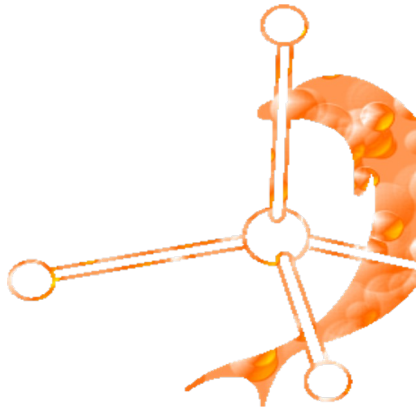
S. Hanessian

University of Montréal (Canada)

ISCHIA PORTO (NAPOLI), ITALY
HOTEL CONTINENTAL TERME
SEPTEMBER 18-23, 2004

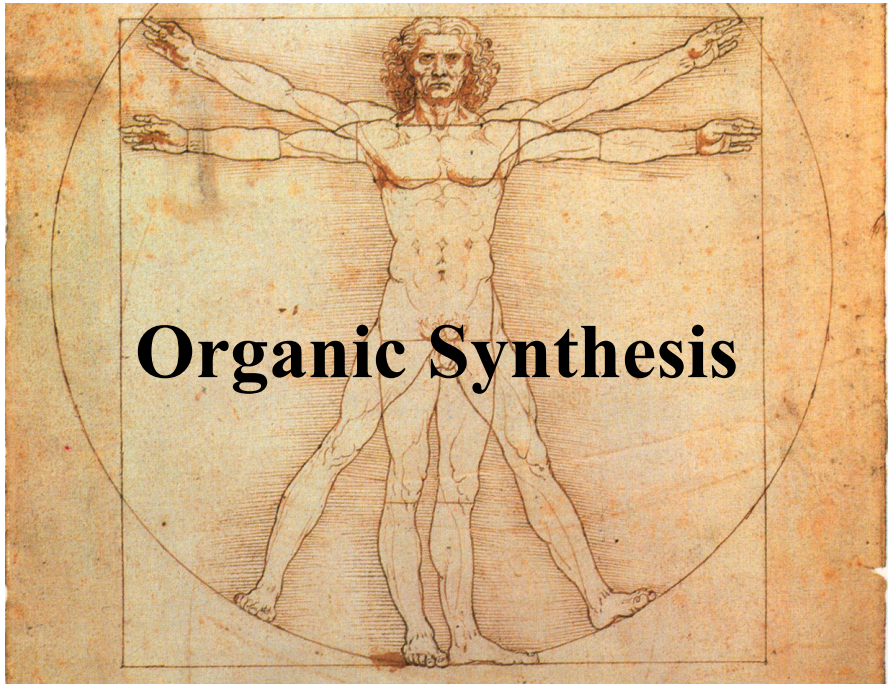


ORGANIC CHEMISTRY - A *CENTRAL* SCIENCE

Food and Commodities

Drug Design

Unnatural Products



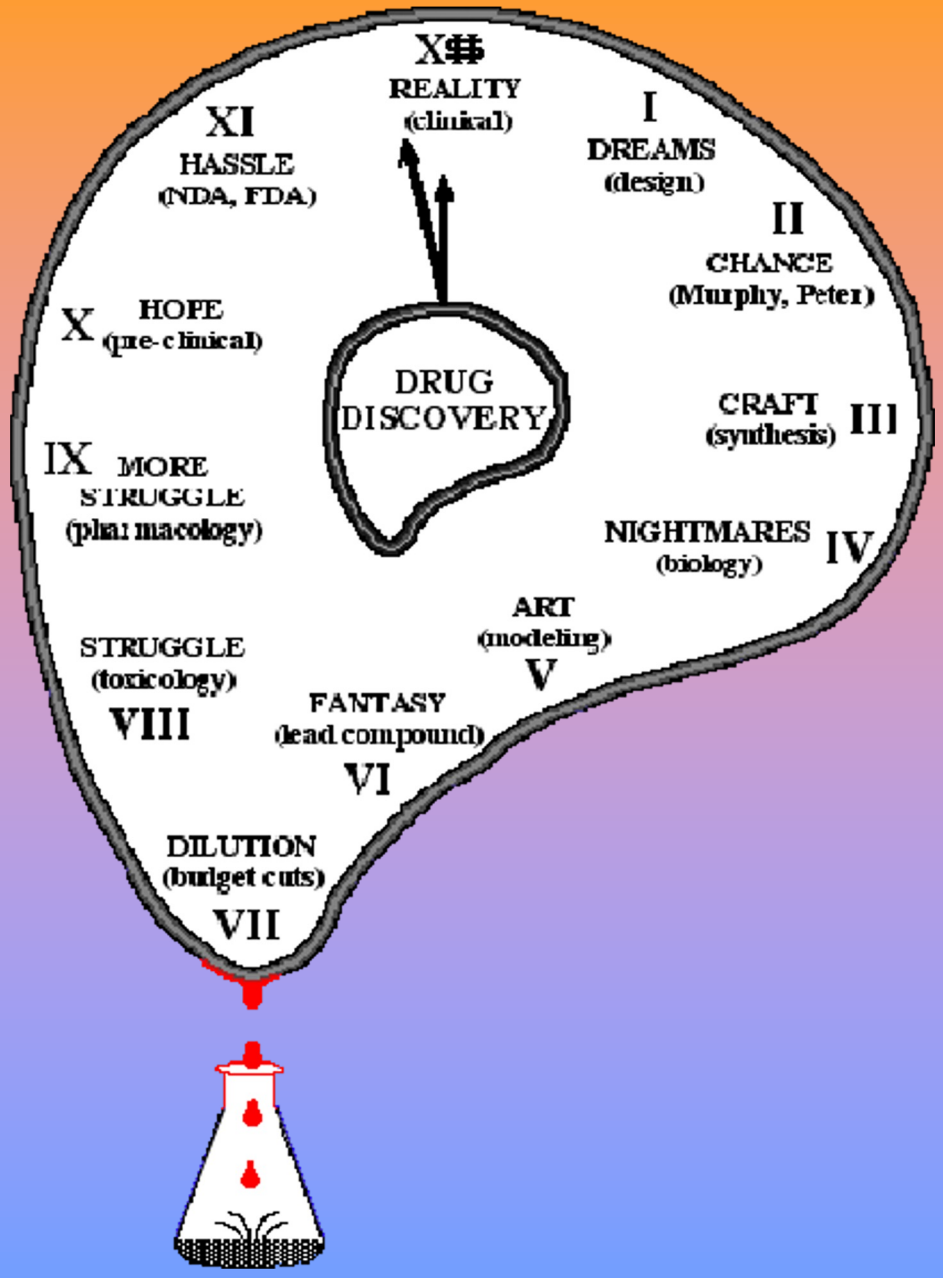
Natural Products

Materials

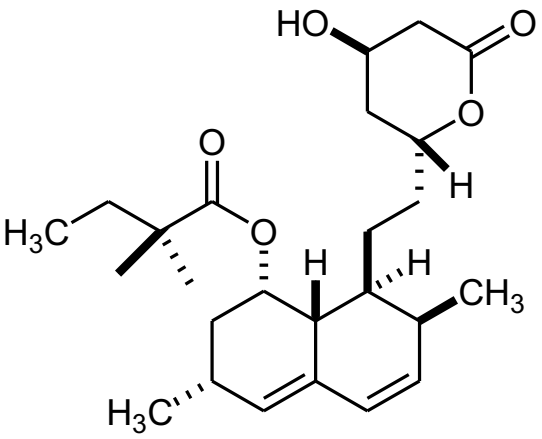
Life Processes

☠

The Drug Discovery Clock

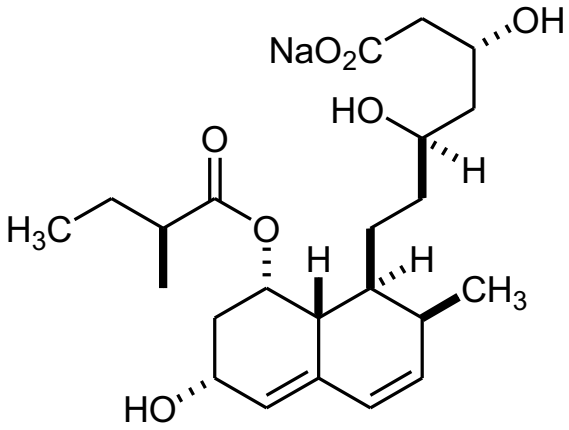


What a Difference a Methyl Make$



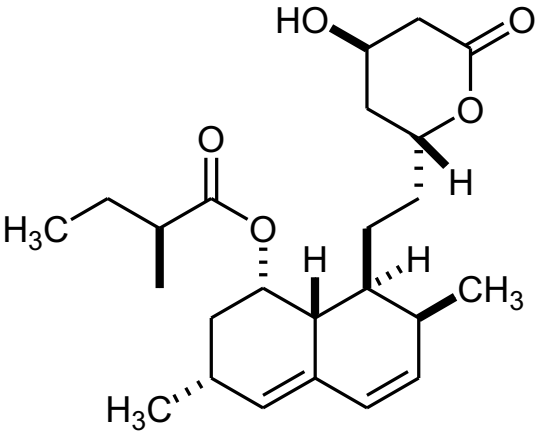
(optically active)

A. Zocor
B. Simvastatin
C. Merck & Co.
D. $3,575.0
E. Cholesterol reduction



(optically active)

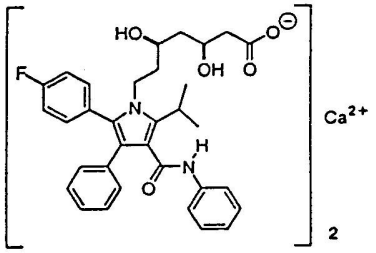
A. Pravastatin
B. Pravachol
C. Bristol-Myers Squibb Co.
D. $1,437.0
E. Cholesterol reduction



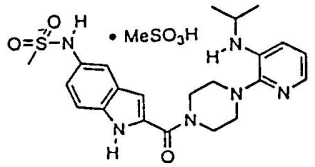
(optically active)

A. Lovastatin
B. Mevacor
C. Merck & Co.
D. $1,100.0
E. Cholesterol reduction

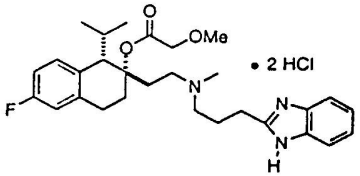
NEW CHEMICAL ENTITIES



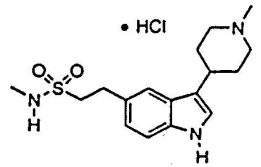
Atrovastin
(dyslipidemia)
Parke-Davis, U.S.



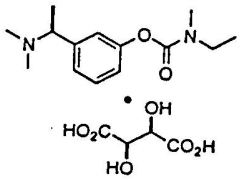
Delaviridine
(antiviral)
Pharmacia & UpJohn, U.S.



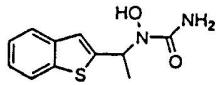
Mebefradil
(antihypertensive)
Roche, U.S.



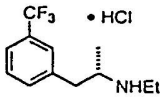
Naratripan
(dyslipidemia)
Glaxo Wellcome, U.K.



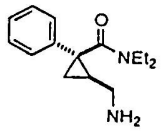
Rivastigmin
