



Advances in Drug Design and Development II: Computational Techniques and *In Silico* Predictive Models

Part A: *In silico* Pharmacophore Development and Identification of
New Therapeutic Agents by Three Dimensional Multi-Conformer
Database Searches – *Apurba K. Bhattacharjee, Ph.D.*

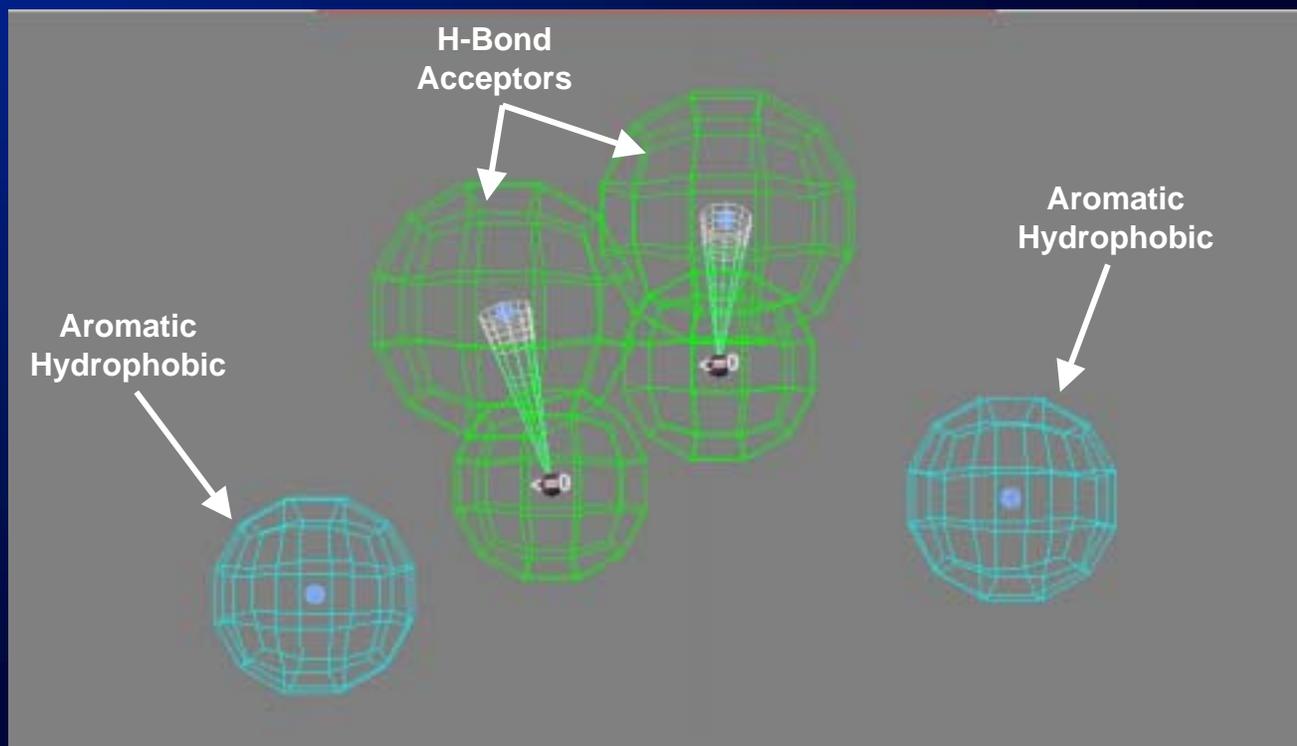
Part B: *In silico* Molecular Properties in the Aid of Bioavailability –
CPT Mark Hartell, Ph.D.



