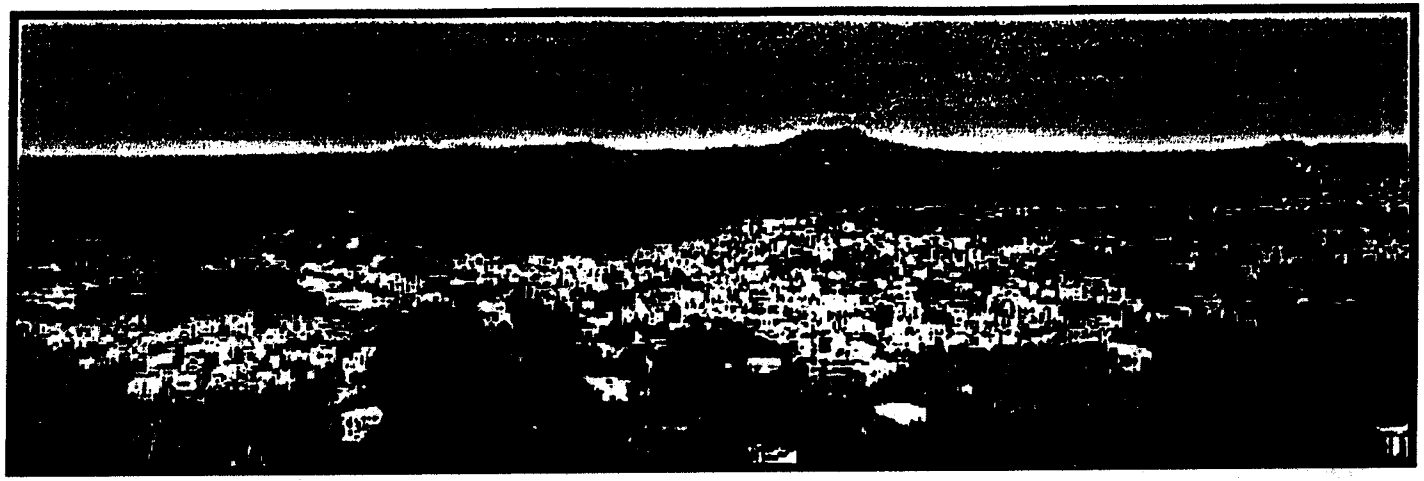


Nine IASOCs and Counting …

Reflections on the Past; Prospects for the Future

Stephen Hanessian

iasoc

IASOC 2000
Thursday, September 28
ISCHIA

Some Organic Chemistry Highlights and Potential Impacts

- Asymmetric Processes

  Catalysis by transition metals and designed ligands
  Auxiliary or reagent-based stereoselectivity

- Methodology

  Transition metal chemistry in bond formation
  Olefin metathesis
  Solid phase chemistry (revisited)

- Total Synthesis

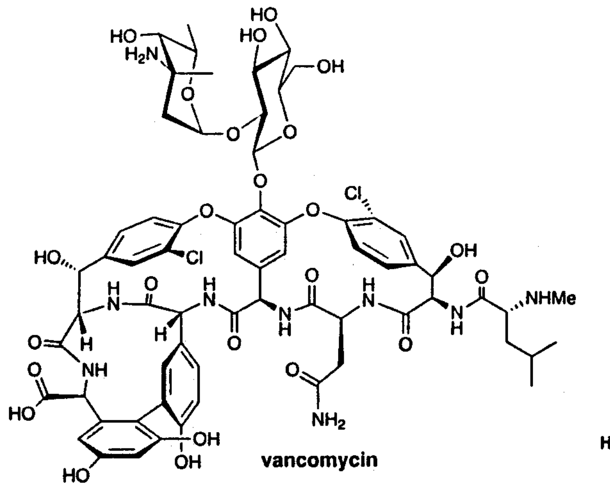
- Bioorganic and Medicinal Chemistry

  DNA, RNA recogition
  Structural biology and drug design
  Genomics, proteomics, etc.
  Glycochemistry

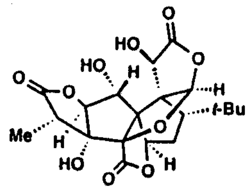
- Supra and Supermolecules

  Organized self-directed assemblies
  Nanotechnology
  Material science and polymers

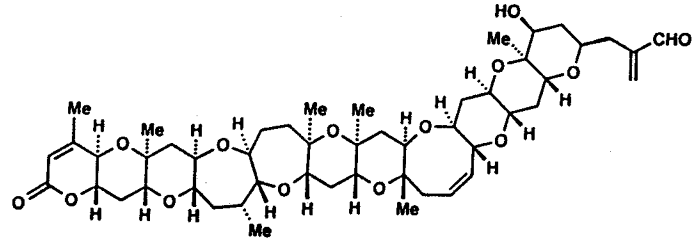
NATURAL PRODUCT CONQUESTS BY TOTAL SYNTHESIS



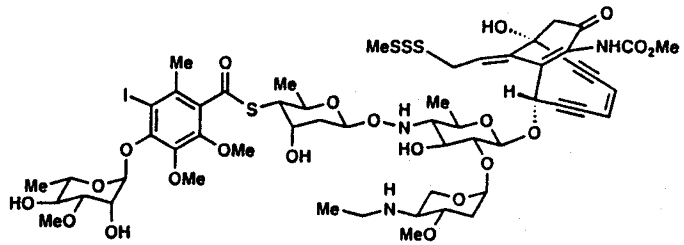
vancomycin



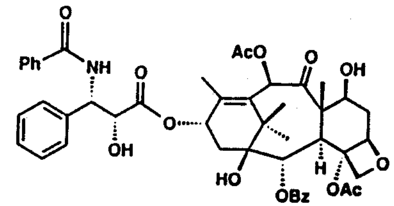
ginkgolide B (1988)



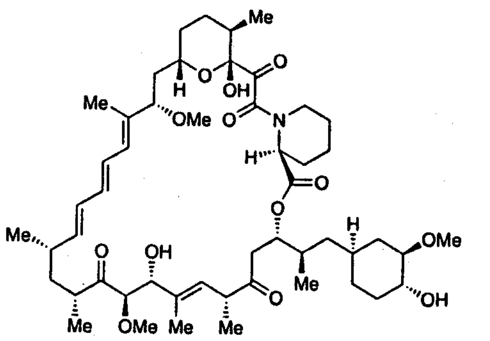
brevetoxin B (1995)