(anti-Alzheimers')
Novartis, Switzerland



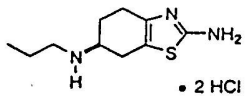
Zileuton
(antiasthma)
Abbott, U.S.



Dexfenfluramine
(antiobesity)
Servier, France



Milnacipran
(antidepressant)
Pierre Fabre, France

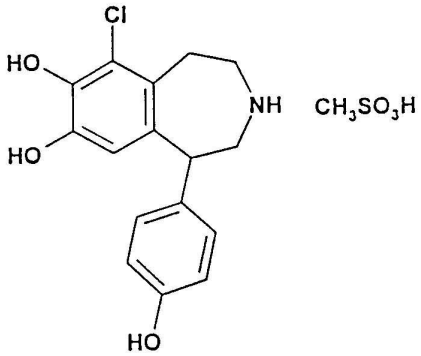


Pramipexole
(anti-Parkinsonian)
Boehringer-Ingelheim, U.S.

NEW CHEMICAL ENTITIES

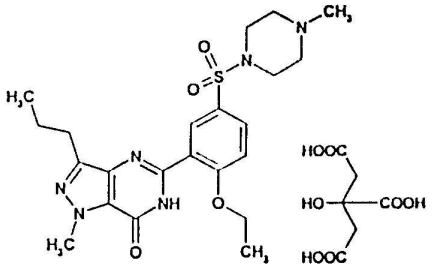
Fenoldopam Mesylate
(antihypertensive) (57 – 64)

Country of Origin : US
Originator : SmithKline Beecham
First Introduction : US
Introduced by : Neurex
Trade Name : Corlopam
CAS Registry No : 67227-57-0
Molecular Weight : 401.67



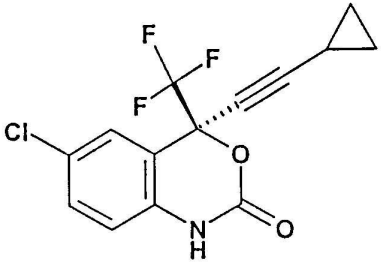
Sildenafil Citrate (Male Sexual Dysfunction) ((187 – 194)

Country of Origin : UK
Originator : Pfizer
First Introduction : US
Introduced by : Pfizer
Trade Name : Viagra
CAS Registry No : 139755-83-2
Molecular Weight : 474.58



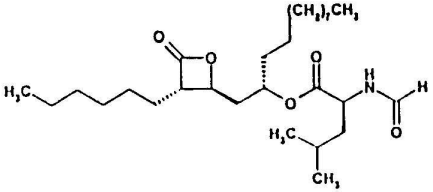
Efavirenz (Antiviral for AIDS) (43 – 48)

Country of Origin : US
Originator : Merck & Co.
First Introduction : US
Introduced by : DuPont Pharm.
Trade Name : Sustiva
CAS Registry No : 154598-52-4
Molecular Weight : 315.68



Orlistat (Antiobesity) (125 – 132)

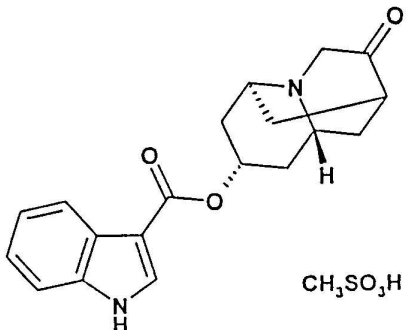
Country of Origin : Switzerland
Originator : Roche
First Introduction : New Zealand
Introduced by : Roche
Trade Name : Xenical
CAS Registry No : 096829-58-2
Molecular Weight : 495.74



Dolasetron Mesylate
(Antiemetic)

