounds.

In conclusion, we have successfully synthesized C11, C12-cyclic urea (as opposed to a cyclic carbamate in telithromycin) analogues of ketolides. The efficient introduction of a prerequisite nitrogen atom at C12 was achieved by utilizing a novel ketene acetal intermediate. The nitrogen atom was introduced regio- and stereo-specifically at the C12 position. The resulting cyclic urea analogues possess in vitro antibacterial activity similar to that of telithromycin. Some of the fluorinated analogues show improved potency against macrolide-resistant *S. pyogenes*. In addition, the chemistry described here may be of use in designing new series of ketolides where the C12 amino group is modified.

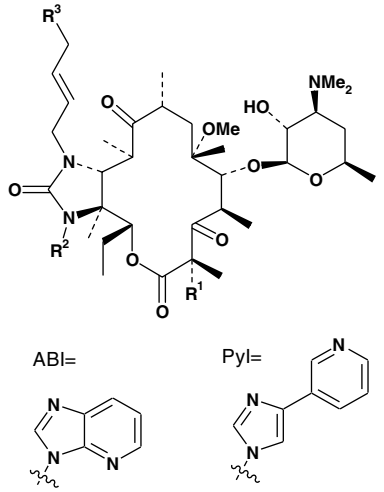
Table 1. Antimicrobial activity of C11, C12-cyclic urea ketolides (MIC μg/mL)



Compound	R^1	R^2	*S. aureus* (s) 0052	*S. aureus* (erm) 1117	*S. pyogenes* (s) 203	*S. pyogenes* (erm) 1079	*S. pneumoniae* (s) 1016	*S. pneumoniae* (erm) 1095	*S. pneumoniae* (mef) 1175	*H. influenzae* 1100
Telithromycin (**1**)			0.049	100	0.012	32	0.013	0.05	0.39	0.5
11a	H	H	0.039	100	0.024	32	0.024	0.049	6.3	8
13a	F	H	0.049	100	0.006	4	0.006	0.012	0.78	2
15a	F	Me	0.024	100	0.024	8	0.013	0.025	0.20	2
15b	F		0.049	100	0.012	64	0.025	0.05	0.39	0.5
15c	F	Et	0.049	100	0.024	32	0.013	0.025	0.39	0.25
15d	F		0.098	100	0.098	64	0.05	0.10	0.78	0.5
15e	F		0.098	100	0.049	32	0.05	0.10	0.39	0.25

S. aureus, *Staphylococcus aureus*; *S. pyogenes*, *Streptococcus pyogenes*; *S. pneumoniae*, *Streptococcus pneumoniae*; *H. influenzae*, *Haemophilus influenzae*; (s), erythromycin susceptible.

Table 2. Antimicrobial activity of C11, C12-cyclic urea ketolides (MIC μg/mL)



Compound	R^1	R^2	R^3	*S. aureus* (s) 1146	*S. aureus* (erm) 1095	*S. pyogenes* (s) 203	*S. pyogenes* (erm) 1079	*S. pneumoniae* (s) 1016	*S. pneumoniae* (erm) 1095	*S. pneumoniae* (mef) 1175	*H. influenzae* 1218
Telithromycin (**1**)				0.063	64	0.063	32	0.063	0.063	0.13	0.5
11b	H	H	ABI	0.13	64	0.063	16	0.063	0.063	1.0	1.0
13b	F	H	ABI	0.063	64	0.063	2	0.063	0.063	0.25	0.5
15f	F	Me	ABI	0.063	64	0.063	2	0.063	0.063	0.13	0.25
11c	H	H	PyI	0.25	64	0.063	32	0.063	0.063	4.0	2.0
13c	F	H	PyI	0.063	64	0.063	4	0.063	0.063	0.25	0.5
15g	F	Me	PyI	0.063	64	0.063	4	0.063	0.063	0.063	1

Acknowledgments

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References and notes

1. For a review, see: Kaneko, T.; Dougherty, T. J.; Magee, T. V. In *Comprehensive Medicinal Chemistry II*; Triggle, D. J., Taylor, J. B., Eds.; Elsevier: Oxford, 2006; Vol. 7, pp 519–566.
2. Denis, A.; Agouridas, C.; Auger, J.-M.; Benedetti, Y.; Bonnefoy, A.; Bretin, F.; Chantot, J.-F.; Dussart, A.; Fromentin, C.; D'Ambrieres, S. G.; Lachaud, S.; Laurin, P.; Le Martret, O.; Loyau, V.; tesson, N.; Pejac, J.-M.; Perron, S. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3075.
3. FDA News P07-19, February 12, 2007.
4. Kaneko, T.; McMillen, W.; Keaney Lynch, M.; Bordner, J. *Heterocycles*, published online, 23 February, 2007.
5. Agouridas, C.; Denis, A.; Auger, J. M.; Benedetti, Y.; Bonnefoy, A.; Bretin, F.; Chantot, J. F.; Dussarat, A.; Fromentin, C.; D'Ambrieres, S. G.; Lachaud, S.; laurin, P.; Le Martret, O.; Loyau, V.; Tessot, N. *J. Med. Chem.* **1998**, *41*, 4080.
6. Baker, W. R.; Clark, J.; Stephens, R. L.; Kim, K. H. *J. Org. Chem.* **1988**, *53*, 2340.
7. Phan, L.; Or, Y. S.; Plattner, J. J.; Chen, Y.; Clark, R. F. U.S. Patent 6,124,269, 2000; *Chem. Abstr. 133*, 238249.
8. Kaneko, T.; McMillen, W.; Sutcliffe, J.; Duignan, J.; Petitpas, J. *Abstracts of Papers*, 40th Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto, Canada, 2000; Abstract No. F-1815.
9. National Committee for Clinical Laboratory Standards, 2000, NCCLS Document M7-A5, Vol. 20, Wayne, PA.