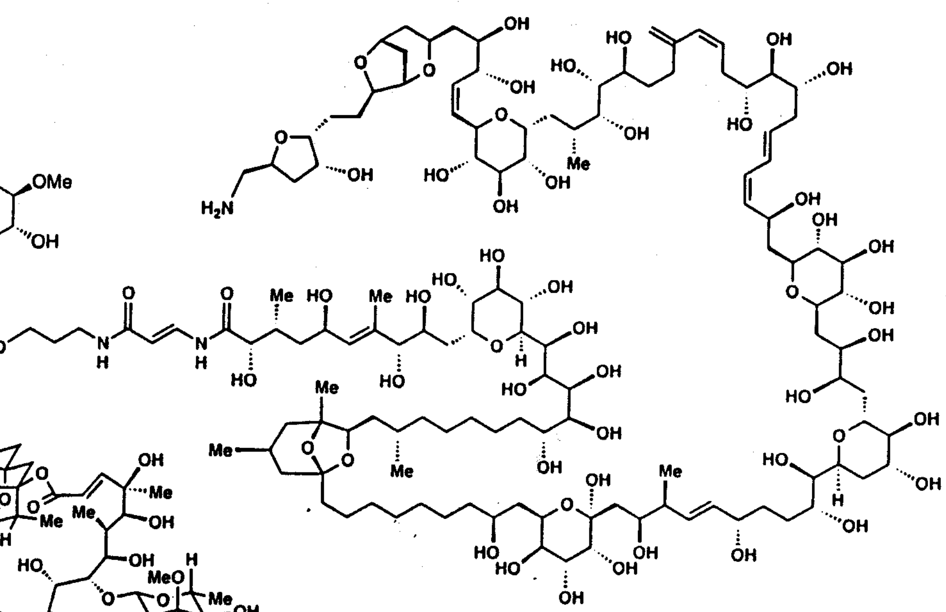
calicheamicin γ_1^I (1992)



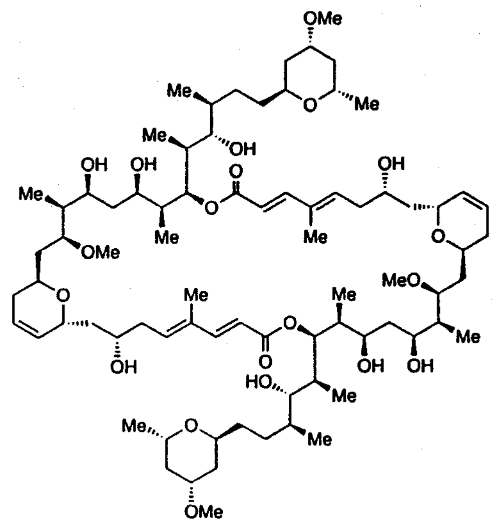
Taxol™ (1994)



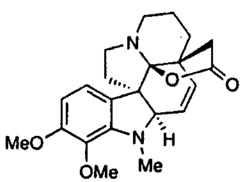
rapamycin



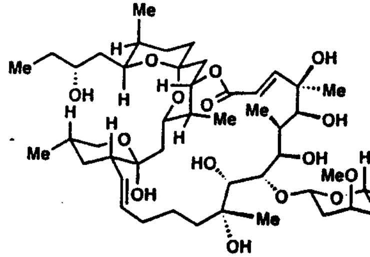
palytoxin (1994)



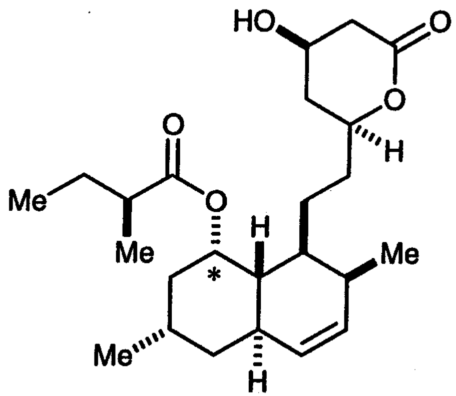
swinholide A



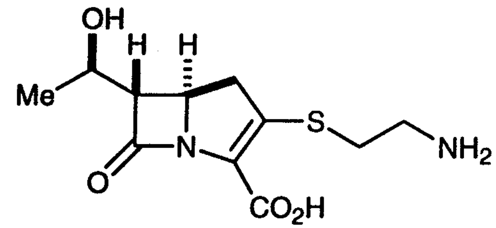
aspidophytine



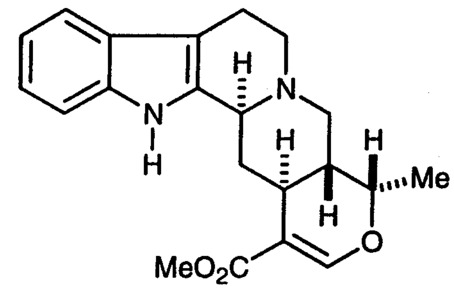
MEMORIES...