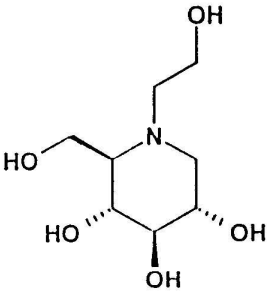
Country of Origin : Germany
Originator : Hoechst Marion Roussel
First Introduction : Australia
Introduced by : Hoechst Marion Roussel
Trade Name : Anzemet
CAS Registry No : 115956-13-3
Molecular Weight : 438.49

(36 – 42)



Miglitol (Antidiabetic) (95 – 102)

Country of Origin : Germany
Originator : Bayer
First Introduction : Germany
Introduced by : Sanofi
Trade Name : Diastabol
CAS Registry No : 72432-03-2
Molecular Weight : 207.23



DRUG DISCOVERY

A SYNTHETIC CHEMIST'S PERSPECTIVE AND INVOLVEMENT:



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)

ACADEMIC TARGETED SYNTHESIS

ORIGIN OF PROBLEM

- Hypothesis
- Proposal
- Theory
- Dogma

- *Biological*
- *Chemical*
- *Theoretical*
- *Computer*

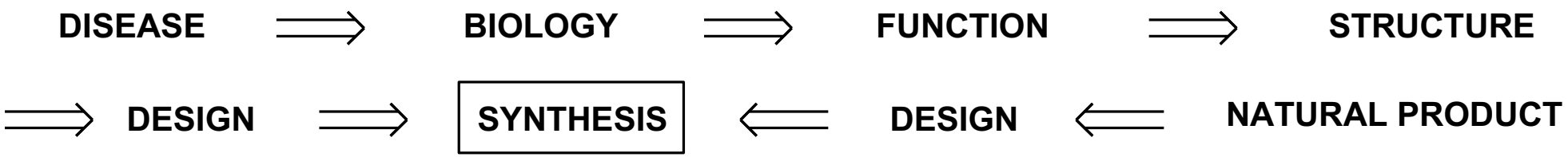
INCENTIVE FOR SYNTHESIS

- Validation
- New insights
- Intuition / Curiosity
- Design / Strategy

TARGET MOLECULE

- New
- Known
- Hybrid
- Analog

UNIVERSITY-INDUSTRY PARTNERSHIPS



UNIVERSITY:

- Fundamental and "curiosity"-orientend research
- Focussed program
- Funding dictates time
- Industrial collaboration "essential"
- Publication priority

INDUSTRY:

- Target-oriented research
- All inclusive program
- University collaboration "informative"
- Patenting priority

- Combining innovation with practicality
- Technology transfer when appropriate
- Coworker training

WHO'S DOING WHAT IN ORGANIC SYNTHESIS

- METHODS PEOPLE
- METHODS AND TARGET PEOPLE
- TARGET PEOPLE
- TARGET AND FUNCTION PEOPLE
- FUNCTION PEOPLE

"Everything is changing…
even the future ain't what it used to be"

Yogi Berra
Yankees catcher
1947-1963

THE PLIGHT OF THE SYNTHETIC ORGANIC CHEMIST OF THE THIRD MILLENIUM

QUESTION:

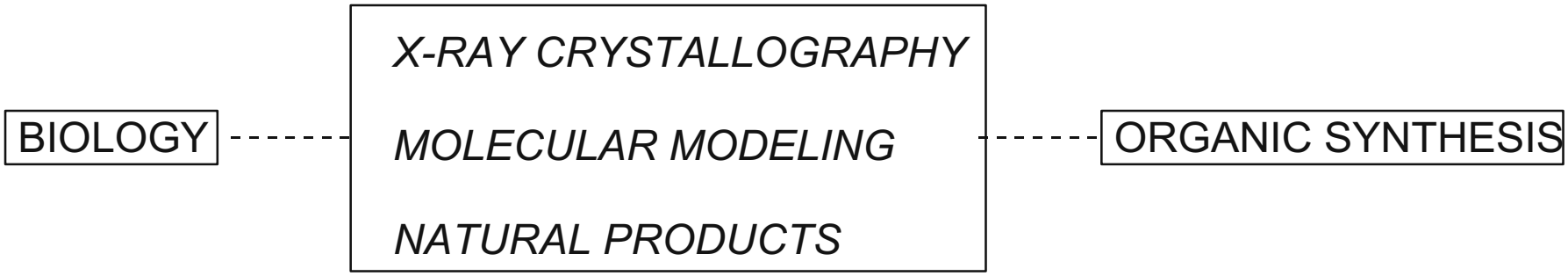
WHAT *IMPORTANT* AND LASTING ROLE CAN SYNTHESIS PLAY IN BIOLOGY, MEDICINE AND OTHER DISCIPLINES ?

PROBLEM:

1. IDENTIFYING A *RELEVANT* BIOLOGICAL PROBLEM WITH A LONG TERM IMPACT

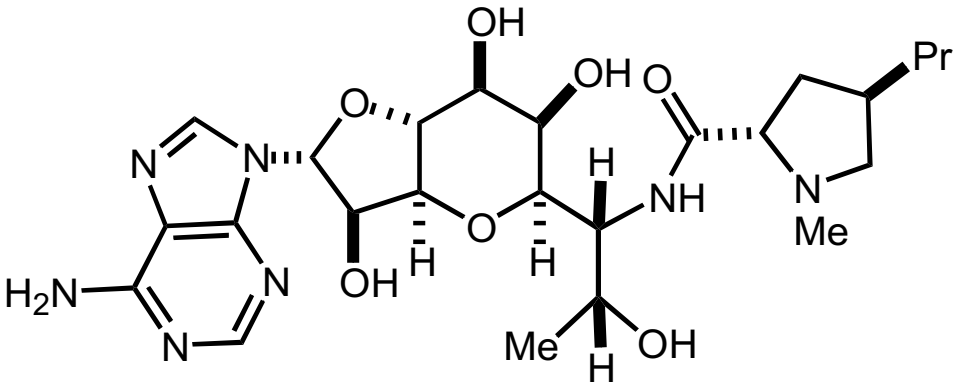
2. FINDING A CHALLENGING TARGET FOR SYNTHESIS THAT BEARS *DIRECTLY* ON THE PROBLEM

3. FINISHING THE SYNTHESIS *BEFORE* THE INTEREST WANES (OR THE THEORY CHANGES !)

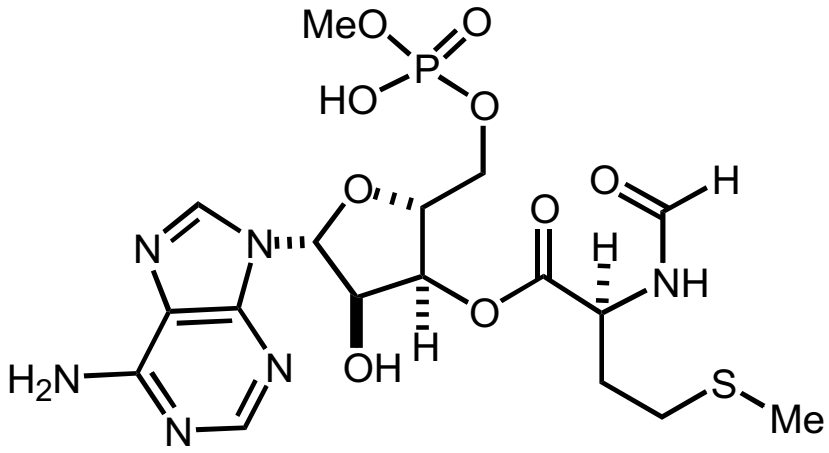


“Quantamycin - A Designed Ribosomal Binder”

