Conference or Workshop Item:
Arsic, B, Regan, A, Morris, G et al. (2017) Conformational studies of tylosin A, tylosin B, erythromycin B and erythromycin C and full assignments of tylosin A in CDCl3 and tylosin B in phosphate buffered D2O. In: 1st RSC Anglo-Nordic Medicinal Chemistry Symposium, 11-14 Jun 2017. (Unpublished)

Conformational studies of tylosin A, tylosin B, erythromycin B and erythromycin C and full assignments of tylosin A in $CDCl_3$ and tylosin B in phosphate buffered D_2O

P01

Biljana Arsic[1], Andrew Regan[2], Gareth Morris[2], Angela Oates[1], Andrew McBain[1], Jill Barber[1]

[1] Division of Pharmacy and Optometry, School of Health Sciences, University of Manchester, Oxford Road, M13 9PT, Manchester, UK

[2] School of Chemistry, University of Manchester, Oxford road, M13 9PL, Manchester, UK

Introduction

Erythromycins and tylosins show similar instability in aqueous solution, so they are worthy of investigation and comparison. Tylosin A decomposes into tylosin B in acid (Figure 1 A). Erythromycin A is in equilibrium with its hemiacetal form, and decomposes easily in the acid medium (Figure 1B). Erythromycins B and C were synthesized in order to increase acid stability while keeping a similar spectrum of antimicrobial activity to erythromycin A (Figure 1C).

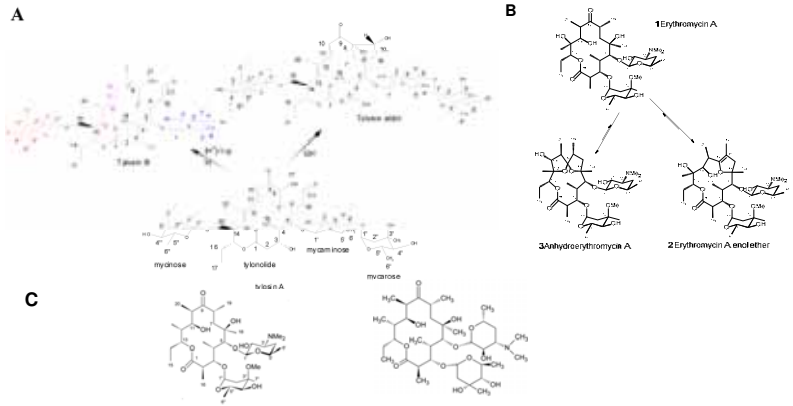

Figure 1. A Tylosin A and its decomposition product in the acid medium-tylosin B; **B** Erythromycin A and its degradation products; **C** Erythromycin B and erythromycin C.

Materials and Methods

Molecular modelling

Conformational searching of tylosin B, erythromycin B and C in water was performed using Macromodel software.

NMR analysis

Full spectral assignments of tylosin A in $CDCl_3$ and tylosin B in phosphate buffered D_2O were achieved using a combination of 1D and 2D NMR techniques : ^1H, ^{13}C, DEPT90, DEPT135, COSY, HSQC and HMBC.

Determination of Minimum Inhibitory Concentrations (MIC)

Minimum Inhibitory Concentrations (MICs) were determined using standard methods (McBain et al., 2004).

Results and Discussion

The global minimum for tylosin B in H_2O found using Macromodel software was similar to that previously found for tylosin A (Arsic et al., 2017) (Figure 2A), and its global minimum is neither folded-out nor folded-in conformation. Erythromycin B at its global minimum (E = 143.86 kJ mol^{-1}) adopts a folded-in conformation, and erythromycin C (E = 73.48 kJ mol^{-1}) a folded-out conformation similar to erythromycin A (Figure 2B). Each global minimum was found multiple times.

Minimum inhibitory concentrations for tylosin A and tylosin B were lower than for clarithromycin and azithromycin (Table 1), as expected, based on our earlier findings connected to the relation between the conformation of the global minimum and the spectrum of anti-bacterial activities (Arsic et al., 2014).

Full assignments for the ^1H and ^{13}C spectra of tylosin A in $CDCl_3$ and tylosin B in phosphate buffered D_2O were achieved.

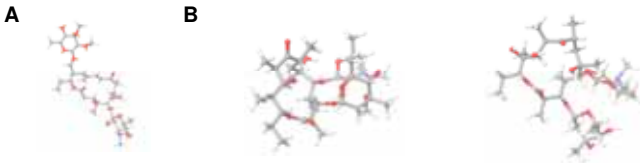

Figure 2. Global minima for **A** Tylosin A in $CHCl_3$; **B** Erythromycin B and erythromycin C.

Bacterial strains	MIC (μg mL^{-1})			
	Clarithromycin	Azithromycin	Tylosin A	Tylosin B
Escherichia coli wound isolate	12	2	125	31.25
Bacillus cereus MRBG 4.21	0.2	4	0.98	0.98
Staphylococcus aureus wound isolate	0.2	8	31.25	>500
Pseudomonas aeruginosa PA01	62.5	15.6	250	62.5
Staphylococcus epidermidis clinical isolate	250	31.2	250	62.5
Serratia marcescens wound isolate	>500	>500	500	250
Corynebacterium xerosis wound isolate	>500	250	500	250

Table 1. Minimum inhibitory concentrations (MICs) expressed in μg mL^{-1} for tylosin A and tylosin B compared to clarithromycin and azithromycin

Conclusions

The antibacterial activities of tylosin A and tylosin B found for the bacterial strains studied are lower than those found for clarithromycin and azithromycin. This is consistent with the global minimum conformations of the tylosins investigated, which are neither folded-out nor folded-in.

References

B. Arsic, J. A. Aguilar, R. A. Bryce, J. Barber, *Magn. Reson. Chem.* **2017**, 55(4), 367-373.

B. Arsic, A. Awan, R. J. Brennan, J. A. Aguilar, R. Ledder, A. J. McBain, A. C. Regan, J. Barber, *Med. Chem. Commun.* **2014**, 5, 1347-1354.

A.J. McBain, R. G. Ledder, P. Sreenivasan, P. Gilbert, *J. Antimicrob. Chemother.* **2004**, *53* (5), 772-777.