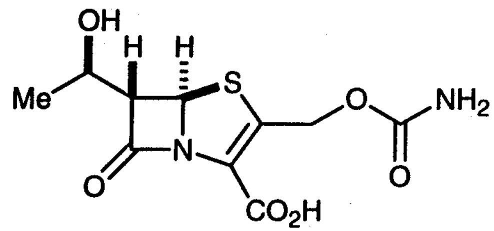
DIHYDROMEVINOLIN



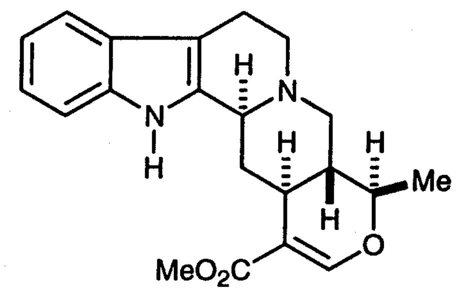
THIENAMYCIN



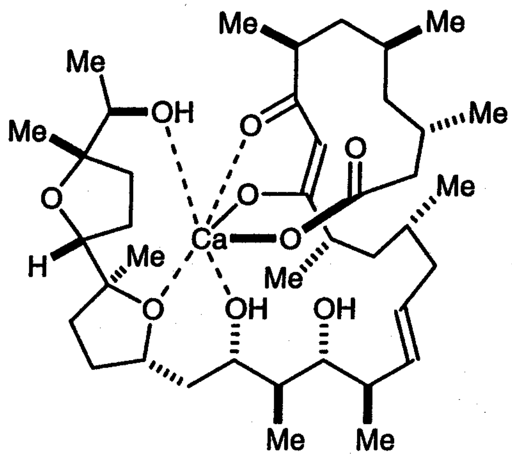
AJMALICINE



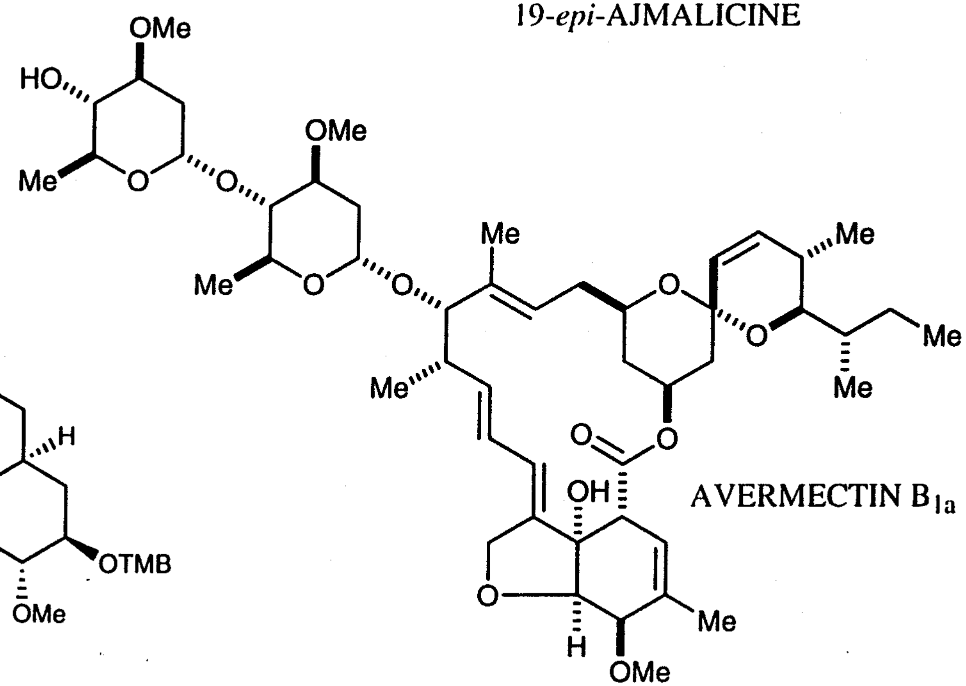
FCE-22101



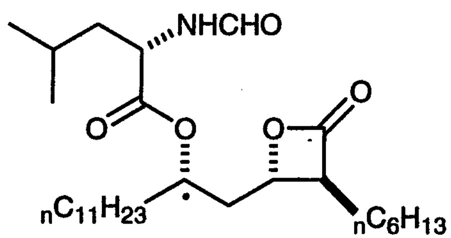
19-*epi*-AJMALICINE



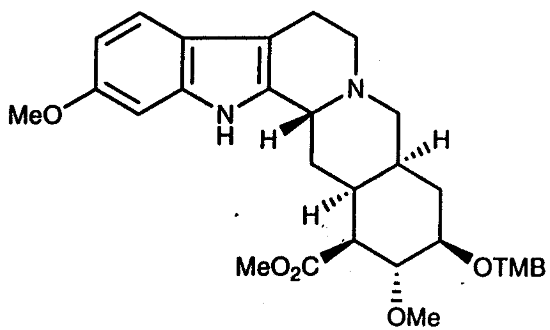
IONOMYCIN Ca salt



AVERMECTIN B_{1a}



(-)-TETRAHYDROLIPSTATIN



RESERPINE

TOTAL SYNTHESIS IN THE Y2K AND BEYOND

EXPECTATIONS:

- *Size, stereocenters, intricacies, novelty; elegance, practicality, etc.*
- *Acceptance*

IMPACT:

- *Biology, medicine, science, mankind*
- *Recognition*

METHODOLOGY:

- *Innovation, generality, utility*
- *Technology transfer, applications*

LESSONS LEARNED:

- *Coworker training, logic, observations, failures turned into success*
- *Etc, etc, etc,*

A Synthesis Chemist's Wish List

- In the lab

1. 100 % yield, 100 % stereoselectivity (O.K., 99% will do)
2. No protective groups
3. Universally applicable reagents
4. A catalytic version for every asymmetric reaction
5. Orthogonal reactivity and selectivity
6. Reactions at unactivated carbon atoms
7. Avoid end-game obstacles in total synthesis
8. Doing reactions in water at room temperature
9. Prediction of physical properties and structure from chemical composition
10. Truely understand bonding

A Synthesis Chemist's Wish List

- Collaborations

  1. Communicate with biologists and learn their alphabet (acronyms!)
  2. Finish the synthesis before the theory changes, or the interest wanes

- Nature

  1. Understand events at the molecular level
  2. Better drug design based on fact not dogma
  3. Use synthesis to solve Nature's mysteries

- Abstract, psychic and personal

  1. Seeing better through the mind's eye
  2. Presence of mind and attention to detail
  3. Exploiting serendipitous and chance observations
  4. Keeping up with the literature (and retrieving information fast)
  5. Stretching the day's hours ... and stopping to smell the roses.

DRUG DISCOVERY

A SYNTHETIC CHEMIST'S PERSPECTIVE AND INVOLVEMENT:

DEFINE PROBLEM → DESIGN → SYNTHESIS → BIOLOGY → DISCOVERY

BIOLOGY → REDESIGN

DEFINE PROBLEM:
DISEASE
PHENOMENON
CONDITION

SYNTHESIS:
METHODOLOGY
STRATEGY
- MIMICS
- ANALOGS
- INHIBITORS
- AGONISTS / ANTAGONISTS

TOOLS:

INSTRUMENTAL, COMPUTATION, PHYSICO-CHEMICAL, BIOTECHNOLOGY, GENOMICS, COMBICHEM

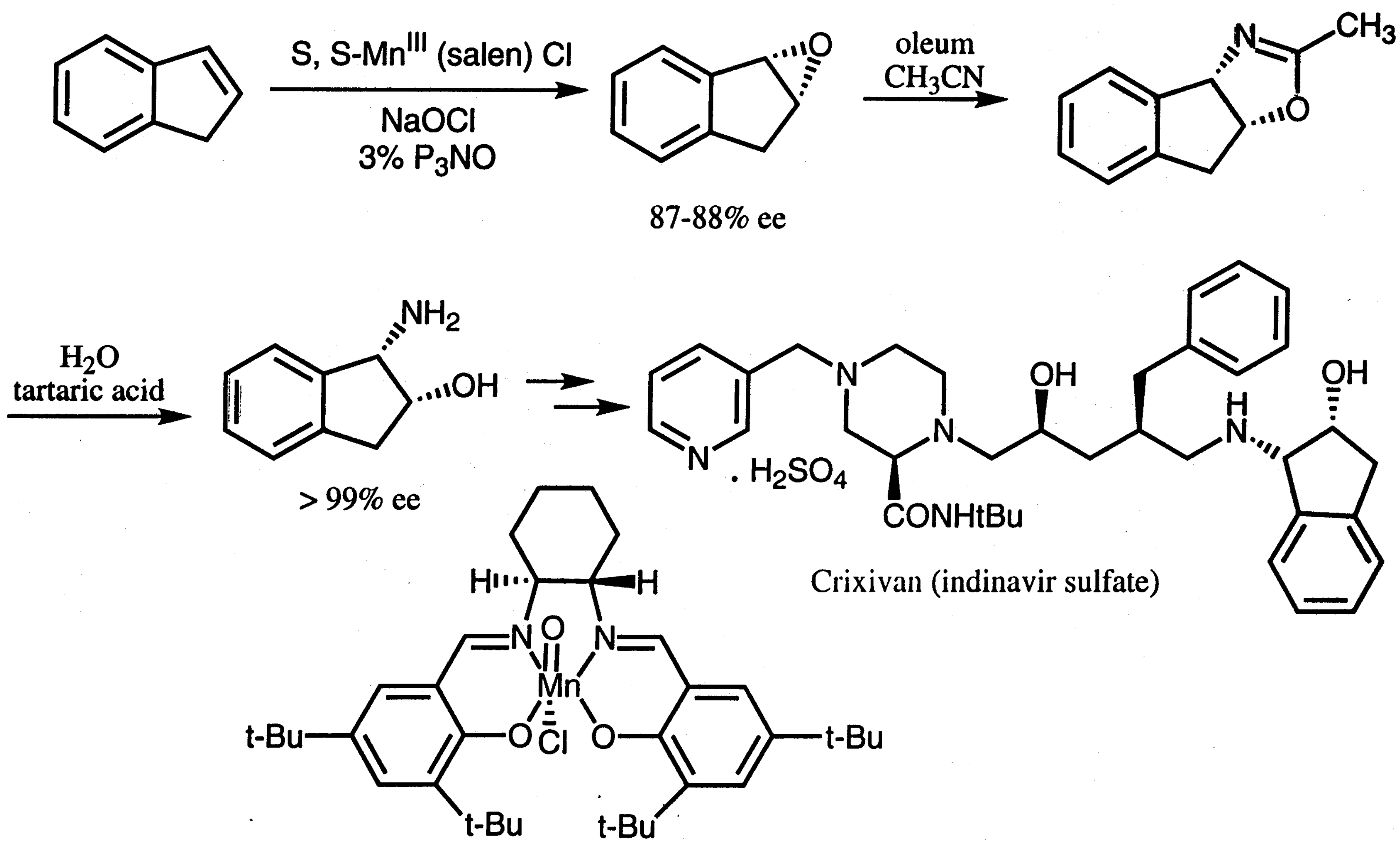
CHALLENGES:

