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Title: Permeation profiles of Antibiotics

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Intended for: Collaboration in drug resistance research

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Permeation profiles of Antibiotics

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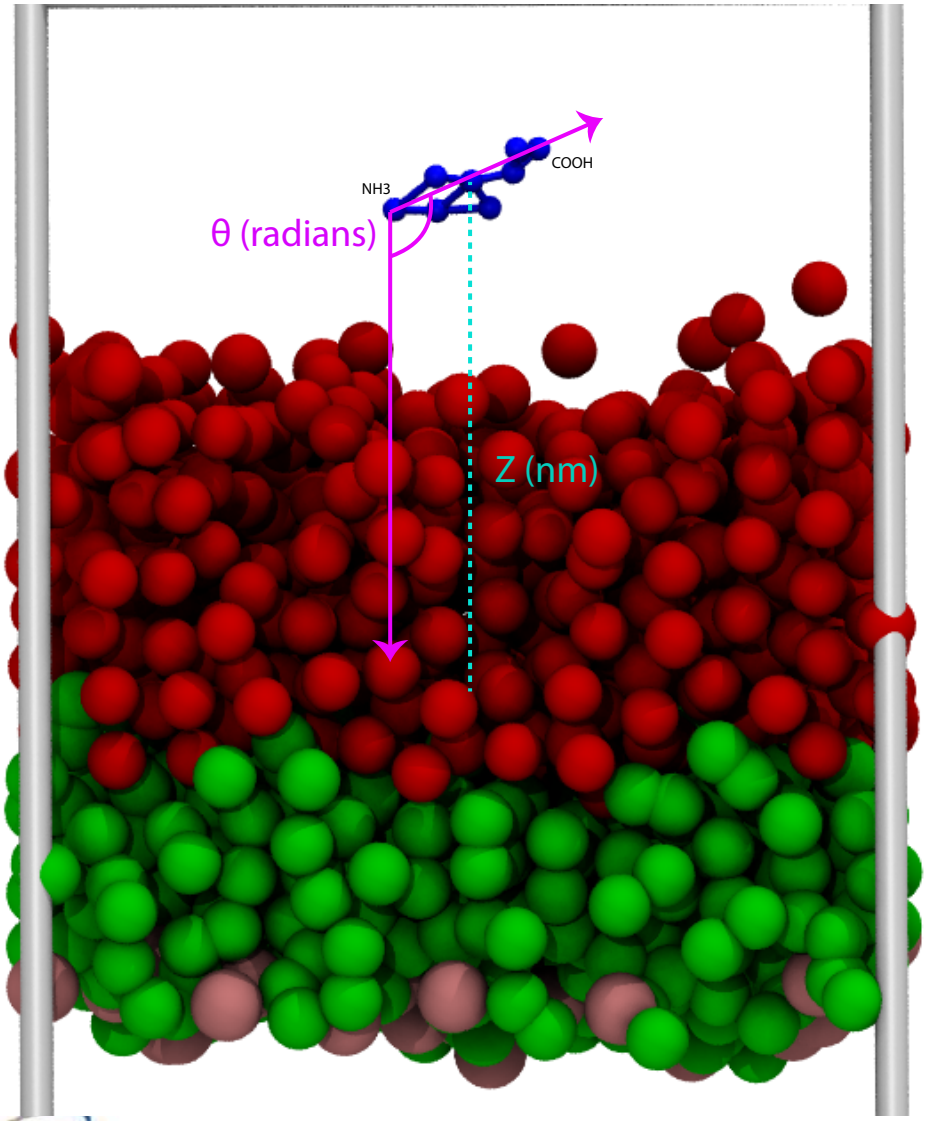
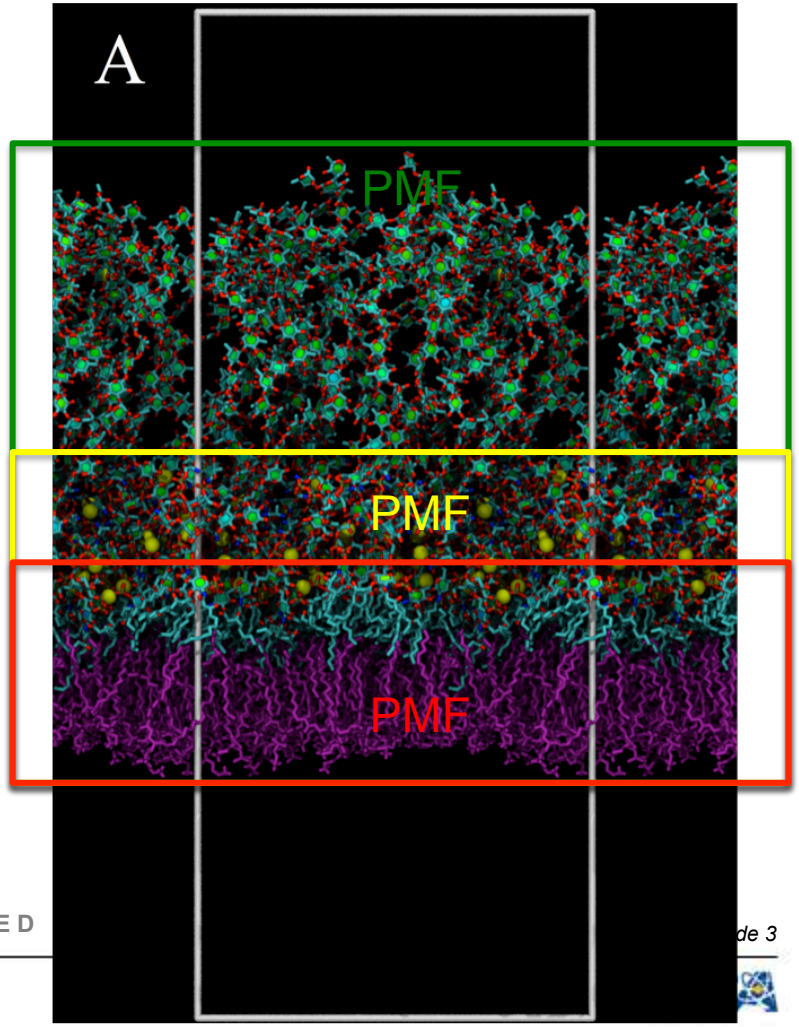
Motivation

