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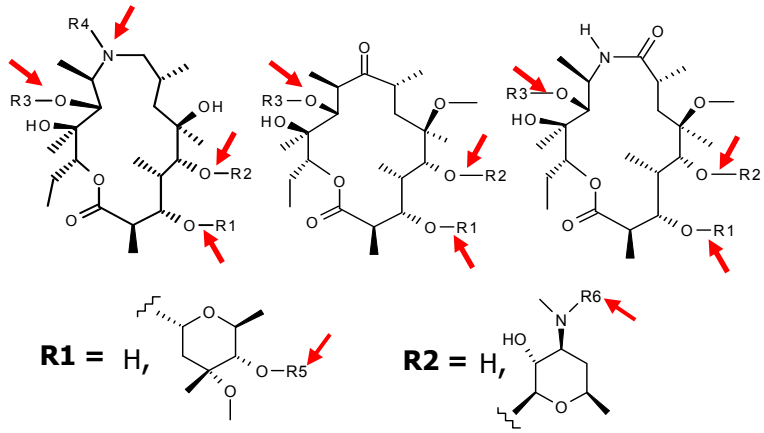
Physicochemical Profiling of Macrocycles: Link to Cellular and *in vivo* PK Parameters

Objectives:

- Profiling of a representative set of 560 macrolides on several PhysChem properties and their comparison with 29000 small molecules
- Investigating the link to cellular and *in vivo* PK properties with a rationally designed subset of macrolides



R3 - R6 = various hydrophilic and hydrophobic, aliphatic, alicyclic, aromatic and heteroaromatic substituents

Methodology:

- HPLC based bio-mimetic binding data were measured - automated platform for high-throughput measurements of physico-chemical properties
  - Lipophilicity determination – ChromLogD
  - Acid/base (pKa) estimation
  - Human serum albumin binding
  - Alpha – 1-acidglycoprotein binfding
  - Immobilised Artificial Membrane partition
- Mimic biological systems - dynamic equilibrium processes on large surfaces
- Cellular accumulation = accumulation in NCI-H292 cells in 3h, expressed relative to azithromycin
- Cellular retention and in vivo PK parameters (rat) ranged from low-high clearance (CL); moderate-high Vdss, moderate-long t1/2, low-moderate oral bioavailability were also measured and used for developing QSAR models

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