- UNDERSTANDING INTERACTIONS AT THE MOLECULAR LEVEL (RECOGNITION, ETC.)

- CHEMICAL SOLUTIONS TO BIOLOGICAL PROBLEMS (DISEASE)

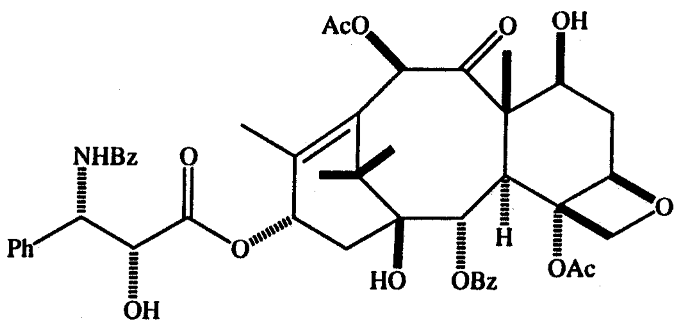
- BETTER DRUGS (QUALITY OF LIFE)

EPOXIDATION OF NON-ALLYLIC ALCOHOLS
(E. JACOBSEN)

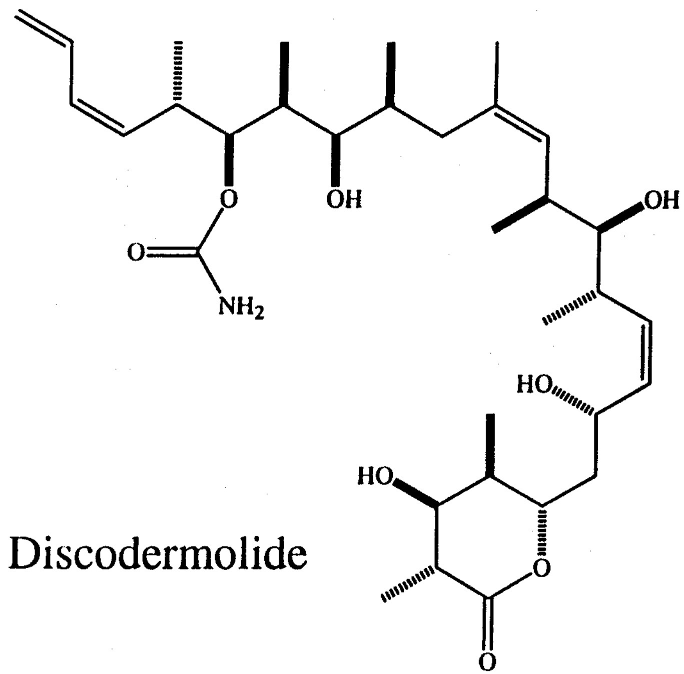


S, S- Mn^{III} (salen) Cl

CLINICALLY IMPORTANT TARGETS IN NEED OF *PRACTICAL* SYNTHESES (20 steps or less)



Taxol



(+)- Discodermolide

Nicolaou (1994)
Holton (1994)
Danishefsky (1995)
Wender (1997)
Mukaiyama (1998)
Kuwajima (1998)

Schreiber (1996)
Marshall (1998)
Smith (1999)
Paterson (1999)