In Silico Pharmacophore Development

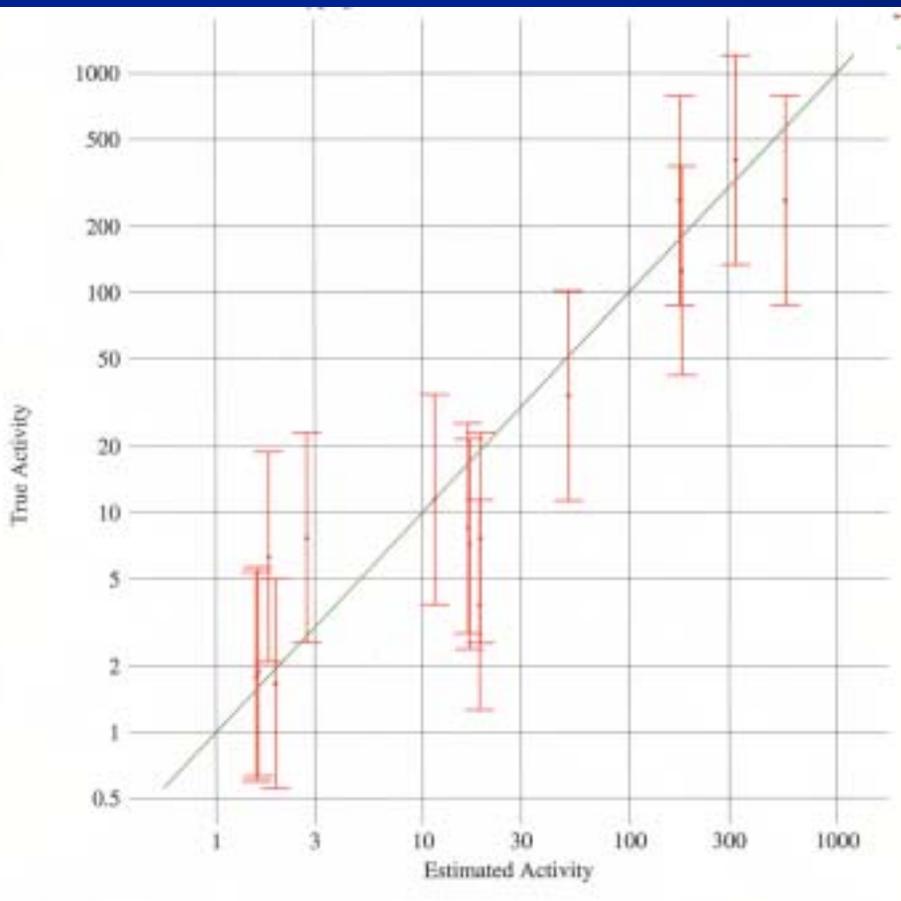
Activity of drug is directly related to unique physico-chemical properties of molecule which causes it to interact in some unique way to yield a specific physiological effect

- 3-D Pharmacophore based on training set of 15-20 diverse analogs
- Cross-validate pharmacophore with known compounds that have shown similar biological activity
- Convert pharmacophore into a 3D shape-based geometric template





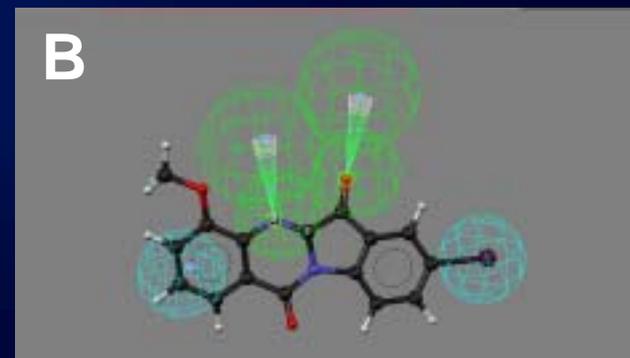
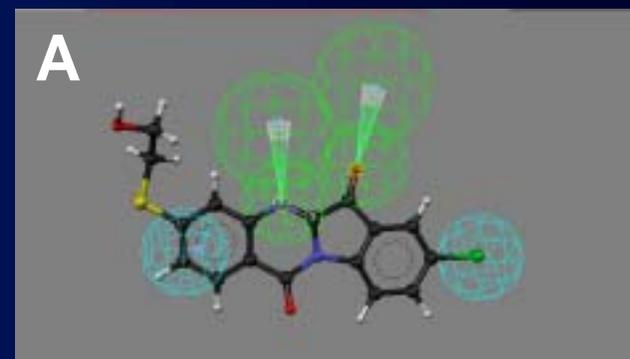
Predictive Model for Antimalarial Activity



