The Solvent Polarity Dependence of Macrocycles' Conformations

Stefan Peintner,[a] Emma Danelius,[a] Vasanthanathan Poongavanam,[a] Máté Erdelyi[a,b,*] Jan Kihlberg[a,*]

[a]Department of Chemistry - BMC, Uppsala University, Box 576, SE-751 23 Uppsala, Sweden
[b]The Swedish NMR Centre, SE-405 30 Gothenburg, Sweden

Macrocyclisation is commonly used to improve binding to targets that have difficult-to-drug, flat and featureless binding sites. Macrocycles have been proposed to possess a conformational flexibility that provides them with both aqueous solubility *and* lipid permeability, i.e. they behave as molecular chameleons.[1] To better understand the structural features responsible for such amphiphilic properties we are investigating the relationship between solvent polarity and conformations of macrocycles.

Macrolide antibiotics are a widely used and orally administrated class of macrocyclic drugs. They have a ≥14 membered ring, several rotatable bonds and two or more flexible side-chains. Despite having a molecular weight of 730-850 Da they have satisfactory cell permeability and aqueous solubility.[2] To investigate if macrolide antibiotics behave as molecular chameleons we determined the solution structure of roxithromycin and telithromycin. This was done by use of NAMFIS[3], an ensemble analysis technique combining solution NMR data with computational conformational sampling.[4] We have used $CDCl_3$ as solvent to mimic the apolar cell membrane, and D_2O as a mimic of the cytosol.

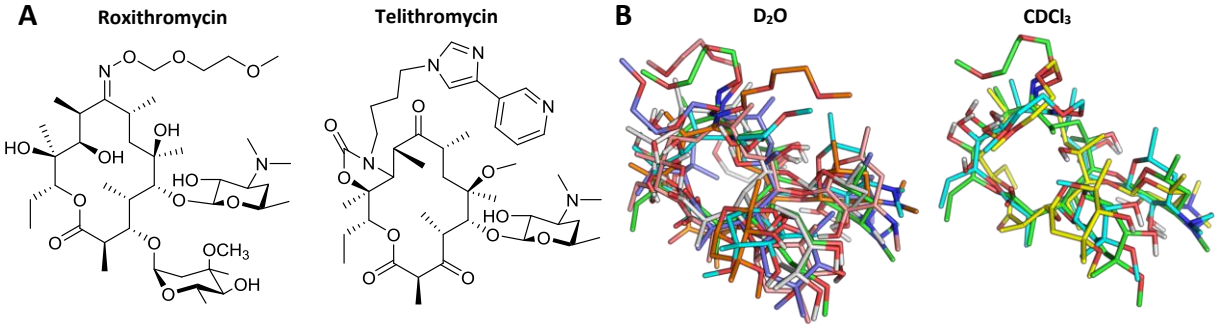

Figure 1. A: The structures of roxithromycin and telithromycin. **B:** The solution ensembles of roxithromycin in D_2O and $CDCl_3$, as determined by the NAMFIS methodology

We found that both macrocyclic drugs populated conformational space that cannot be represented by a single conformation, neither in D_2O nor in $CDCl_3$. Molecular flexibility was higher in D_2O than in $CDCl_3$, and closed conformations with the flexible side chain oriented over the macrocyclic ring dominated in $CDCl_3$ in contrast to in D_2O.

References

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