AN "IDEAL" SCENARIO FOR DRUG DESIGN

Disease ⇒ Biochemical Pathway ⇒ Enzyme ⇒ Function

↕ Hit

Small Molecule Inhibitor (chance) ⇐ Chemistry

Enzyme Crystal Structure

↓

Enzyme-Inhibitor Co-Crystal

↓

Optimizing binding interactions via chemistry

↓

True lead? ⟶ "Rational" Design

Enzyme-Inhibitor Docking

↓ Modeling

Bioactive Conformation

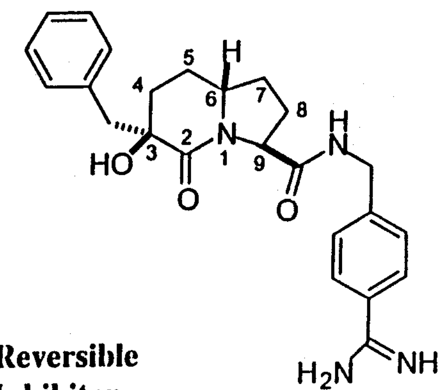
↓

"Rational" Design

Prototypical of Drug Design

Inhibition of Thrombin

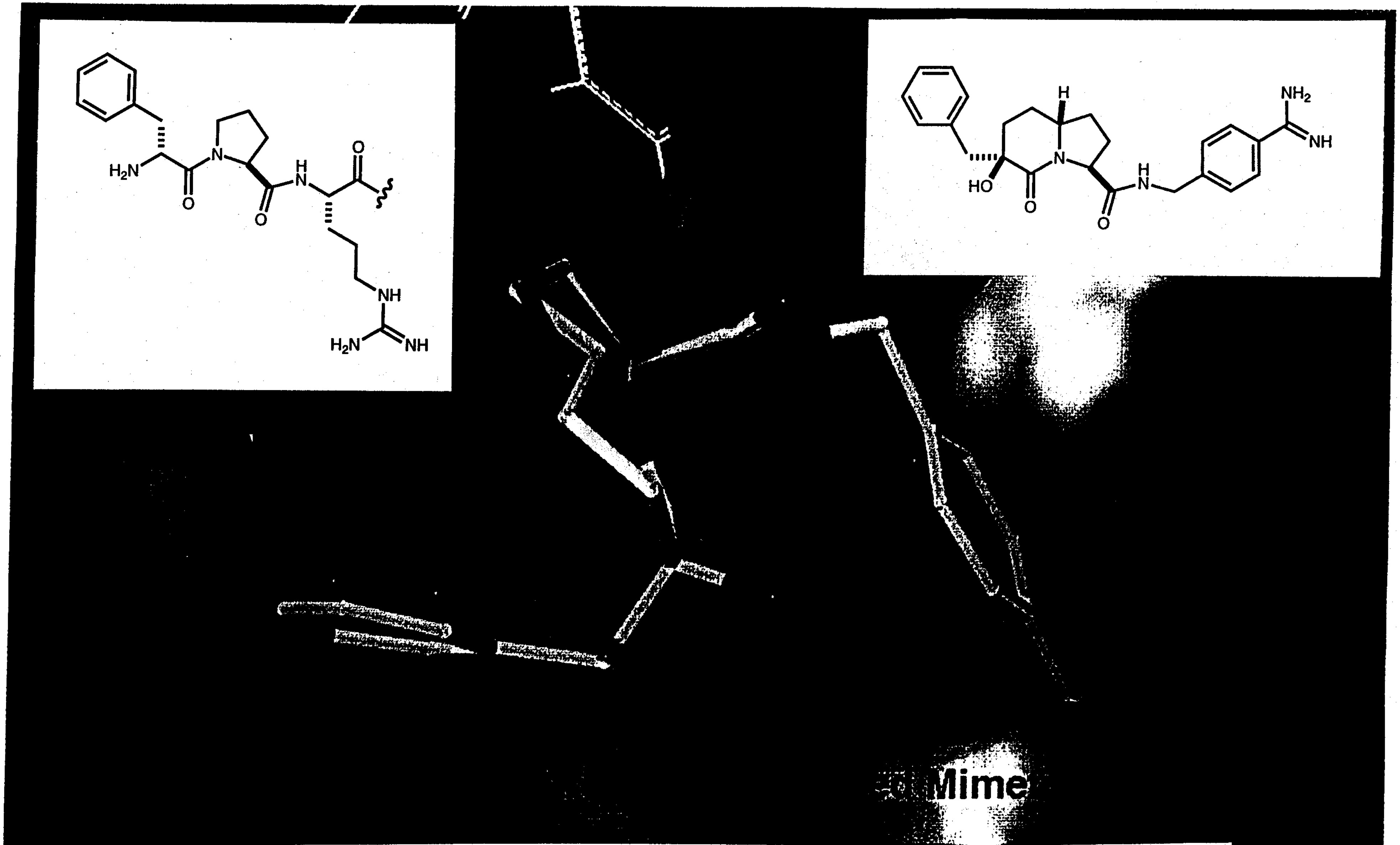
Lessons Learned from Modeling and
Enzyme-Inhibitor X-ray Crystal Structures



Reversible Inhibitor

Ki = 9 nM (Thrombin)

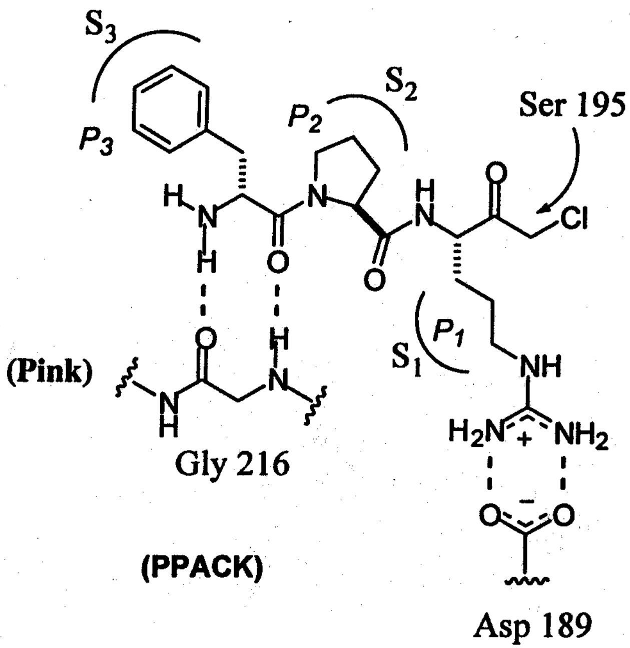
S. Hanessian and coworkers, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 243.



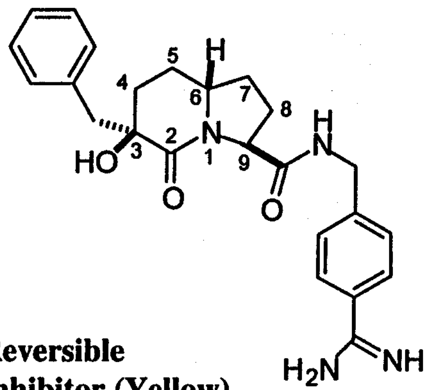
Exploring the Chiral Space within the Active Site of α-Thrombin with a Constrained Mimic of D-Phe-Pro-Arg — Design, Synthesis, Inhibitory Activity, and X-ray Structure of an Enzyme–Inhibitor Complex

X-Ray co-Crystal of Thrombin with Prototypical Inhibitor (Yellow)