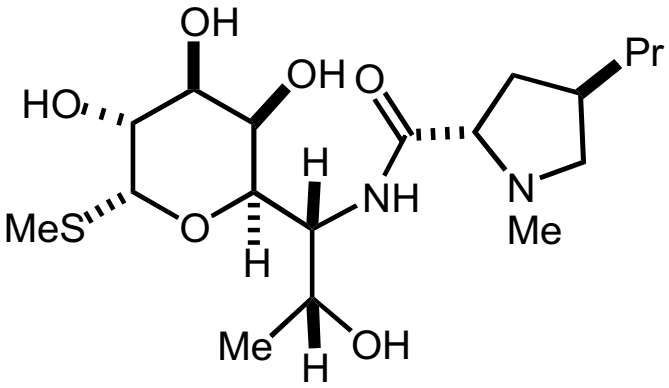
Modifying lincomycin to mimic the first adenine nucleotide of t-RNA linked to an L-Pro-methionine dipeptide



Quantamycin



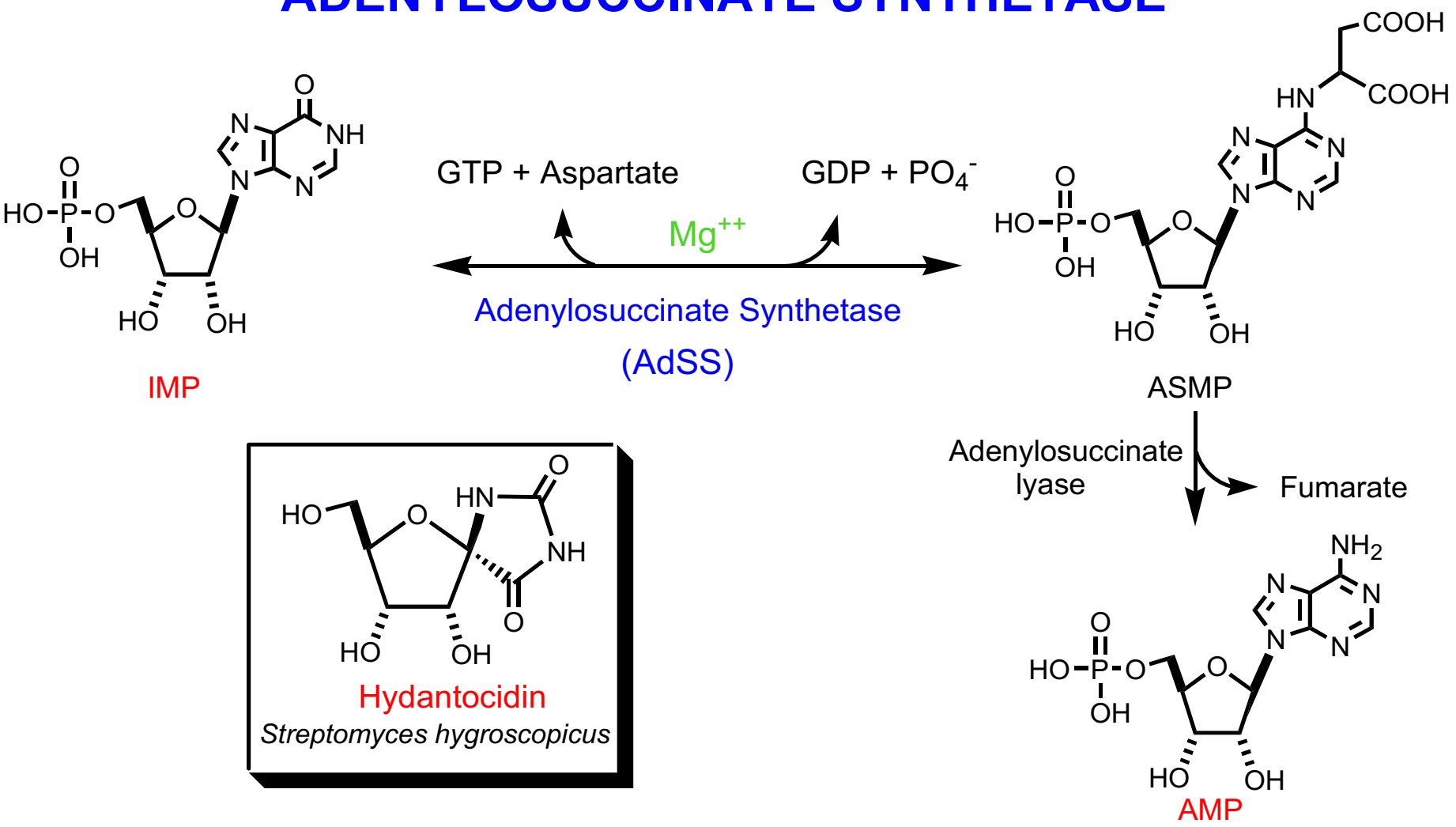
Peptidyl *t*-RNA f-met A Me ester
(P site)



Lincomycin

S. Hanessian, K. Sato, T. J. Liak, N. Danh, D. Dixit, and B. V. Cheney
J. Am. Chem. Soc. **1984**, *106*, 6114

ADENYLOSUCCINATE SYNTHETASE

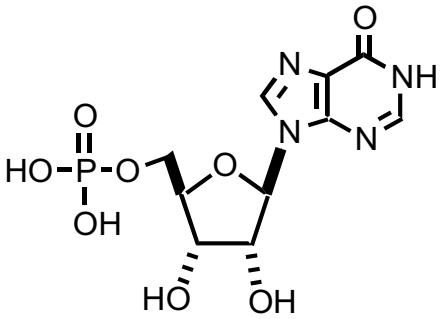


R. Fonne-Pfister[1], P. Chemla[1], E. Ward[3], M. Girardet[1], K.E. Kreuz[1], R. B. Honzatko[4], H. J. Fromm[4], H.-P. Schar[1], M. G. Grutter[2], and S. W. Cowan-Jacob[2]

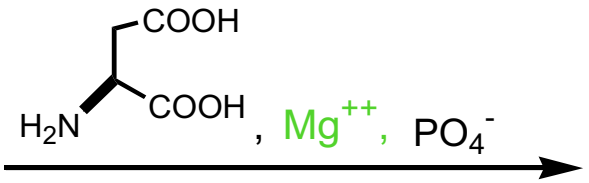
[1]Research and Development, Crop Protection, and [2]Core Drug Discovery Technologies, Pharmaceutical Division, Ciba-Geigy Ltd., Switzerland; [3]Biotechnology, Research Unit, Ciba-Geigy Ltd., U.S.A.; [4]Iowa State University;

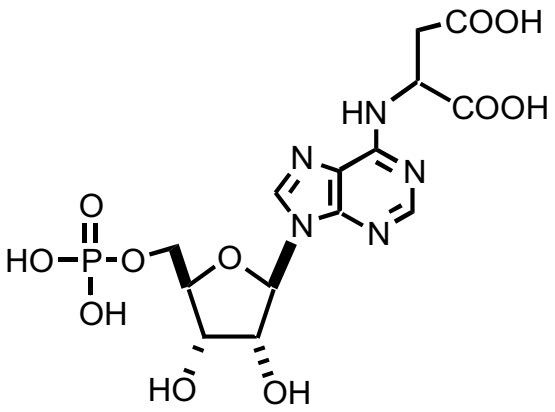
Proc. Natl. Acad. Sci. USA, **1996**, *93*, 9431

