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Title: Permeation profiles of Antibiotics

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Permeation profiles of Antibiotics

César A. López

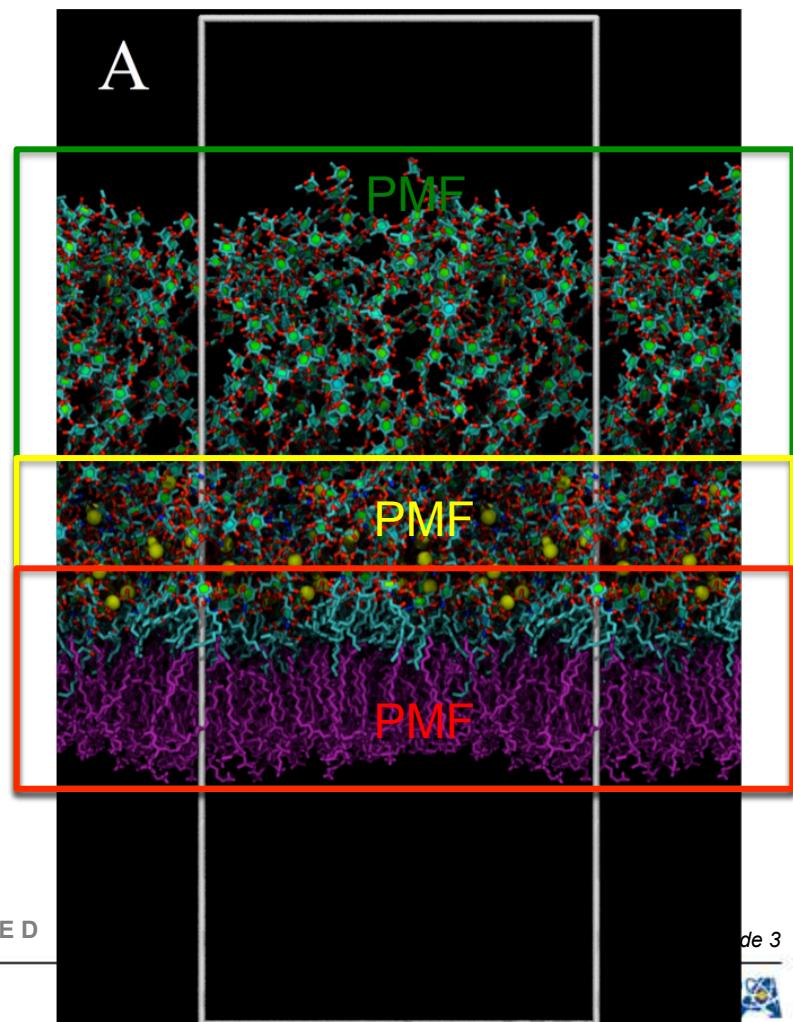
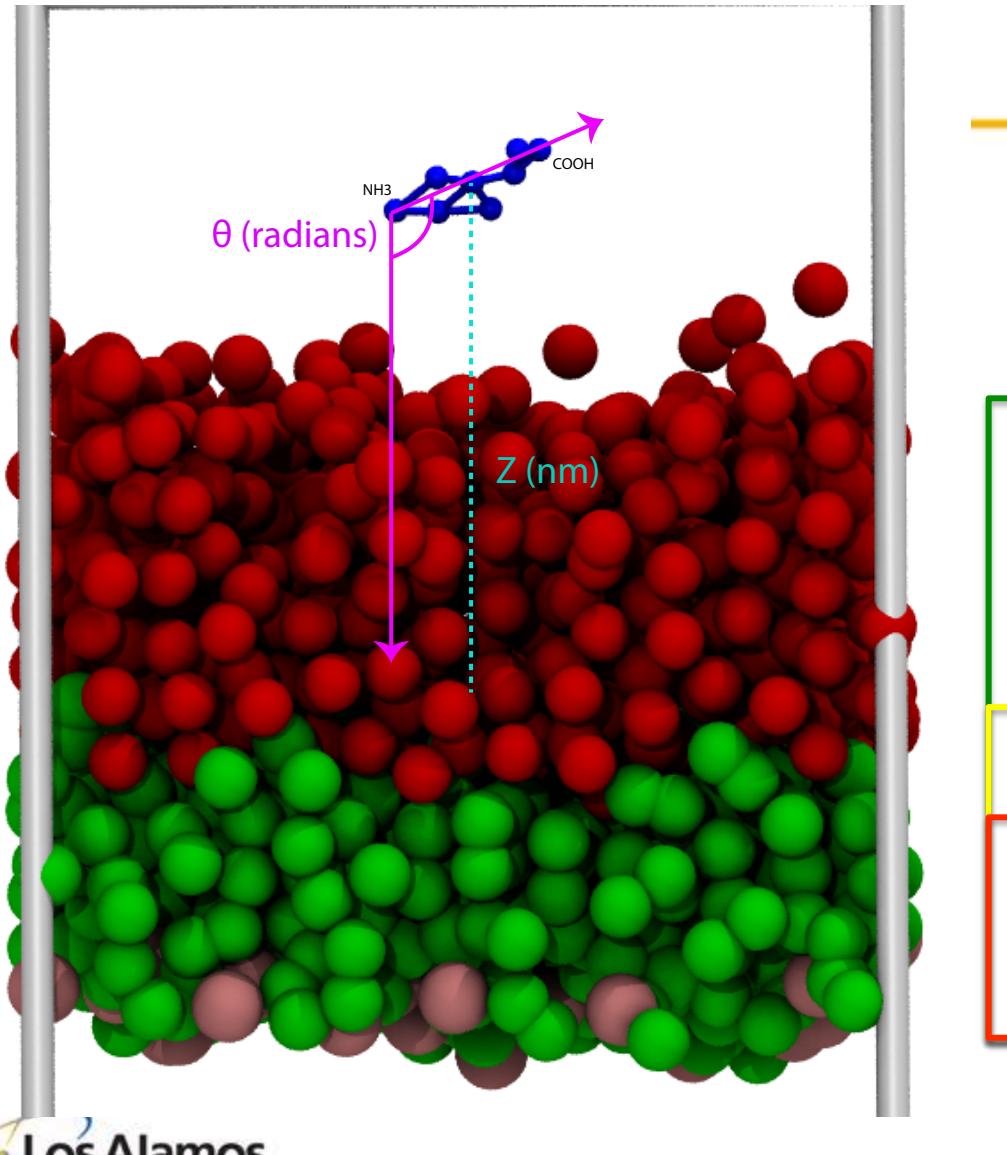
Theoretical biology and biophysics