Irreversible inhibitor

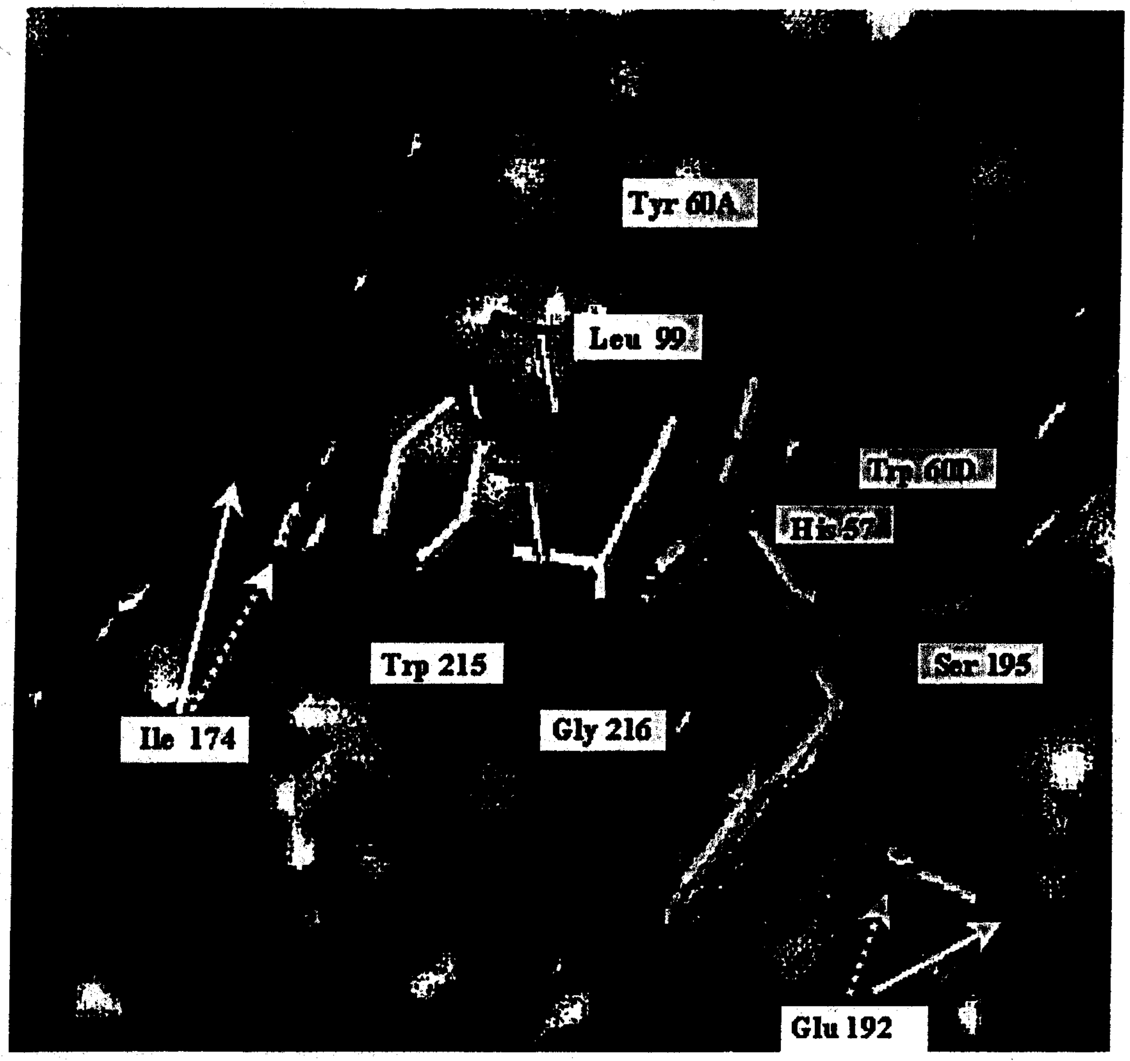


(PPACK)



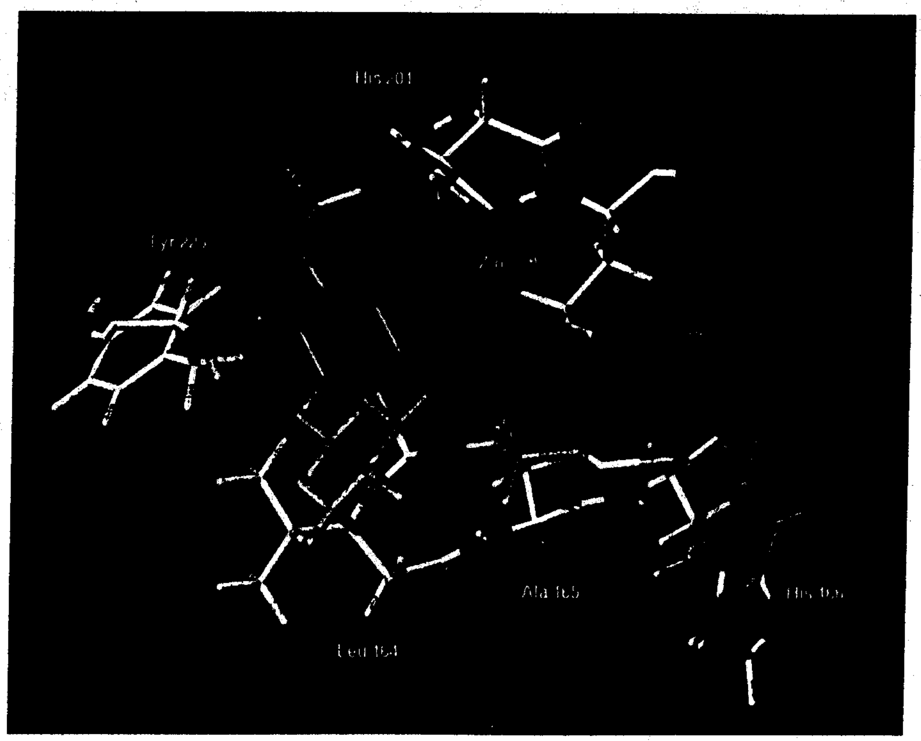
Reversible Inhibitor (Yellow)

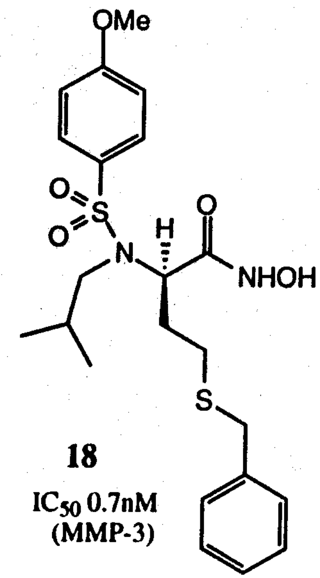
Ki = 9 nM (Thrombin)