Predictive model validated in test set yielding 0.92 correlation with measured activity

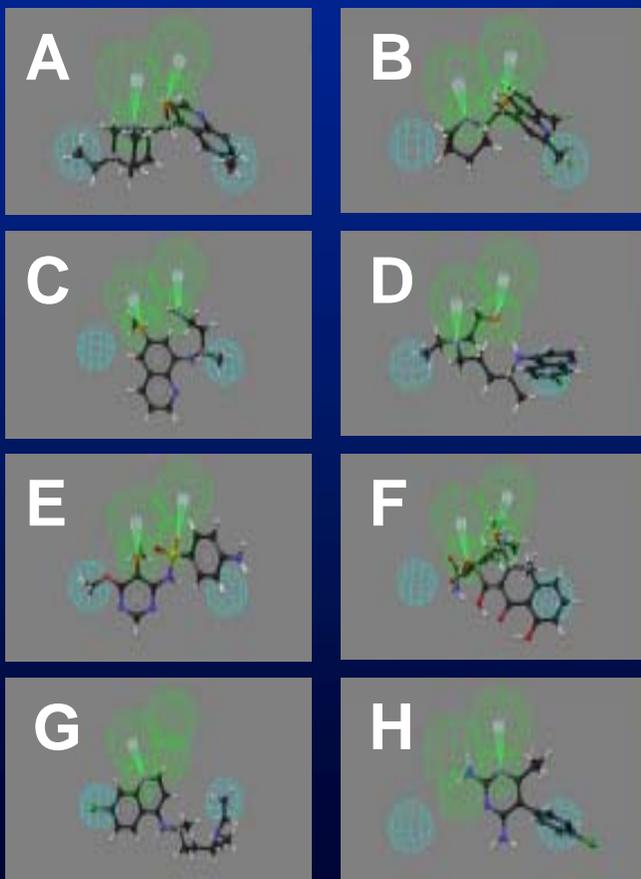
Maps of most potent analogs indicate molecular “areas of interest”

Know what areas of molecule to “touch” and what to “leave alone”





Applications of 3D Mapping

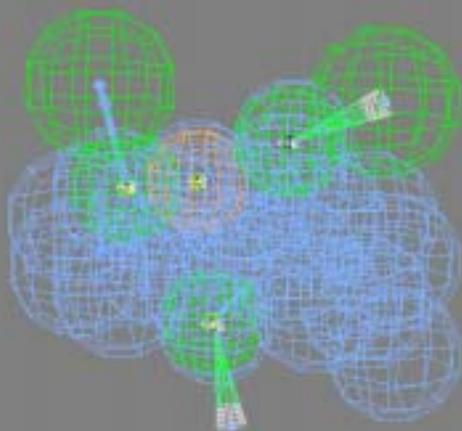


- Can map 3-D trypanthrin pharmacophore onto other common antimalarials:
 - (a) quinine
 - (b) mefloquine
 - (c) primaquine
 - (d) hydroxychloroquine
 - (e) sulfadoxine
 - (f) doxycycline
 - (g) chloroquine
 - (h) pyrimethamine
- Can be used to discover novel *“non-trypanthrin” trypanthrins*



Pharmacophore for Database Search

(3D shape-based single template)



How We Build a 3D Multi-Conformer Database?

By generating and storing the energy minimized 3D structure for each compound from a 2D database.

And

By generating all possible conformers in the range of 0-20 kcal/mol for each molecule of the database and storing them as multi-conformer 3D database.