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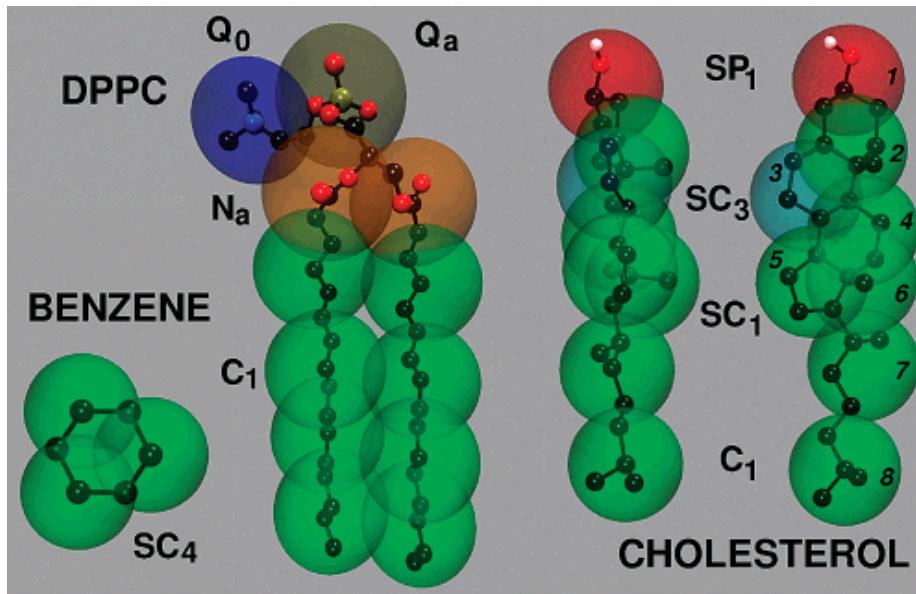
Motivation

- Combating bacterial inherent resistance.
- Drug development mainly uses brute force rather than rational design.
- Current experimental approaches lack molecular detail.

How to compute this?



Coarse-graining + enhanced methods= success



can everything be coarse grained?