Prototypical Drug Design

Inhibition of Matrix Metalloproteases



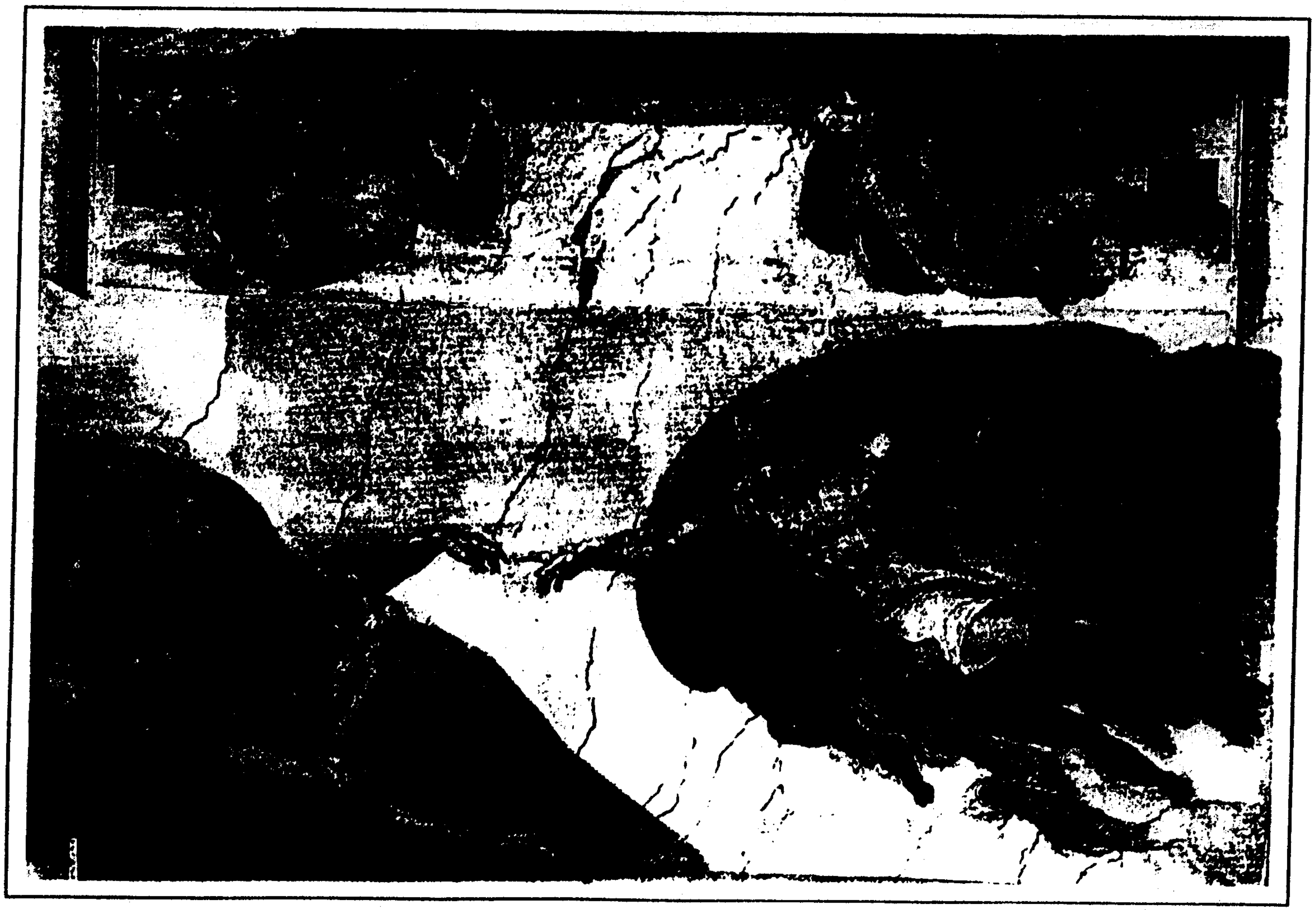


18

IC_{50} 0.7nM
(MMP-3)

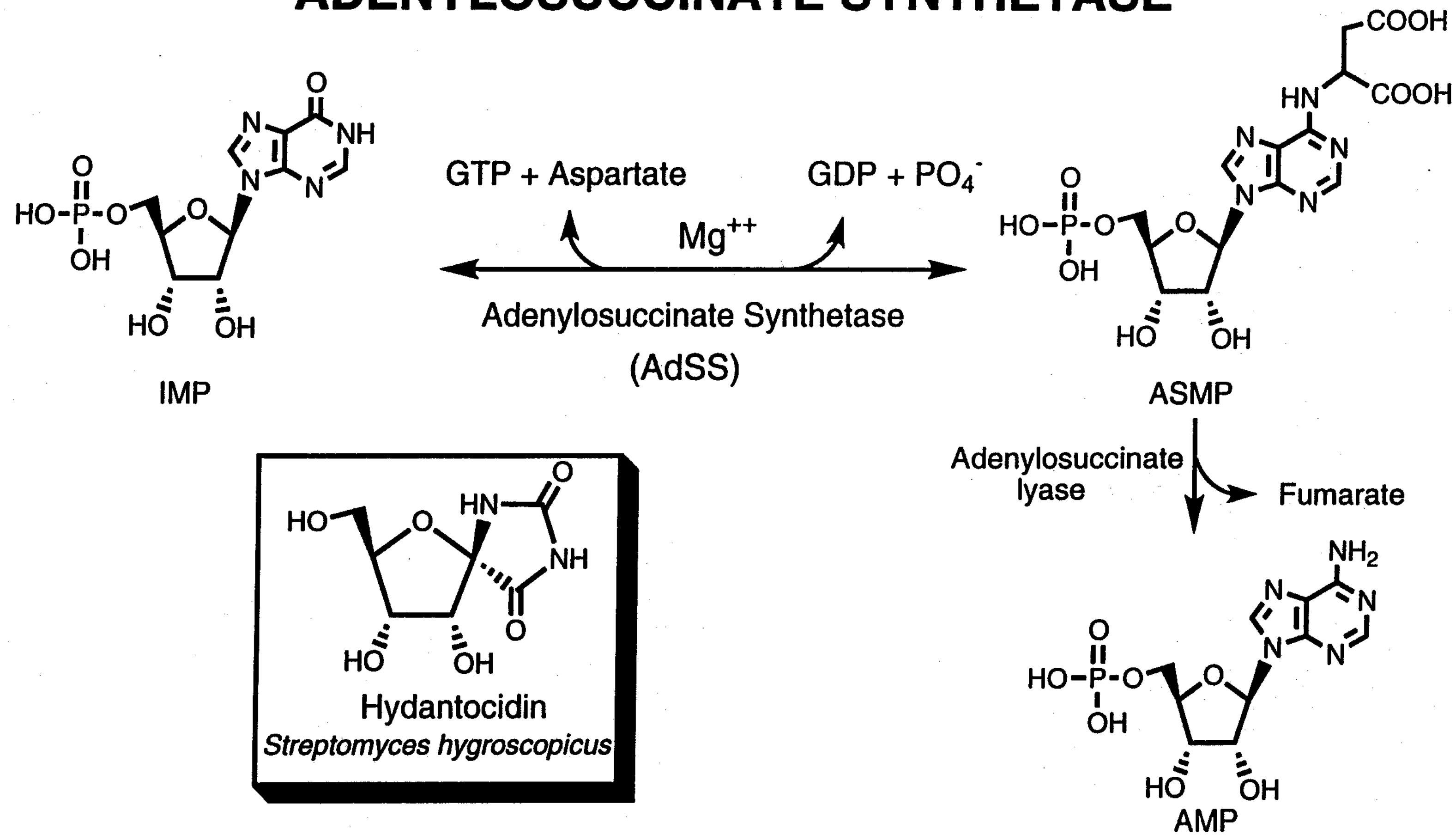
S. Hanessian and coworkers, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1691.

INHIBITION OF ADENYLOSUCCINATE SYNTHETASE
(The « Creation » of an Inhibitor)