ONE ENZYME: TWO INHIBITORS



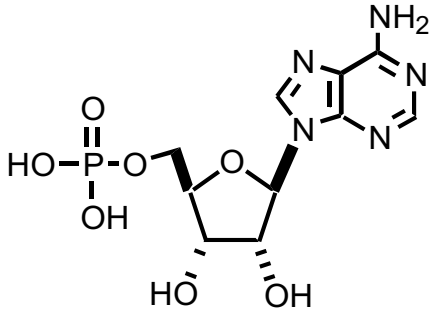
IMP



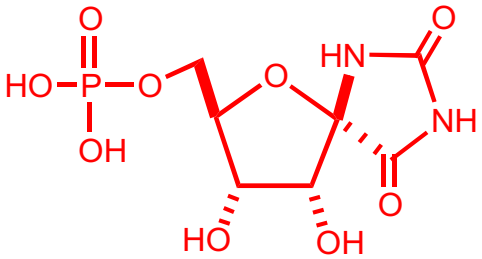


ASMP

Adenylosuccinate lyase → Fumarate

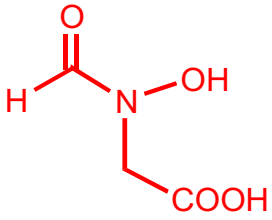


AMP



HMP

IMP mimic



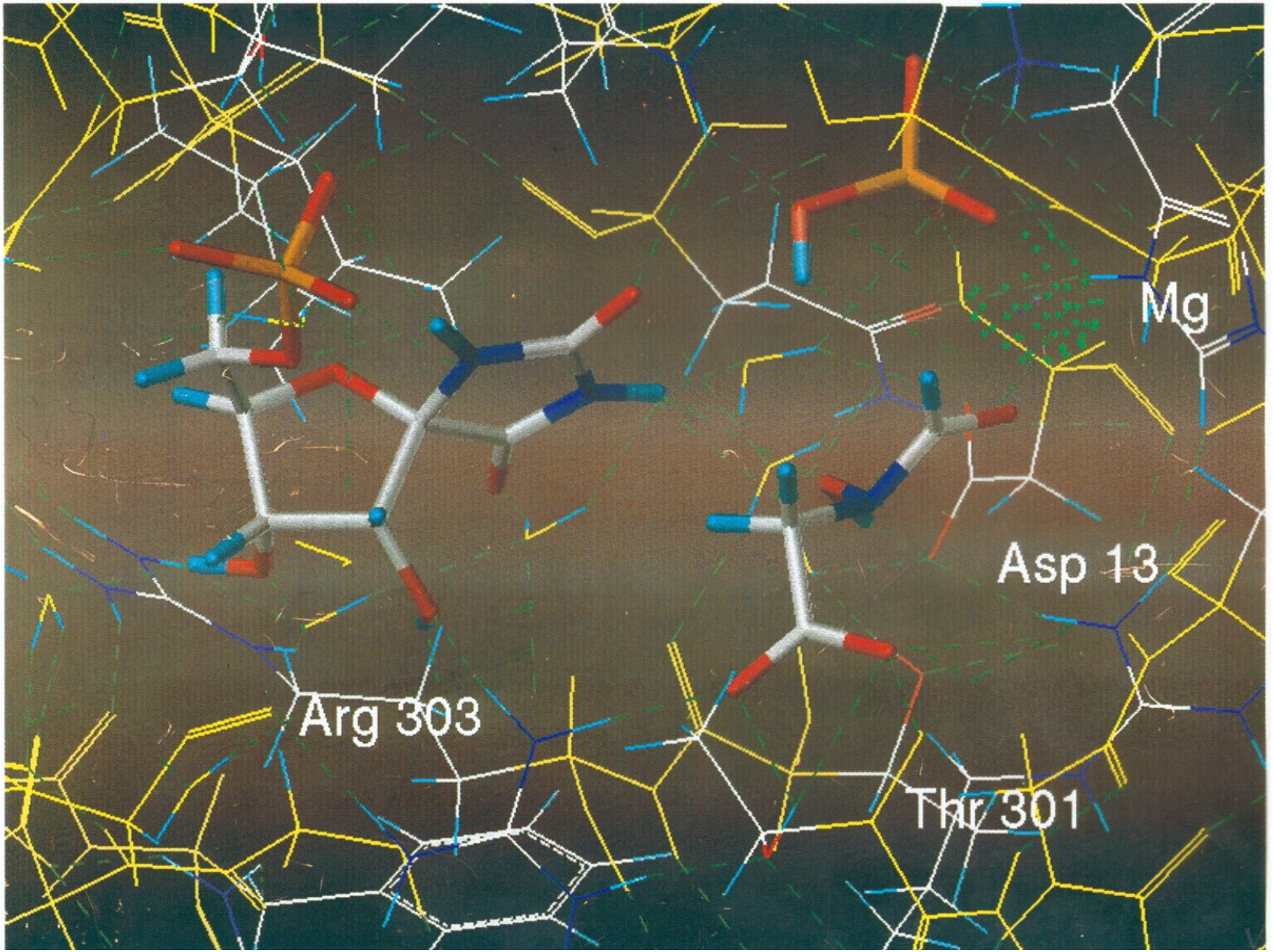
Hadacidin

Aspartate mimic

(competitive inhibitor)

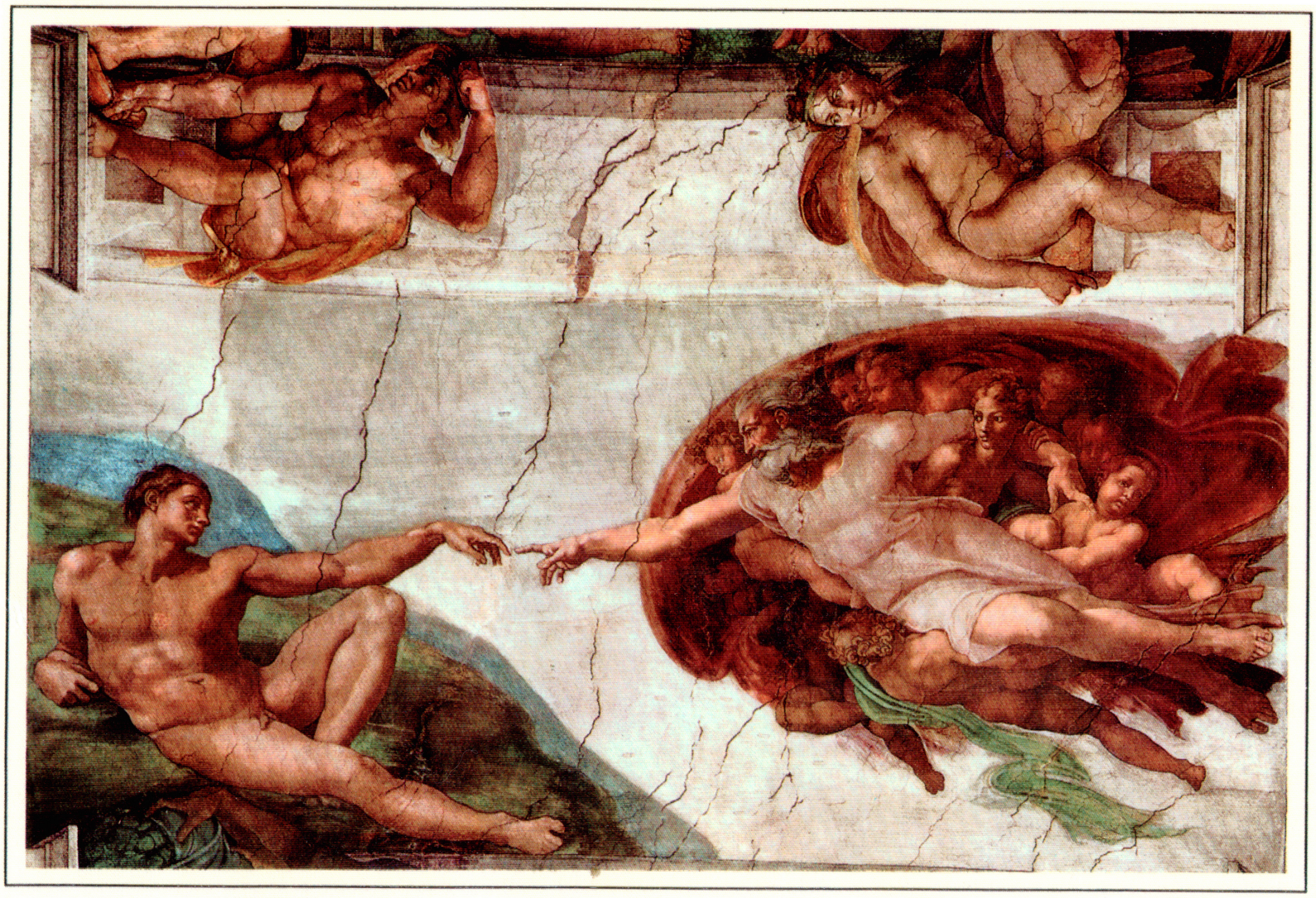
R. B. Honzatko *et al*, *Biochemistry*, **1996**, *35*, 15753
Iowa State University