	Atomistic level	Coarse-grained level	Exp.
Water	1.4×10^{-3} (1) 6.8×10^{-2} (2) 4×10^{-2} (2) 1.3×10^{-2} (3) 1.6×10^{-2} (4) 7×10^{-2} (5)	4.44×10^{-4}	8.3×10^{-3} (6) 7×10^{-3} (7) 4×10^{-4} (8) 6×10^{-4} (9)
Acetamide	8.2×10^{-2} (1) 6.6×10^{-3} (3)	4.6×10^{-4}	1×10^{-4} (10) 1.7×10^{-4} (11) 2.9×10^{-4} (5)
Acetic acid	1.4×10^{-1} (1) 1.3×10^{-1} (3)	4.7×10^{-3}	6.9×10^{-3} (11) 6.6×10^{-3} (12) 5×10^{-3} (13)
Butane	7.3 (1)	1.1	-----

- They both help to overcome energy barriers while transitioning between states.
- When properly combined they become a very powerful sampling technic.

First Guinea pig

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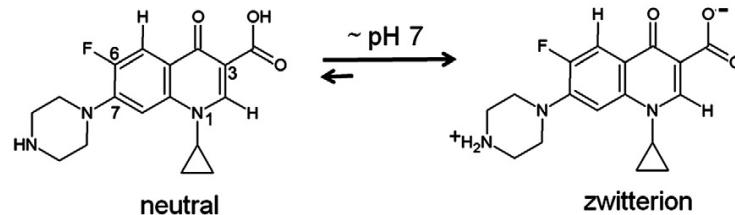
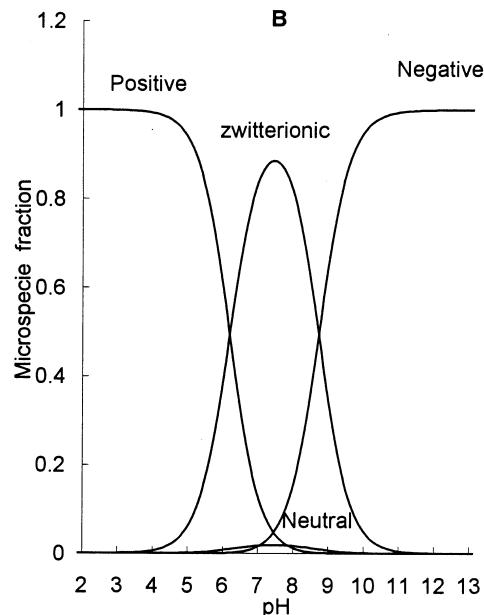
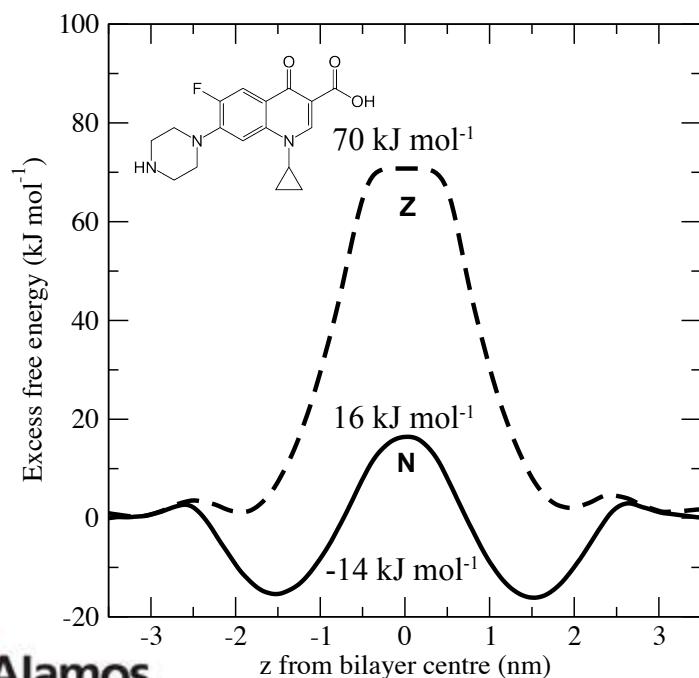
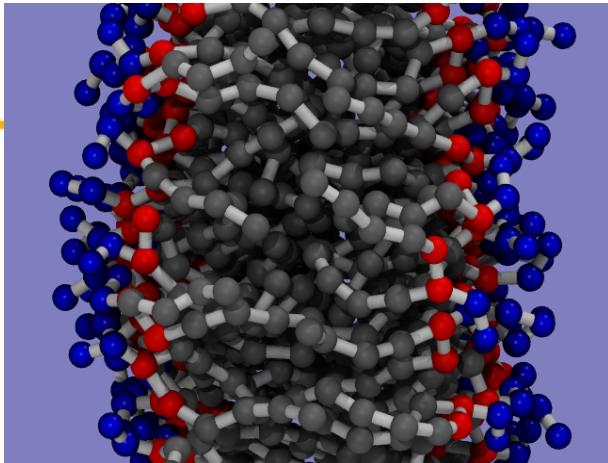