S. Hanessian and coworkers, *Angew. Chem. Int. Ed.* **1999**, *38*, 3159.

ADENYLOSUCCINATE SYNTHETASE

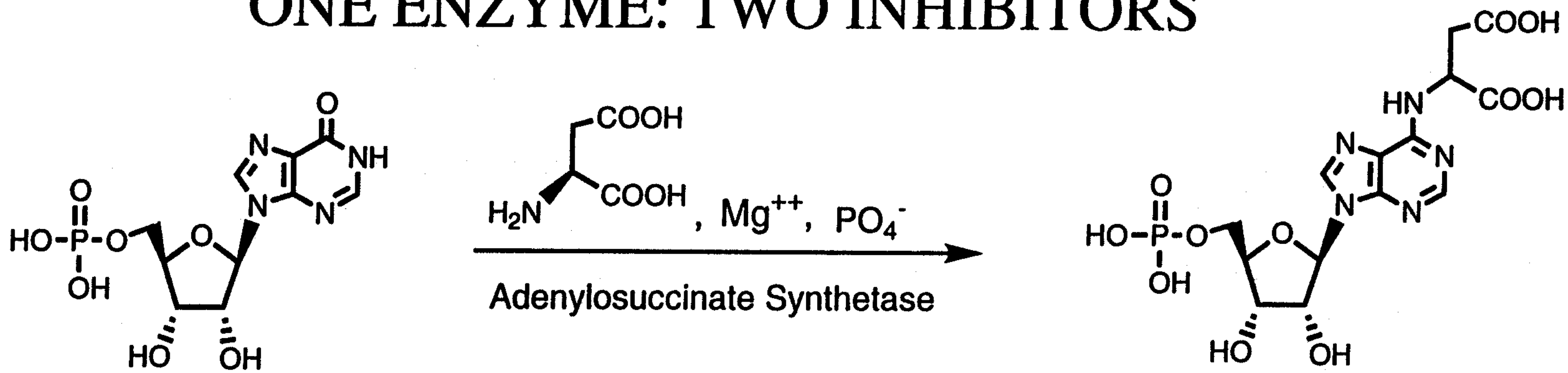


R. Fonne-Pfister[1], P. Chemla[1], E. Ward[3], M. Girardet[1], K.E. Kreuz[1], R. B. Honzatko[4], H. J. Fromm[4], H.-P. Schar[1], M. G. Grutter[2], and S. W. Cowan-Jacob[2]

[1]Research and Development, Crop Protection, and [2]Core Drug Discovery Technologies, Pharmaceutical Division, Ciba-Geigy Ltd., Switzerland; [3]Biotechnology, Research Unit, Ciba-Geigy Ltd., U.S.A.;.[4]Iowa State University;

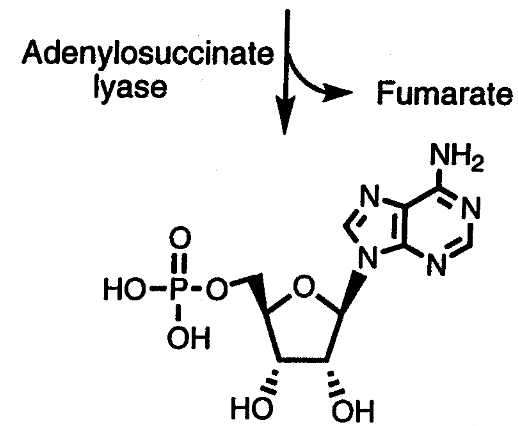
Proc. Natl. Acad. Sci. USA, **1996**, *93*, 9431

ONE ENZYME: TWO INHIBITORS

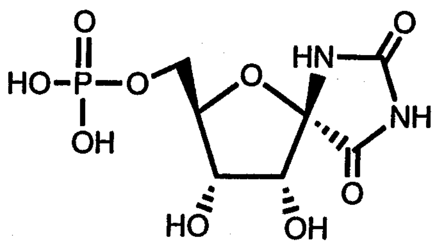


IMP

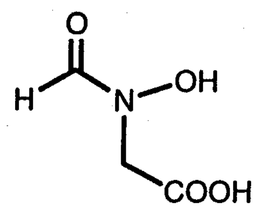
ASMP



AMP



HMP
IMP mimic

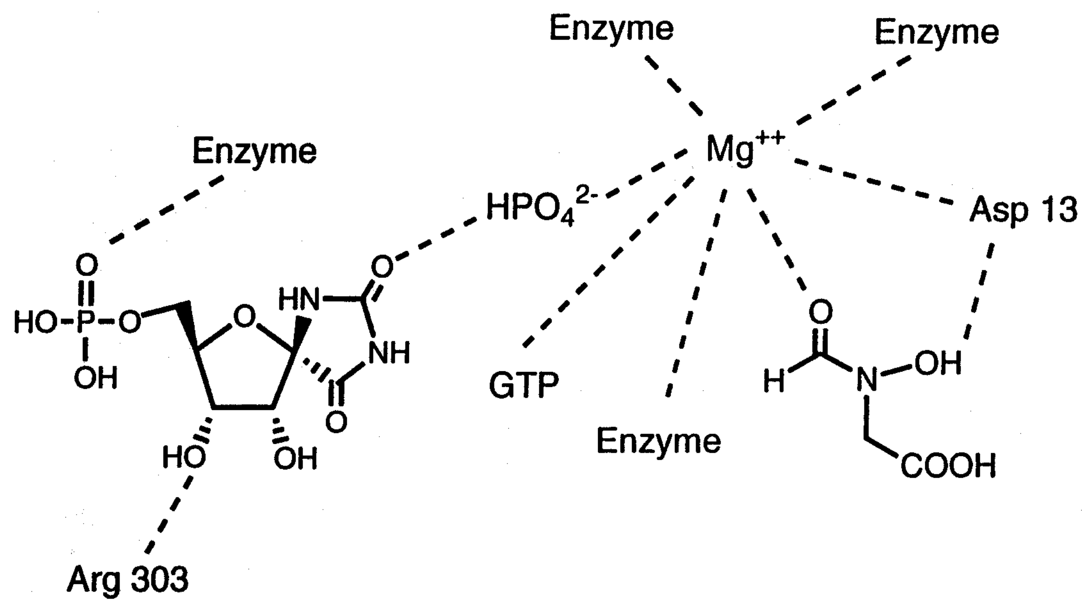


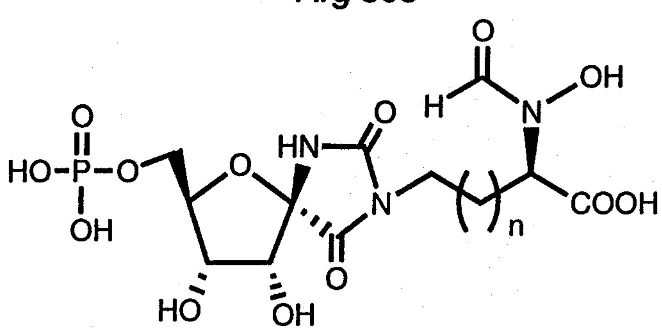
Hadacidin
Aspartate mimic
(competitive inhibitor)

R. B. Honzatko *et al*, *Biochemistry*, **1996**, *35*, 15753
Iowa State University

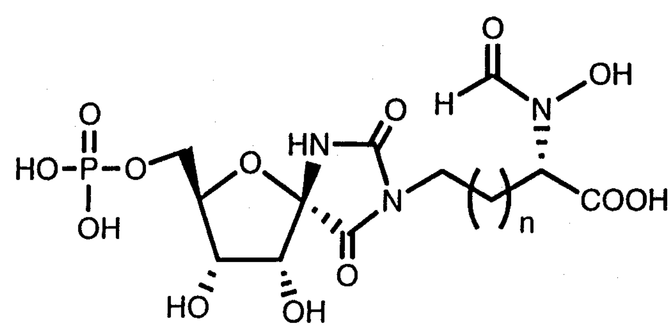
S. W. Cowan-Jacob
Novartis Crop Protection

JOINING FORCES AND BRIDGING THE GAP





n = 0, 1; *R*-Hybrid



n = 0, 1; *S*-Hybrid

University of Montreal - Novartis Crop Protection

Dr. P. Chemla; Dr. K. Gohda