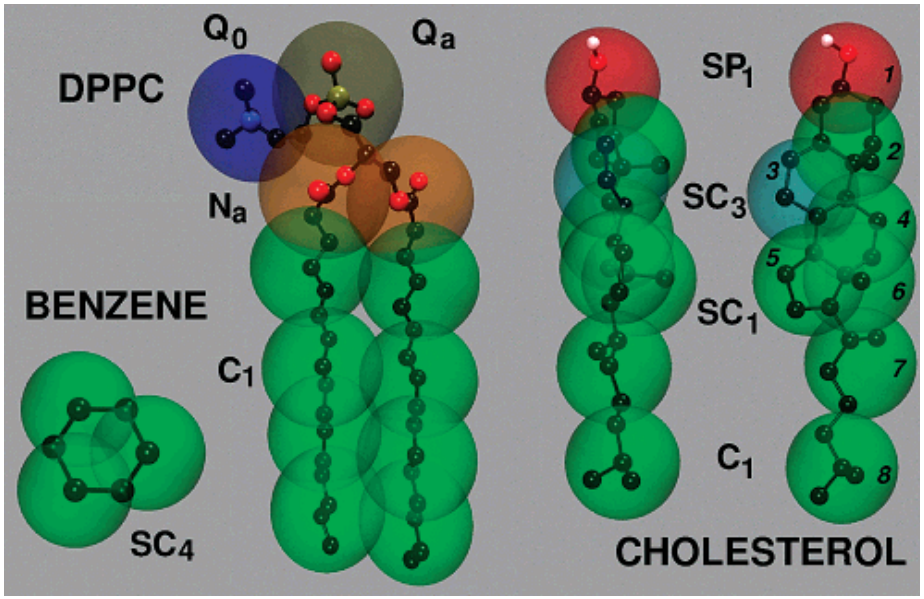
- Combating bacterial inherent resistance.
- Drug development mainly uses brute force rather than rational design.
- Current experimental approaches lack molecular detail.