Fig. 1. Molecular structures of neutral and zwitterionic CPFX. The central structural unit of CPFX is a quinolone ring with the fluorine atom at C-6, a piperazine moiety at C-7, a cyclopropyl ring at position 1 and a carboxyl group at position 3.



Given that Cipro can be neutral, is there any advantage for translocation?



The CG force field can be parameterized to quantitatively match atomistic calculations

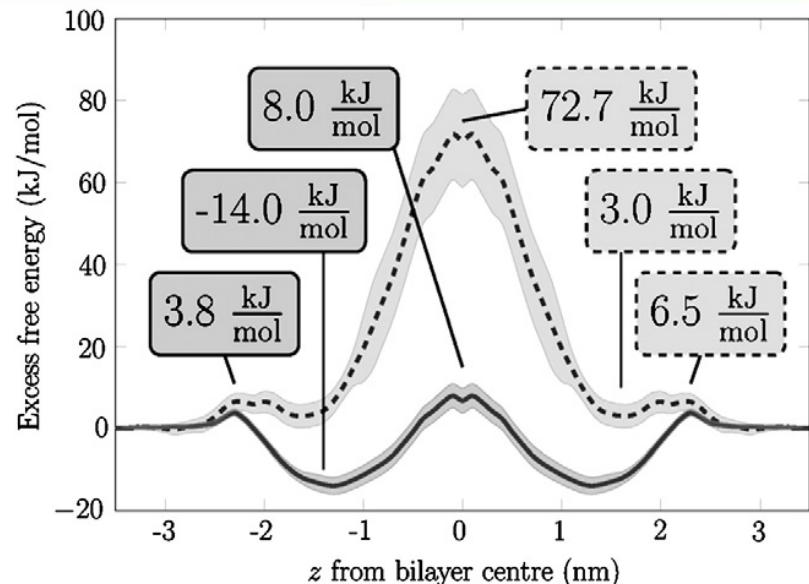


Fig. 5. Excess free energy of both zwitterionic (dashed line) and neutral (full line) CPFX molecules as a function of distance from the center of the bilayer. The curves are mirrored to show the values in the whole bilayer system. Error limits are drawn as gray areas. Key values of the curves are explicitly listed in the figure. Membrane center is at $z = 0$.

