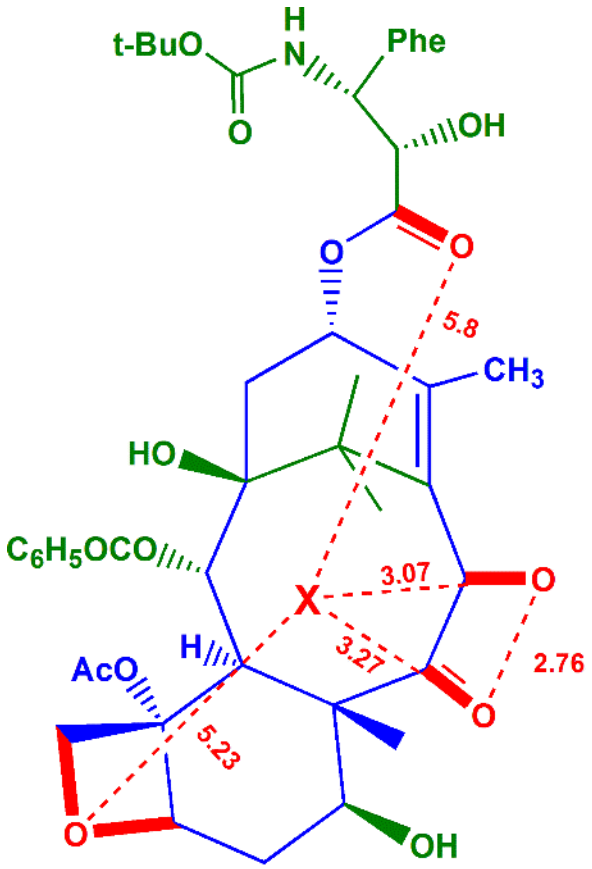
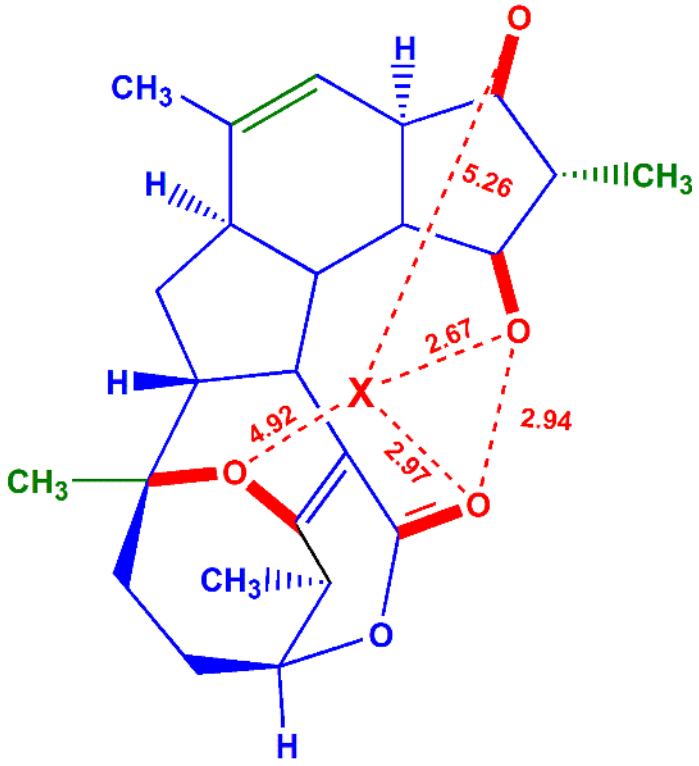
Cyclostreptin: a water-soluble natural product that is active in tubulin

CIFHER note: ***Many oncologists reject tubulin inhibitors as drugs due to their neuropathy side effects. However, bioconjugate coupling affords a new era in tubulin inhibitors as drugs. Maytansine is a successful example when coupled to the Her2 antibody. Would a bioconjugate coupling with Cyclostreptin afford even better advantages as a therapeutic?***