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

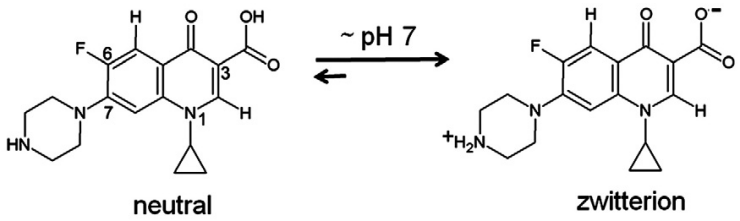
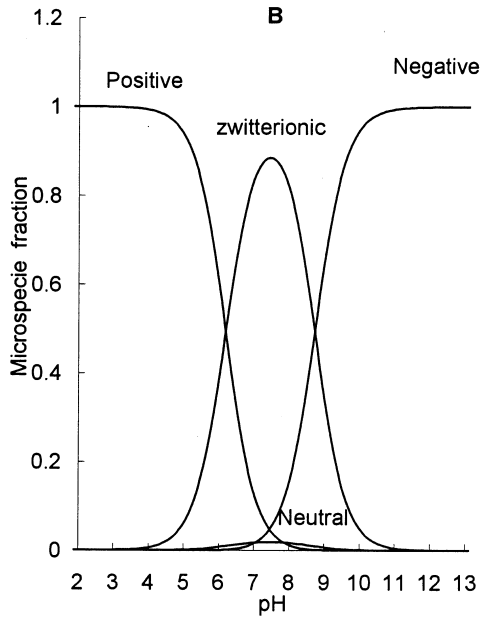
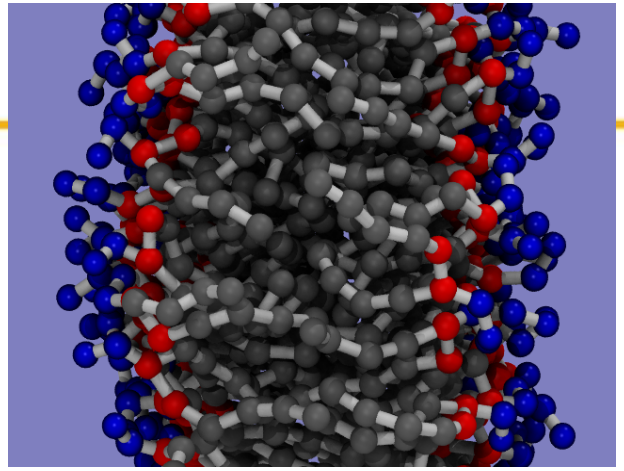


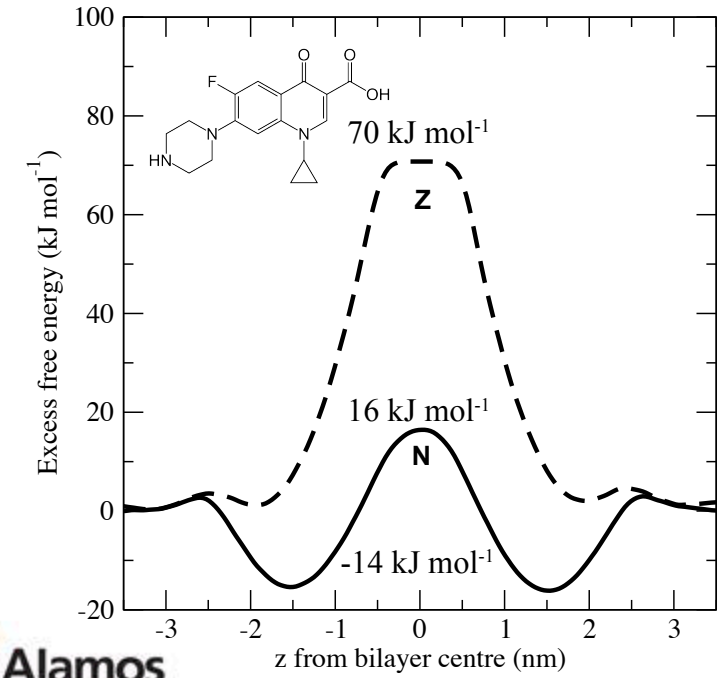
Fig. 1. Molecular structures of neutral and zwitterionic CPFX. The central structural unit of CPFX is a quinolone ring with the fluorine atom at C-6, a piperazine moiety at C-7, a cyclopropyl ring at position 1 and a carboxyl group at position 3.