Mechanism for translocation of fluoroquinolones across lipid membranes

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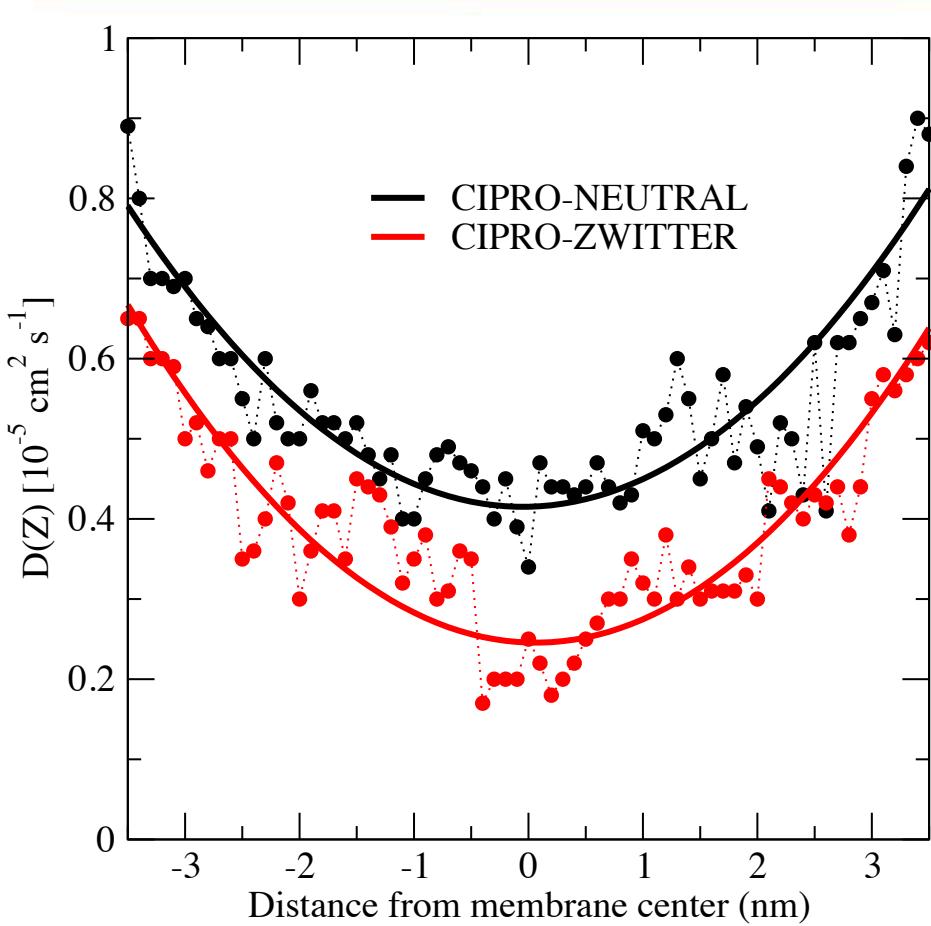
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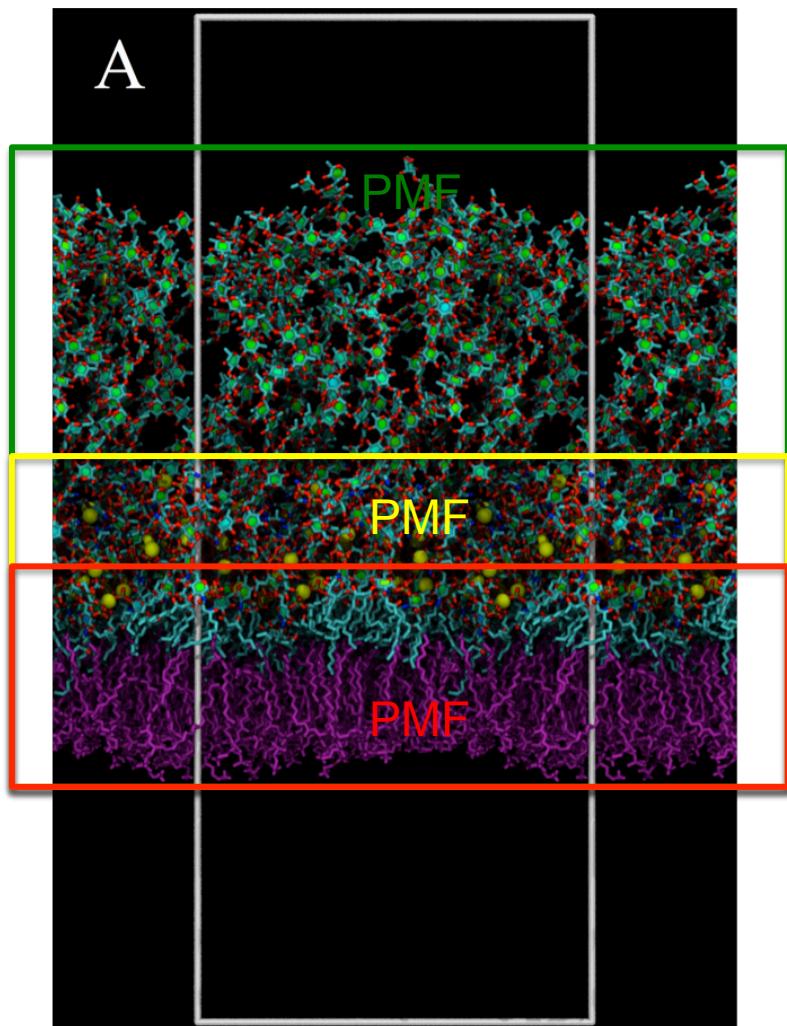
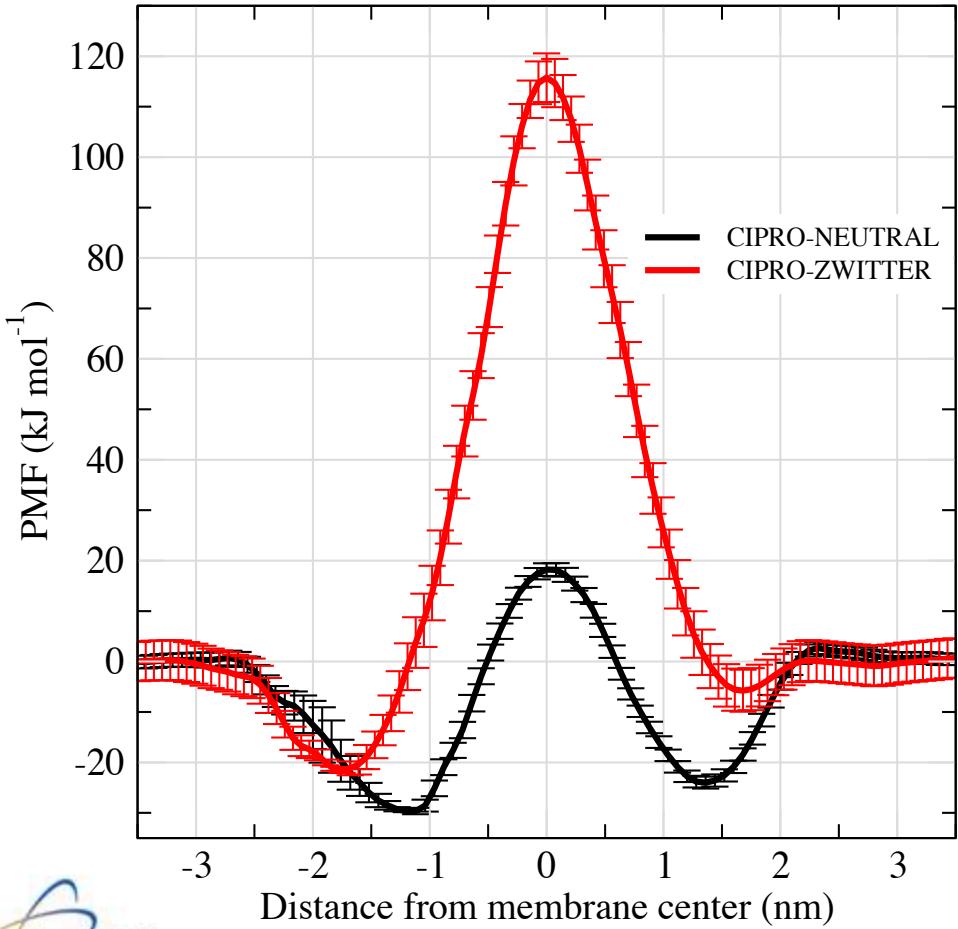