Docetaxel

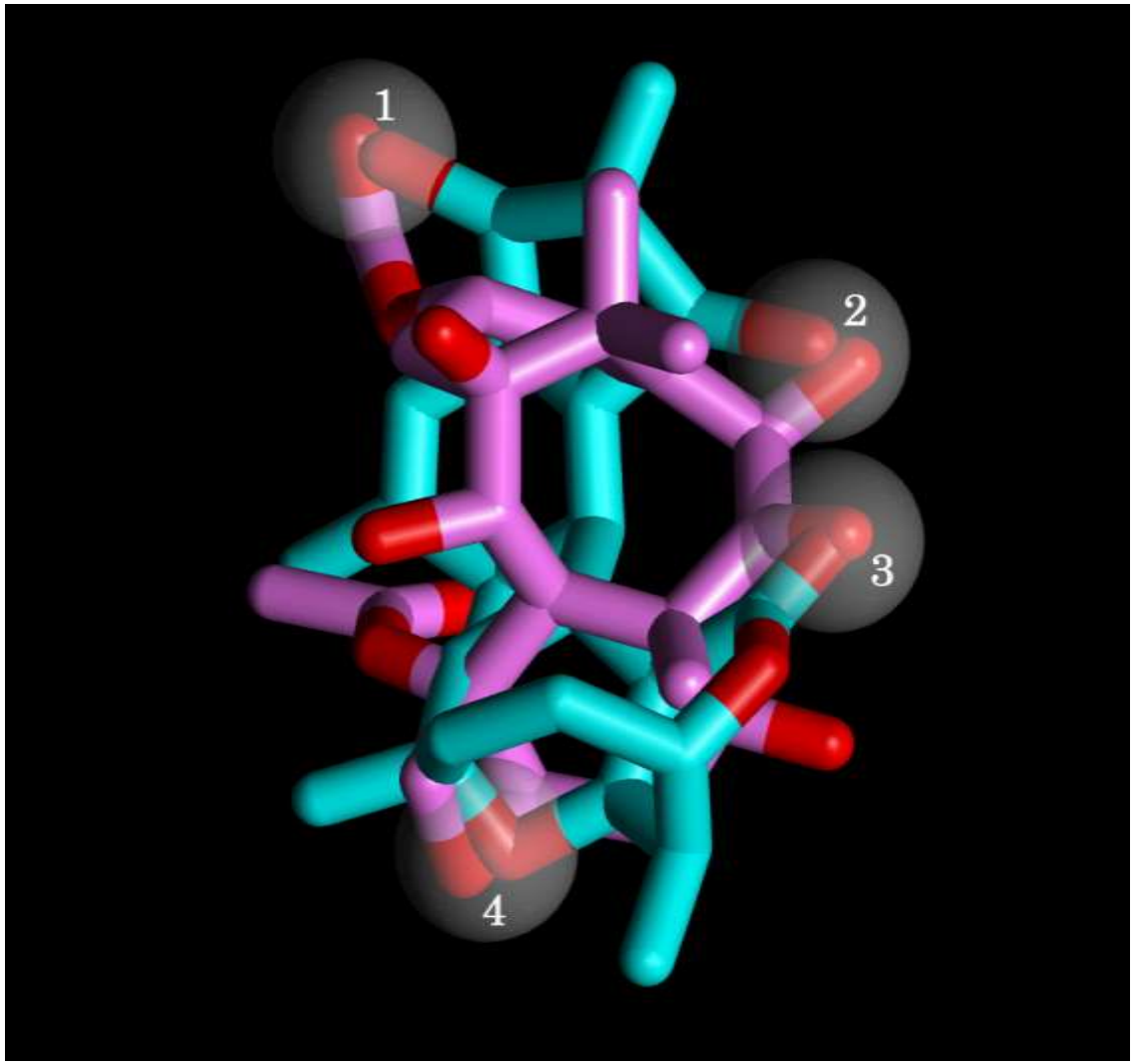


Cyclostreptin

Edler MC, Buey RM, Gussio R, Marcus AI, Vanderwal CD, Sorensen EJ, Díaz JF, Giannakakou P, Hamel E. Biochemistry. 2005 Aug 30;44(34):11525-38. doi: 10.1021