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

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





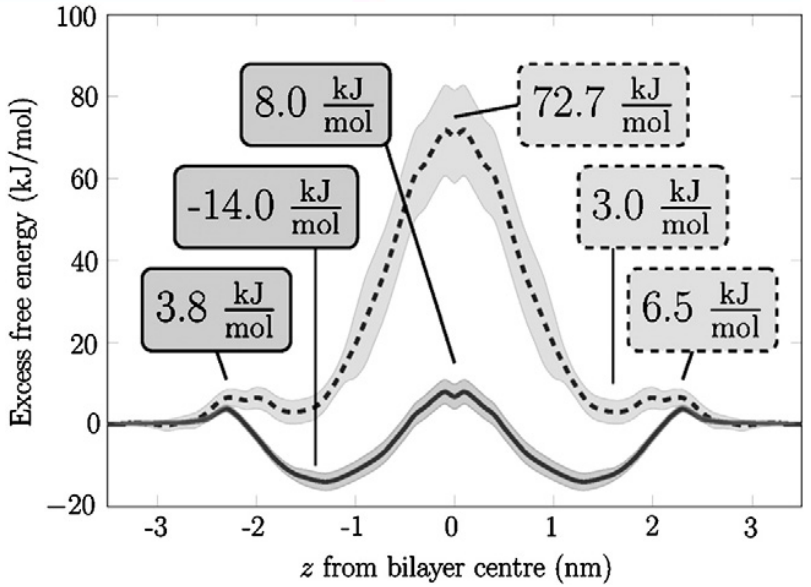


Fig. 5. Excess free energy of both zwitterionic (dashed line) and neutral (full line) CPFX molecules as a function of distance from the center of the bilayer. The curves are mirrored to show the values in the whole bilayer system. Error limits are drawn as gray areas. Key values of the curves are explicitly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