S. W. Cowan-Jacob
Novartis Crop Protection


Mg
Asp 13
Arg 303
Thr 301

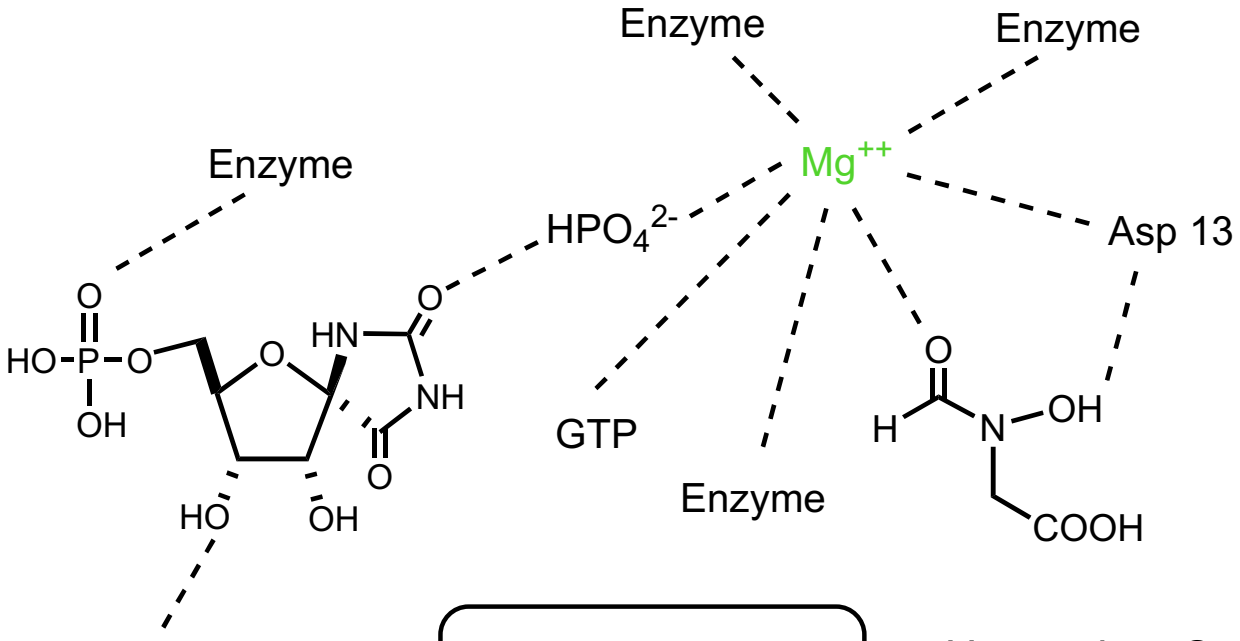
INHIBITION OF ADENYLOSUCCINATE SYNTHETASE

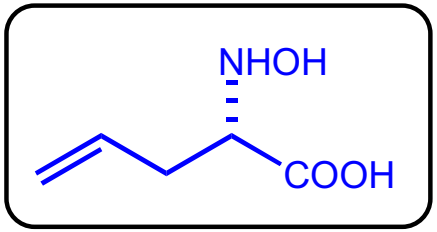
(The « Creation » of an Inhibitor)



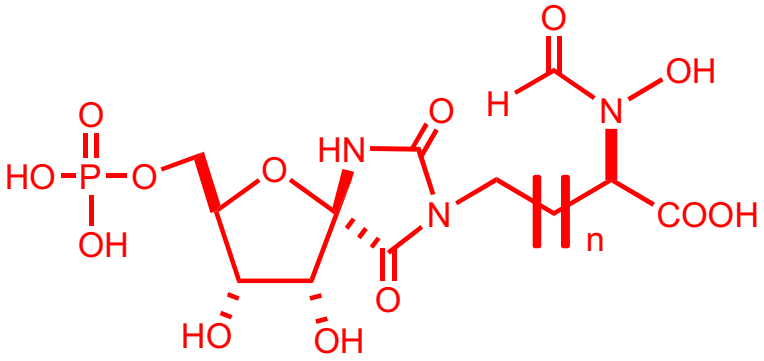
Hanessian, S.; Lu, P-P.; Sanceau, J-Y.; Chemla, P.; Gohda, K.; Fonne-Pfister, R.; Prade, L.; Cowan-Jacob, S. W. *Angew. Chem. Int. Ed.* **1999**, *38*, 3159.