3D Overlap with Docetaxel and Key Pharmacophore Centers

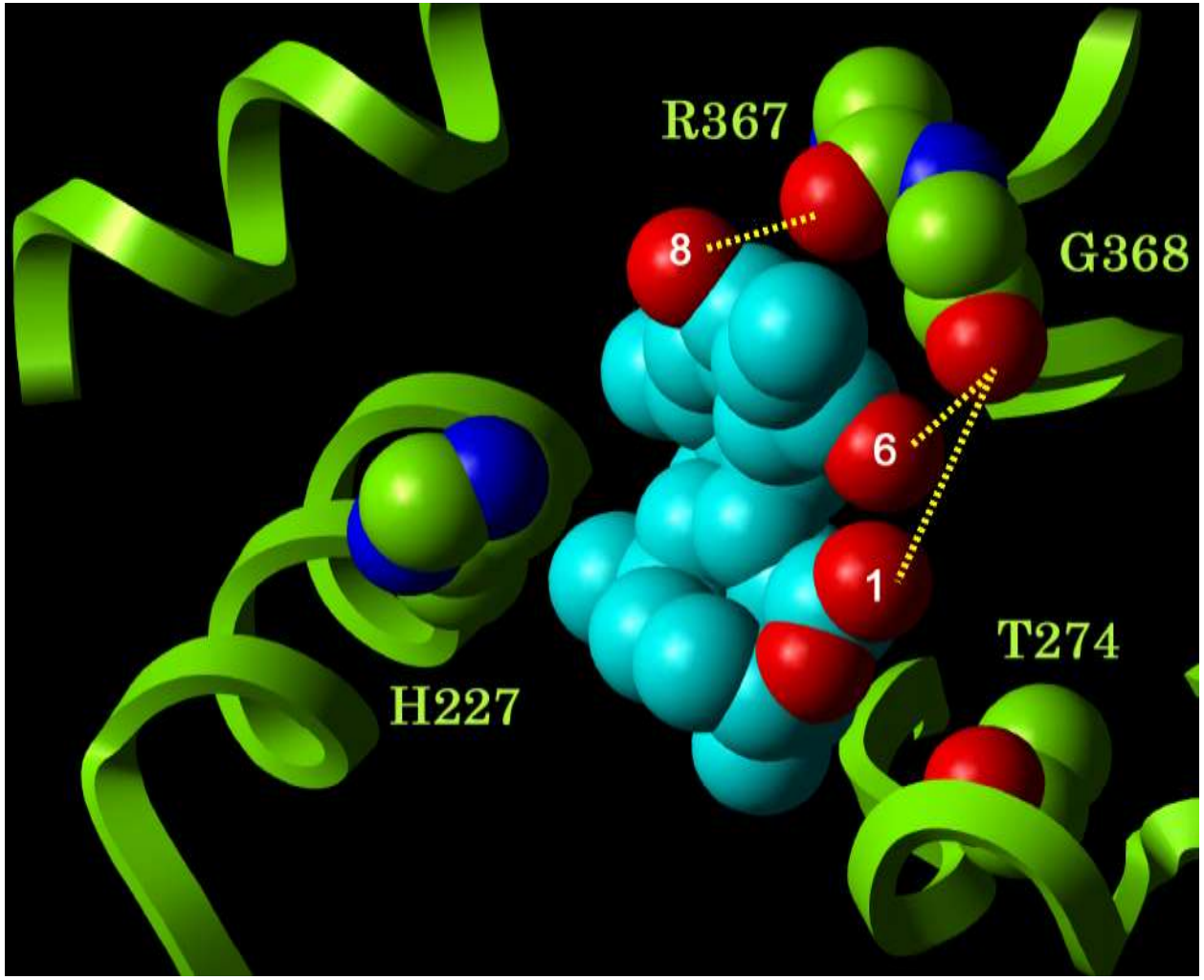
- 1 -3: Critical hydrogen bonding groups required for activity in the taxane site of tubulin
- 4: Epoxide overlap with taxol: for possible covalent bond formation



3D model of Cyclostreptin in the taxane site of tubulin

- Meets the structure-based pharmacophore requirements for the taxane site
- However, Cyclostreptin binds very uniquely