The database created would allow the matching of the 3D pharmacophore more accurately to identify promising hits



C2.ADME Modules

C2 ADME

C2 Absorption

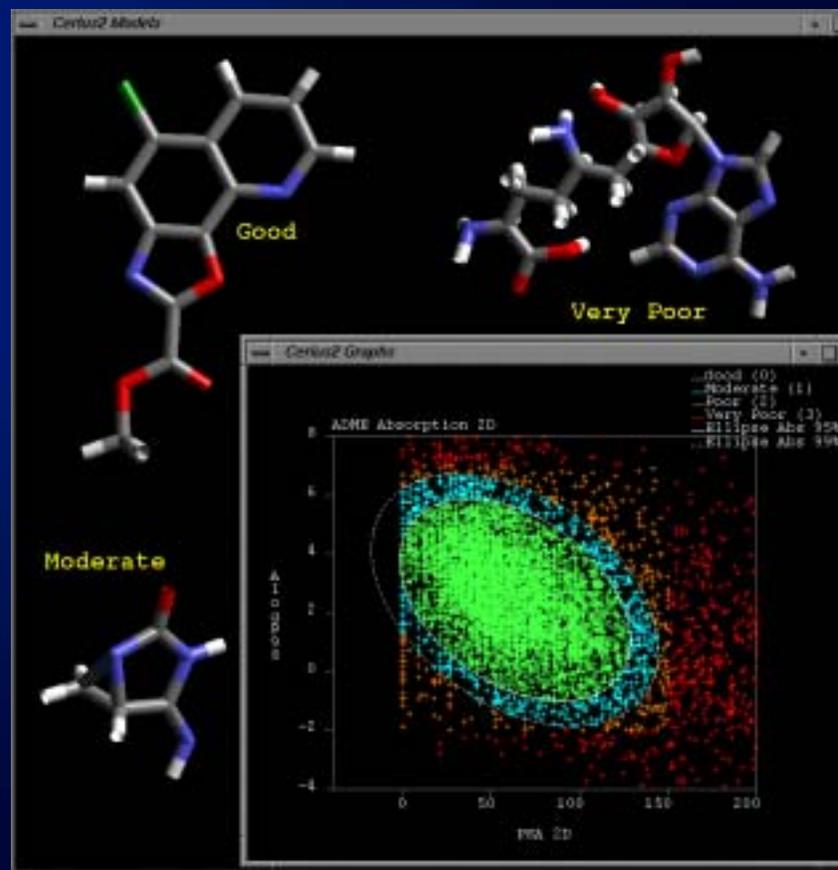
Human Intestinal Absorption Model

C2 BBB

Blood-Brain Barrier Penetration

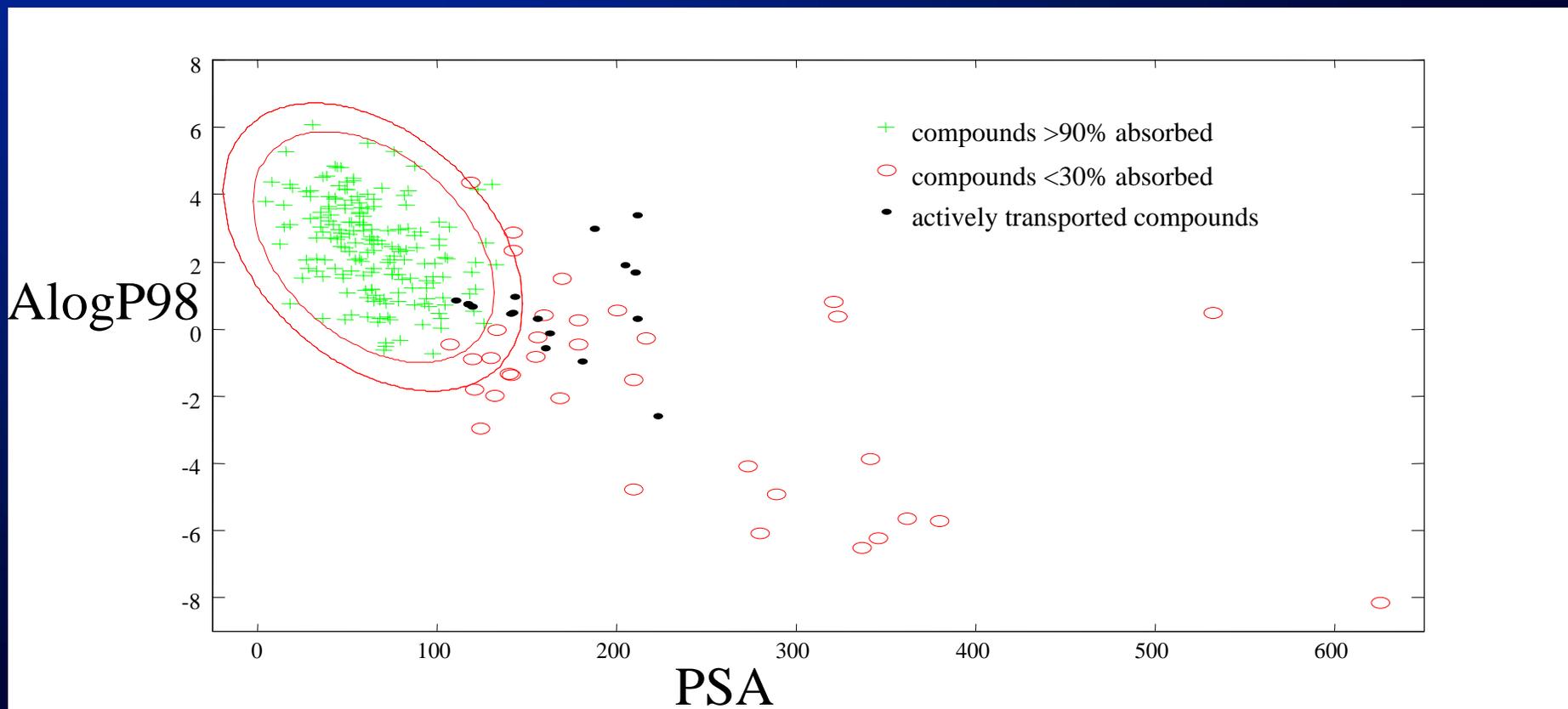