JOINING FORCES AND BRIDGING THE GAP

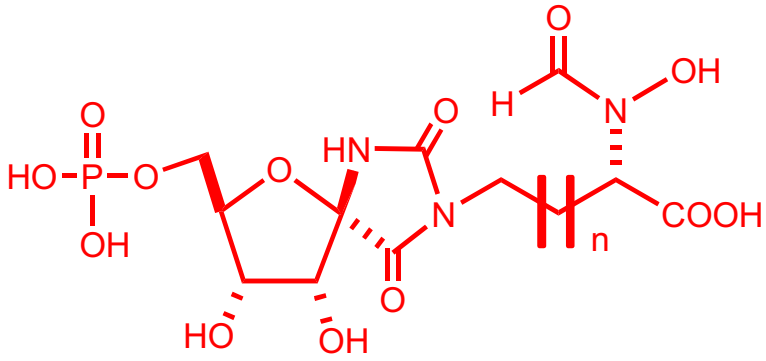




Hanessian, S.; Yang, R-Y. *Tetrahedron Lett.* **1996**, *37*, 5273

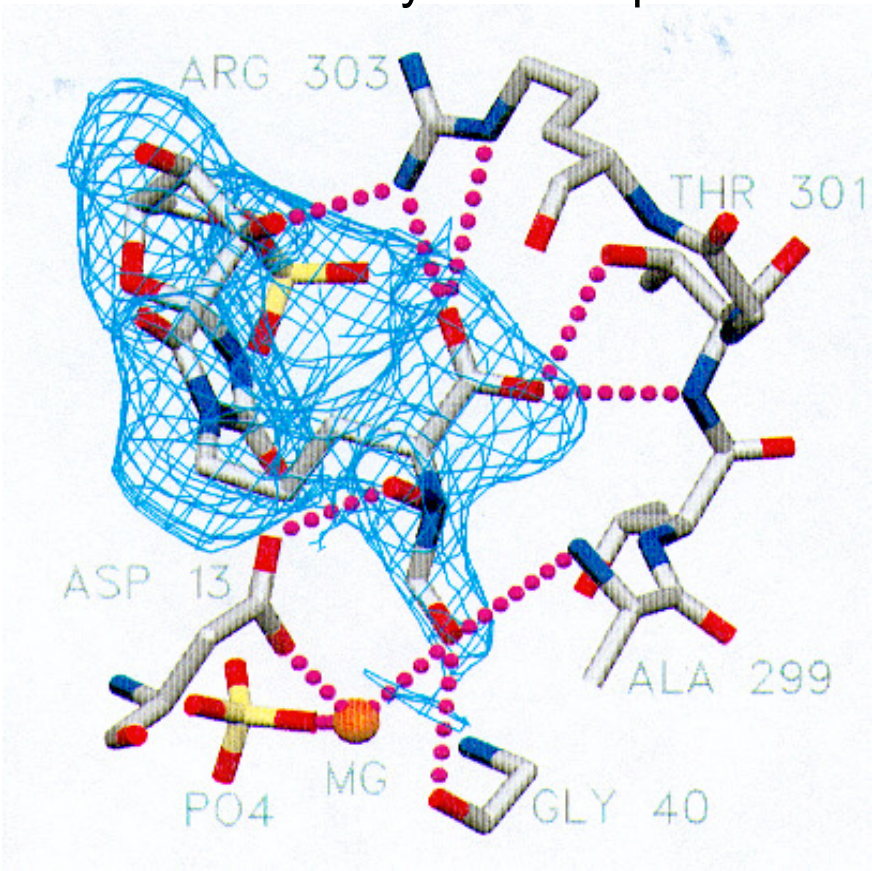


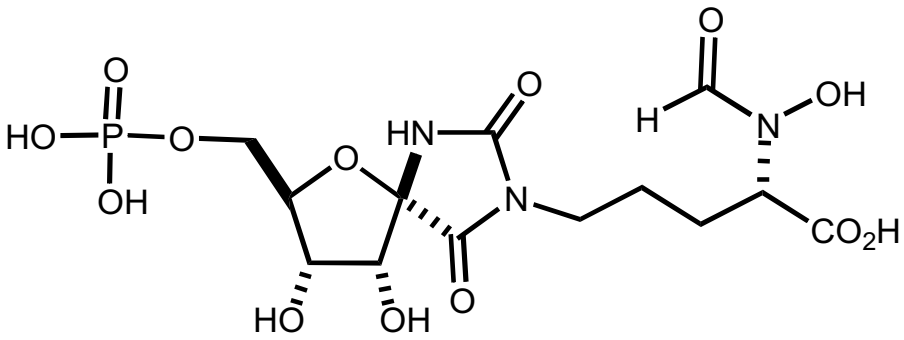
n = 0, 1; *R*-Hybrid



n = 0, 1; *S*-Hybrid

AdSS - *S*-hybrid Complex

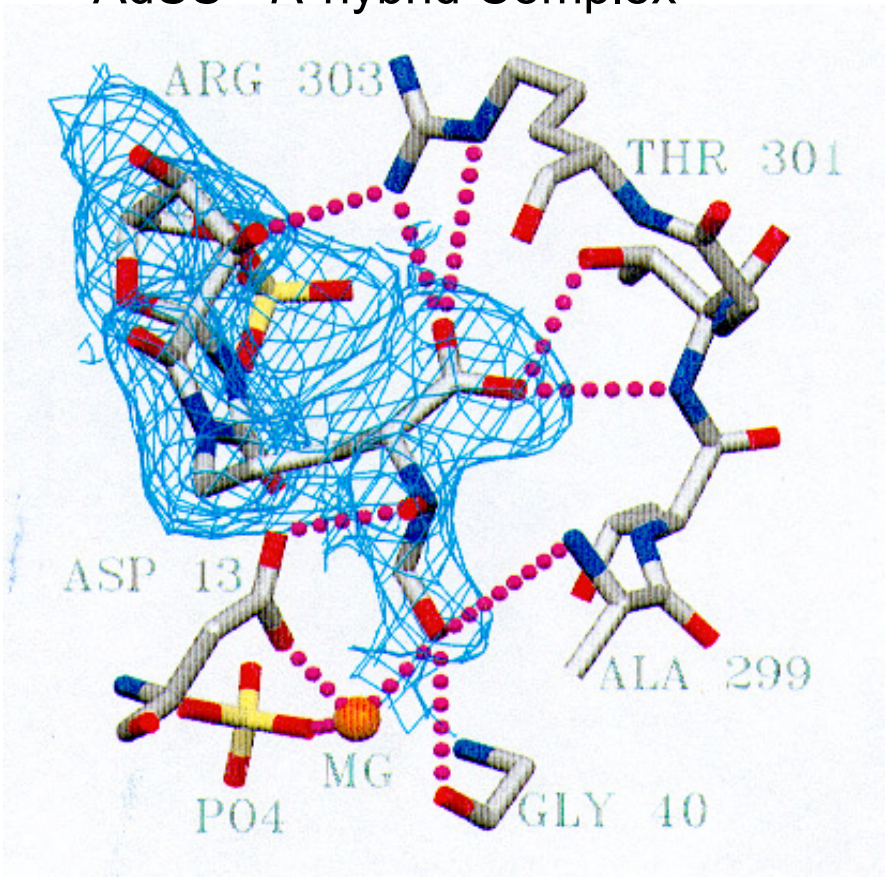


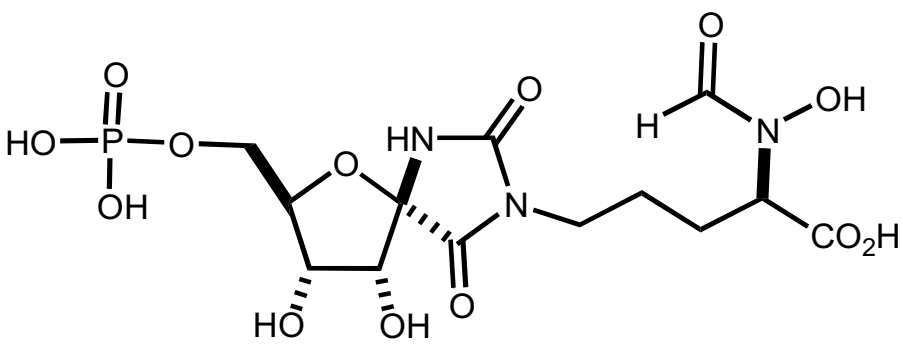


S-hybrid

Ki = 43 nM (E. coli AdSS)