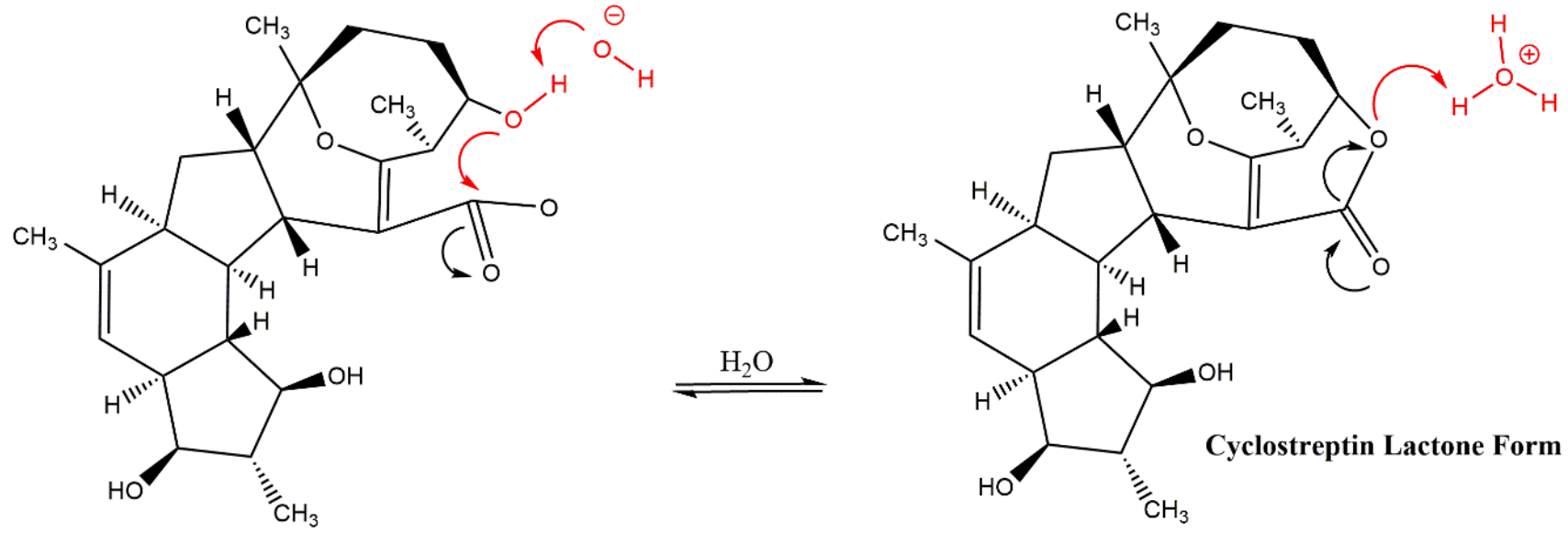
Cyclostreptin may offer very unique pharmacological properties as a drug if formed as a bioconjugate coupled agent



Is Cyclostreptin's water solubility in part, due to self-assembly?

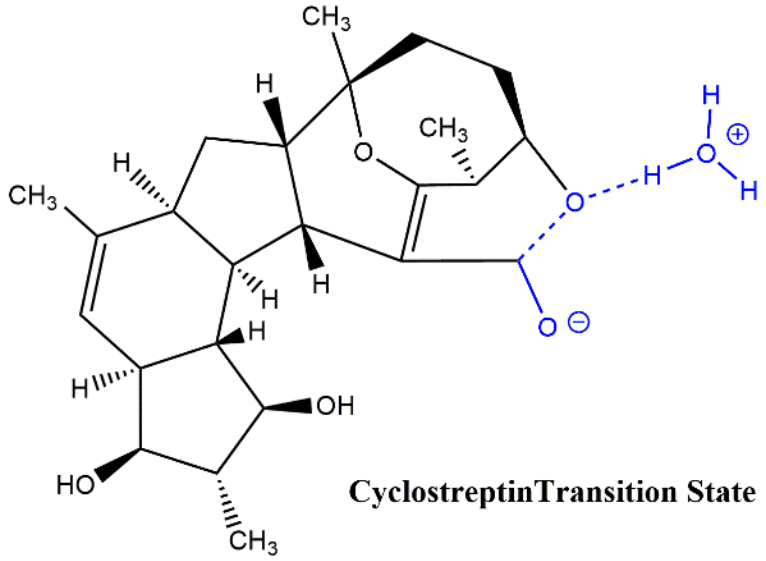
- Cyclostreptin's rigid structure is ideal to study self-assembly
- It has a complex natural product structure
- Nature's design evolved Cyclostreptin with 12 chiral centers-why?
- Dynamic lactone ring opening is a probable contributor to its water solubility
- A combination of properties (lactone ring opening and self-assembly) may lead to a water soluble, unique cancer drug candidate
- This is especially true if a bioconjugate coupling strategy is employed
- Principles evolved from the study of self-assembly may be generalizable to other scaffolds