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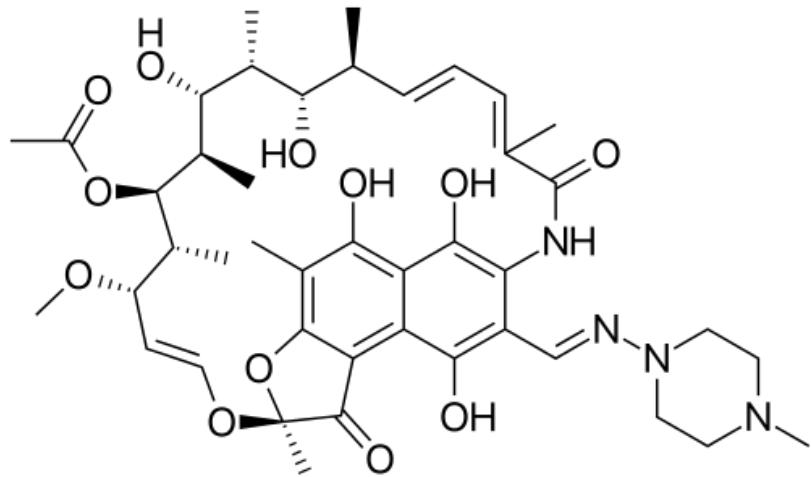
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Larger drugs can also be targeted



Computed permeability
across POPC bilayer =
 $5 \times 10^{-6} \text{ cm s}^{-1}$