C2 Solubility

Aqueous Solubility



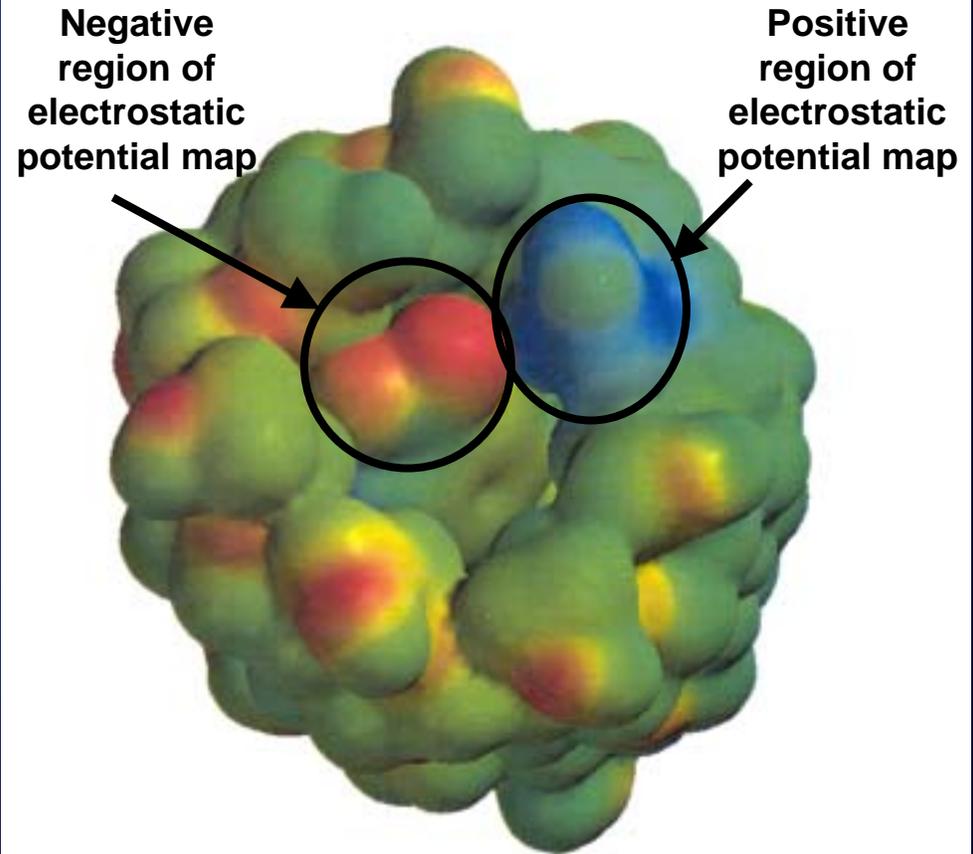
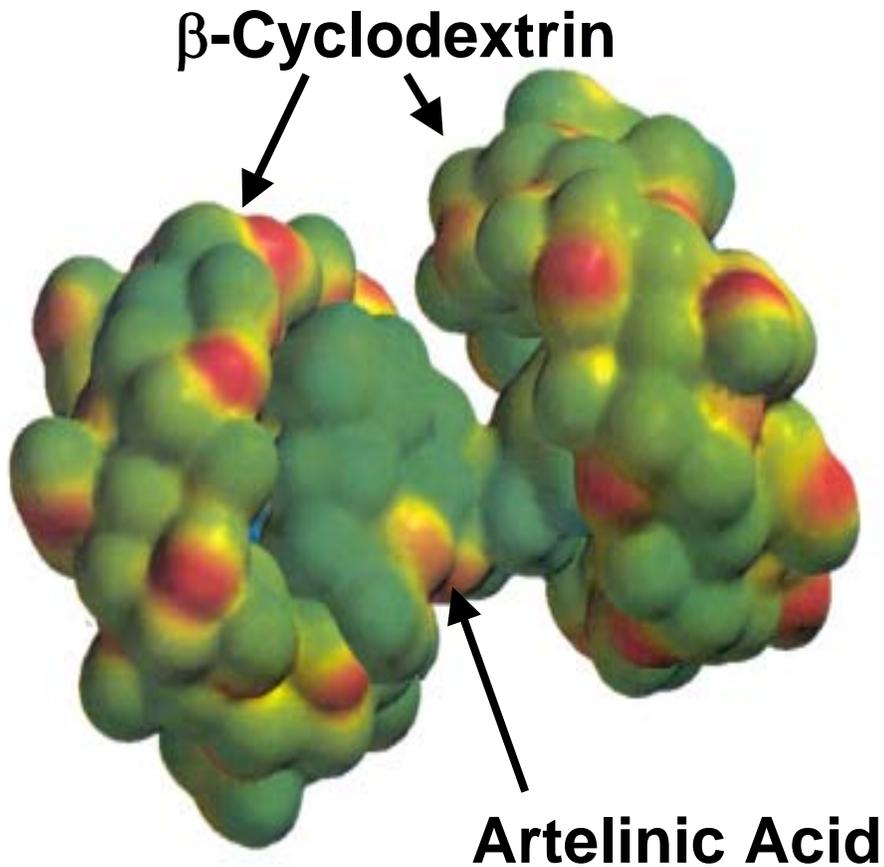


Absorption Model





Physico-Chemical Modeling





Further Success Stories

- Identified 25 potent inhibitors for Plasmodium falciparum plasmepsin II
- Identified 16 promising inhibitors for the Pfmrk cyclin dependent protein kinase
- Identified 10 promising novel inhibitors for the antimalarial FabH target
- Bhattacharjee et al. *J. Chem. Info & Comput. Sci.* 2002, 42, 1212-1230
- Bhattacharjee et al. *Bioorg. Med. Chem.* 2002, 10, 1979-1989