Cyclostreptin: a dynamic ring opening from carboxylate to closed lactone forms



Cyclostreptin Open Form

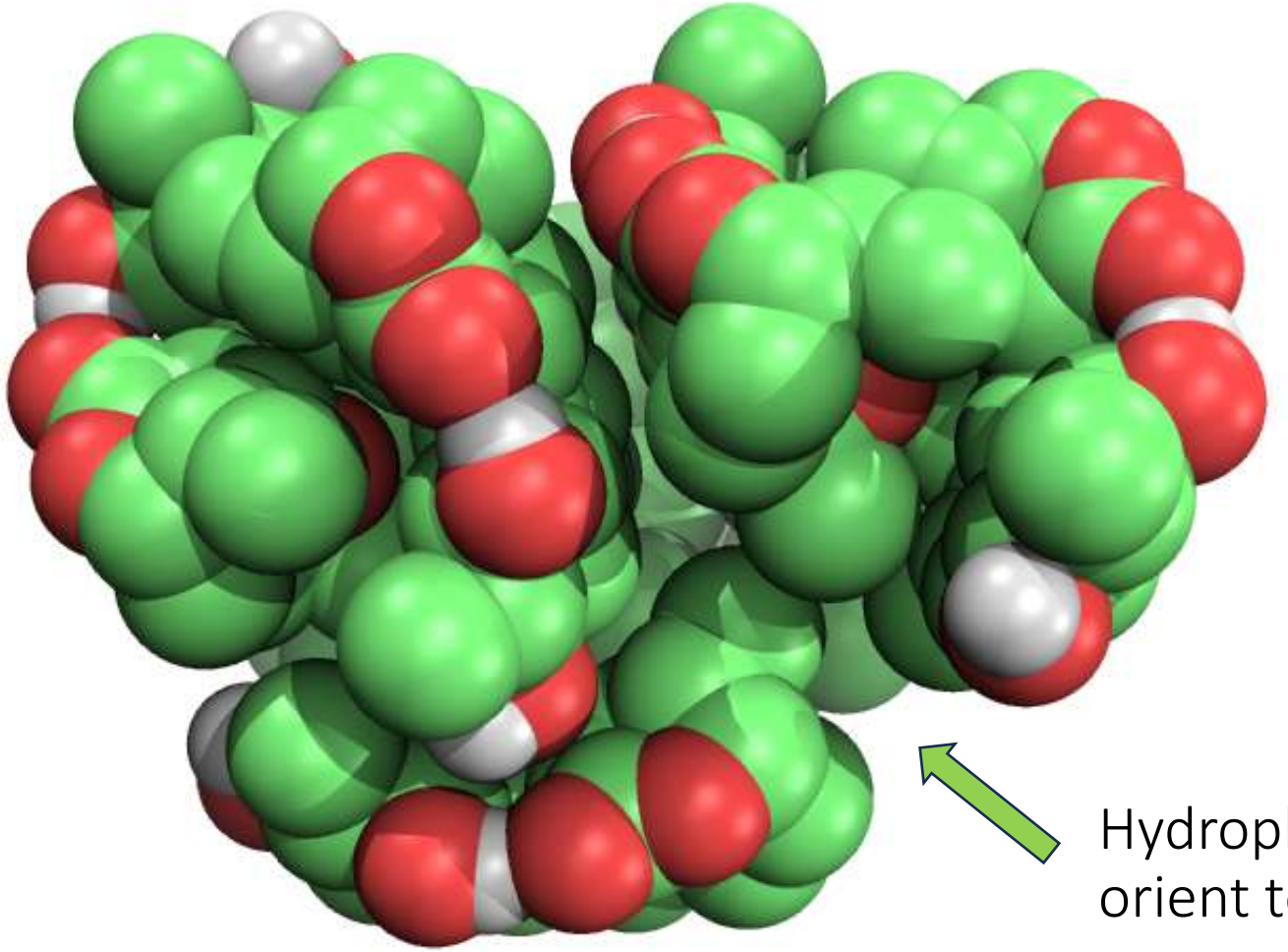
Cyclostreptin Lactone Form



CyclostreptinTransition State

7 Cyclostreptins can self-assemble into a primary micellar unit

Polar groups orient to the outside

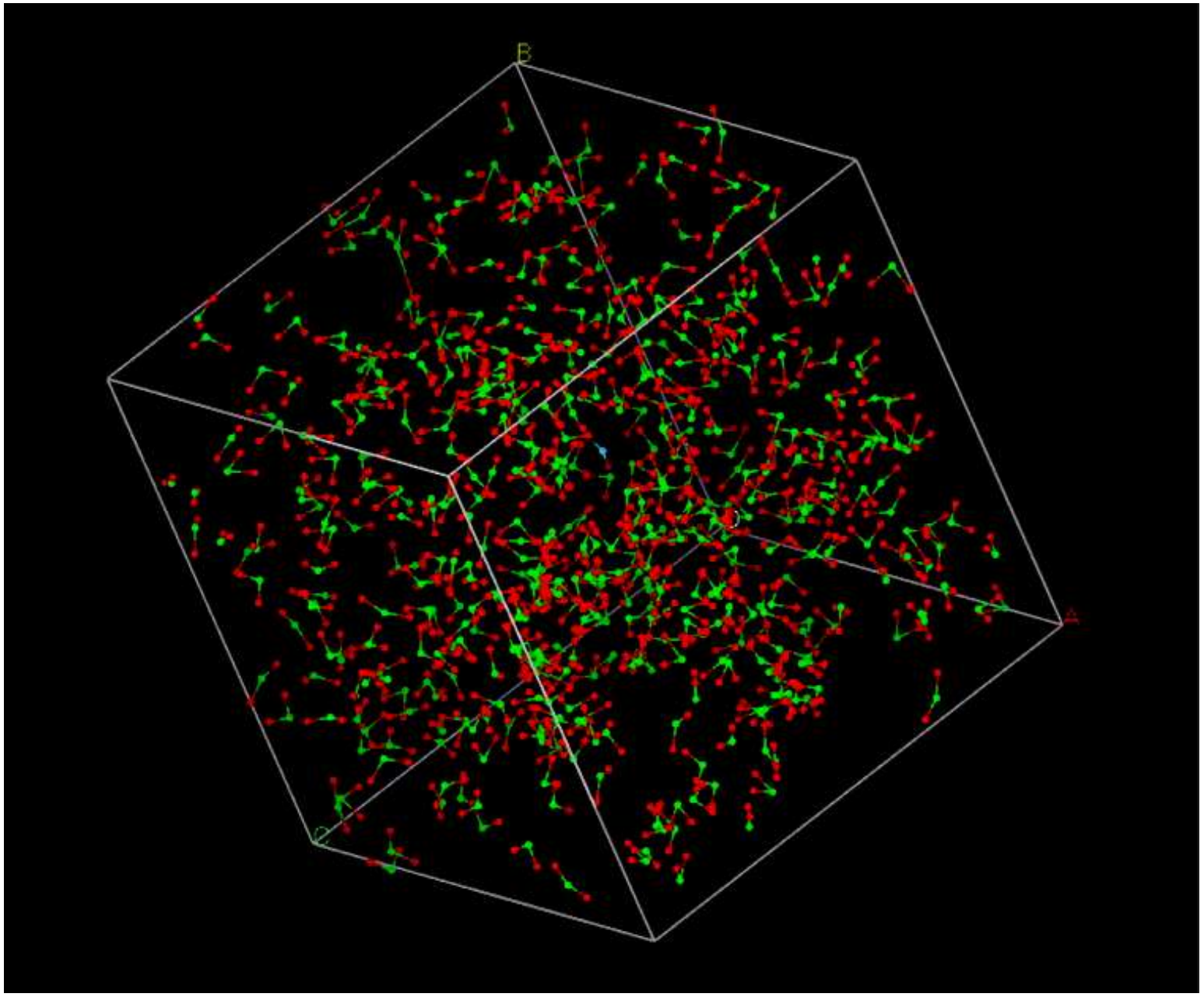


Hydrophobic groups orient to the inside

Space filling rendering shown without nonpolar hydrogens

This mesoscale molecular dynamics simulation of the primary Cyclostreptin micellar unit simulates its self-assembling capabilities

Curvature of the final self-assembled structure may help “deliver” Cyclostreptin to proteins and cell-membranes from the plasma or in the cytosol



Is the study of self-assembling molecules the missing key to evolving principles of Rational Drug Design?

- Rational drug design does not exist, only rational ligand design
- Molecular scaffolds that are optimized in the target often lose activity in cells and animal assays
- Large pharmaceutical industry relies on 2nd dimension parameters (e.g., RO5, etc.) and large empirical resources to discover drugs. These calculations are inadequate to develop principles of a rational drug design architecture
- Clearly, new concepts to study molecular architecture are needed
- These principles need to be investigated in the 3rd and 4th dimensions
- Self-assembly may be the first stage for such studies