Mechanism for translocation of fluoroquinolones across lipid membranes

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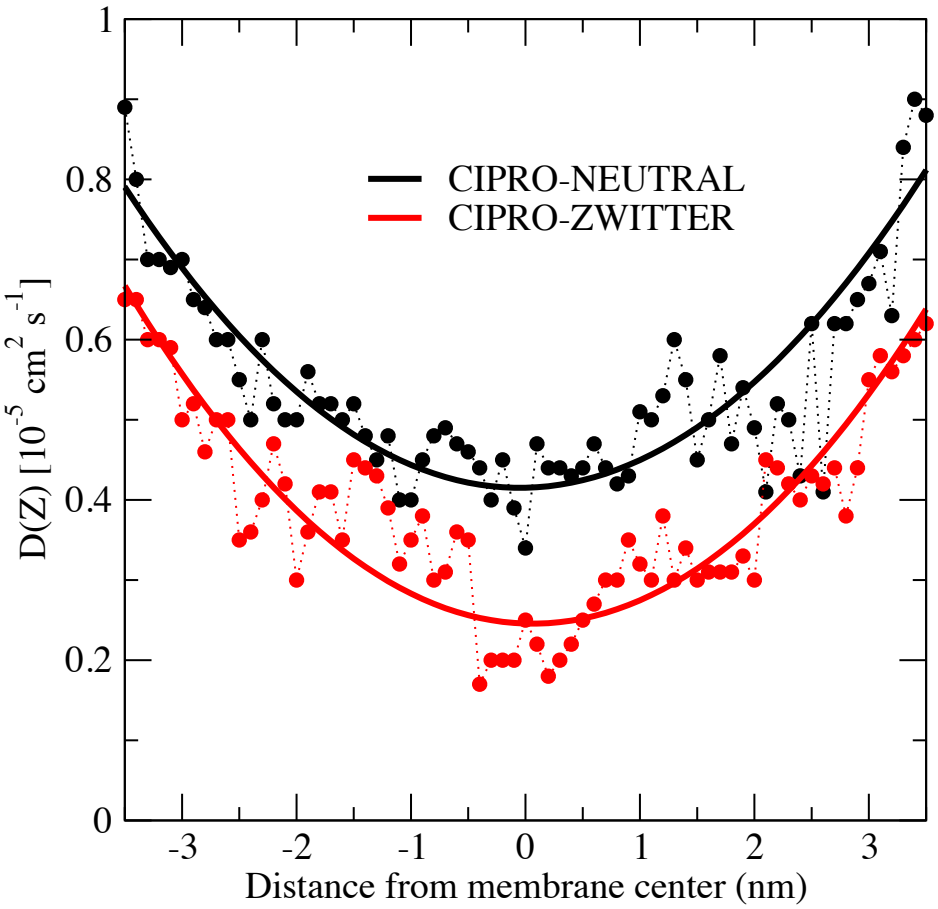
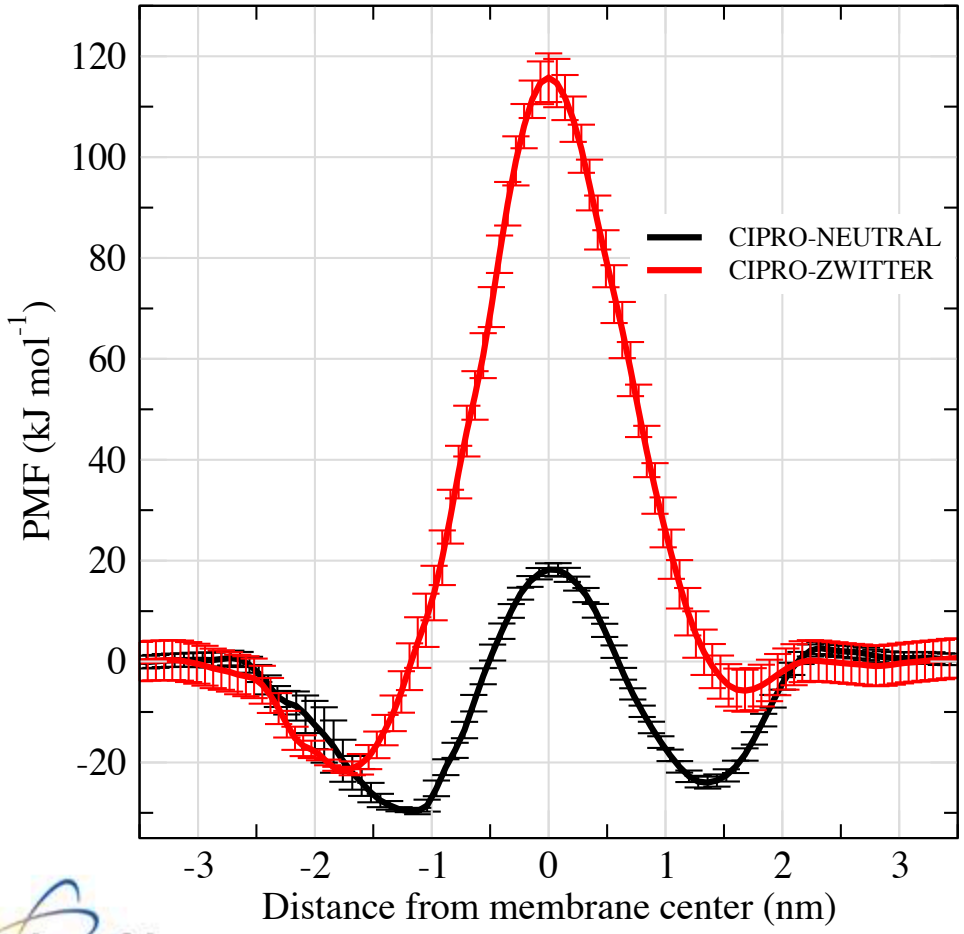
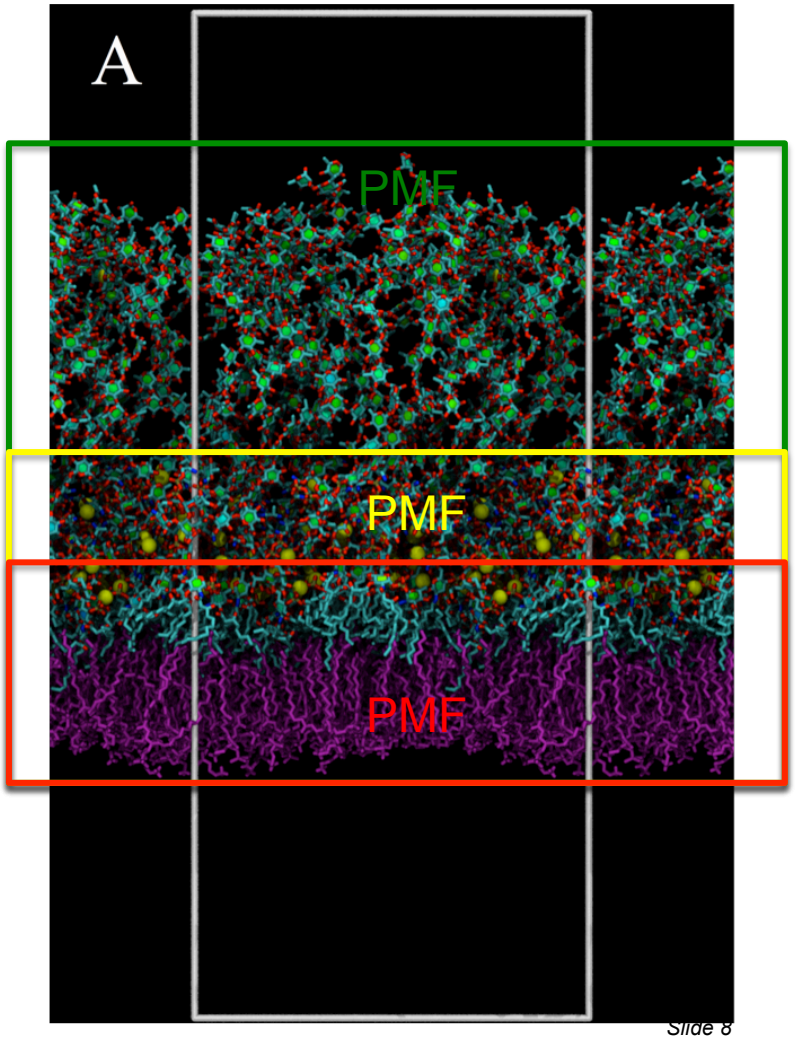
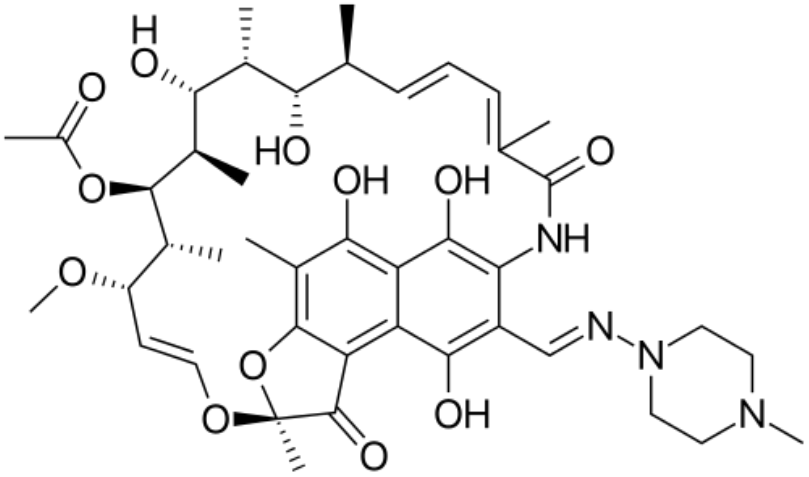


Given energy profile and diffusion we obtain:
$3.2*10^{-3}$ cm s^{-1} for neutral
$5*10^{-7}$ cm s^{-1} for zwitter


120
100
80
60
40
20
0
-20
PMF (kJ mol^{-1})
-3
-2
-1
0
1
2
3
Distance from membrane center (nm)
CIPRO-NEUTRAL
CIPRO-ZWITTER


A
PMF
PMF
PMF

Larger drugs can also be targeted



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