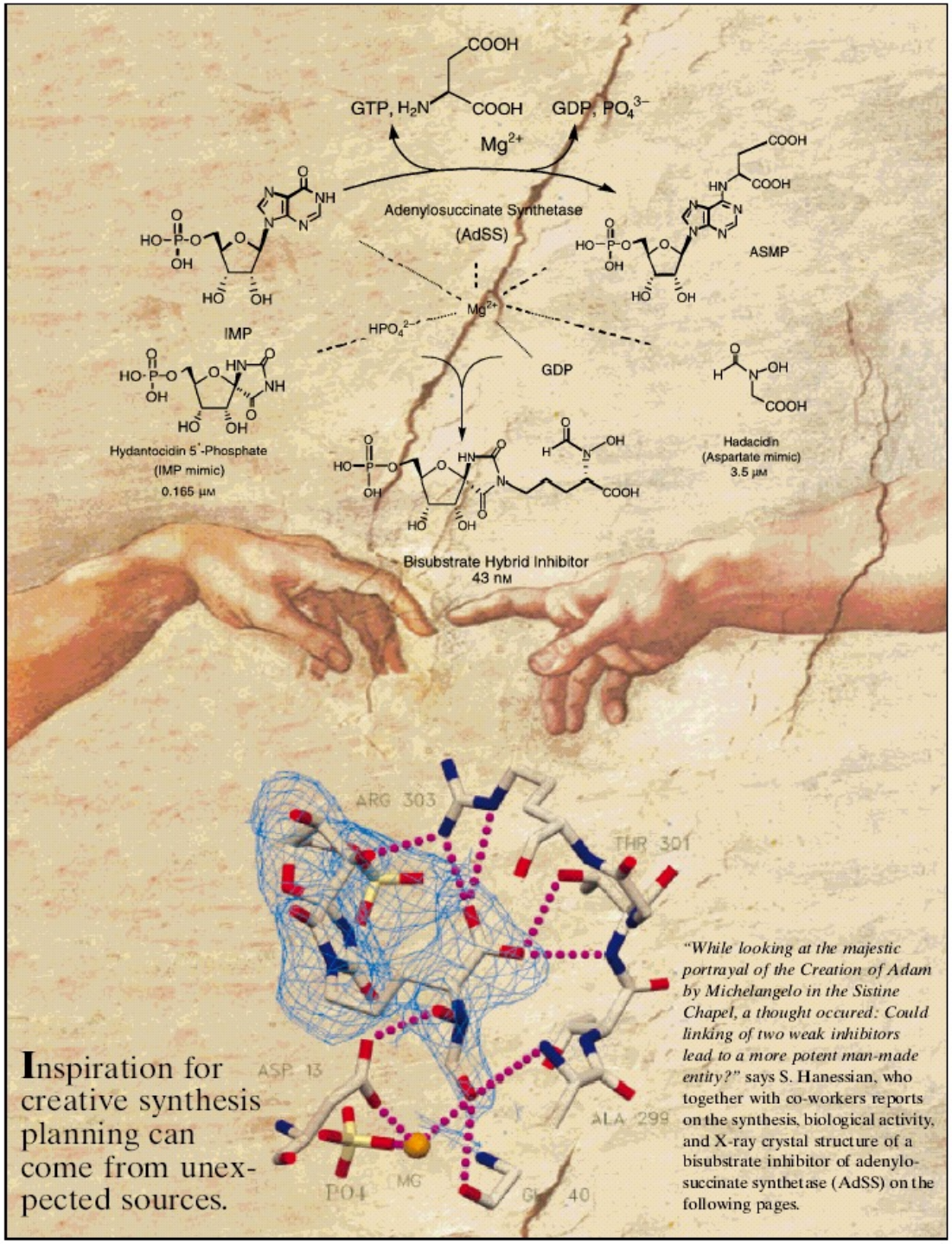
AdSS - *R*-hybrid Complex





R-hybrid

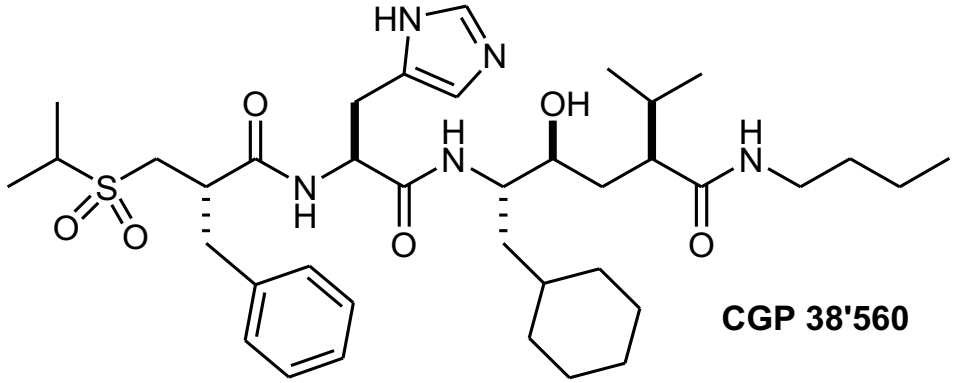
Ki = 665 nM (E. coli AdSS)



Inspiration for creative synthesis planning can come from unexpected sources.

"While looking at the majestic portrayal of the Creation of Adam by Michelangelo in the Sistine Chapel, a thought occured: Could linking of two weak inhibitors lead to a more potent man-made entity?" says S. Hanessian, who together with co-workers reports on the synthesis, biological activity, and X-ray crystal structure of a bisubstrate inhibitor of adenylosuccinate synthetase (AdSS) on the following pages.

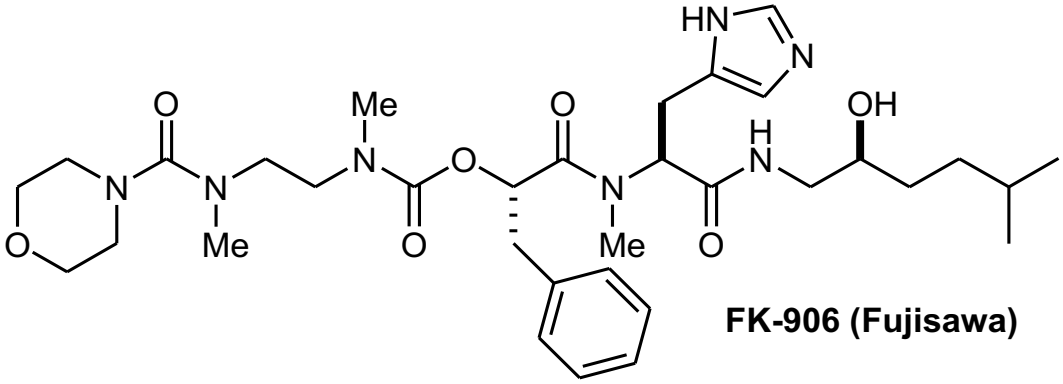
RENIN AND HYPERTENSION: THE SEARCH FOR "SMALL" INHIBITORS



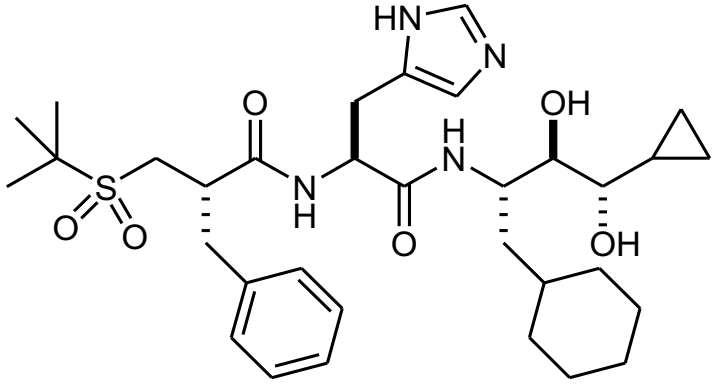
CGP 38'560

≡

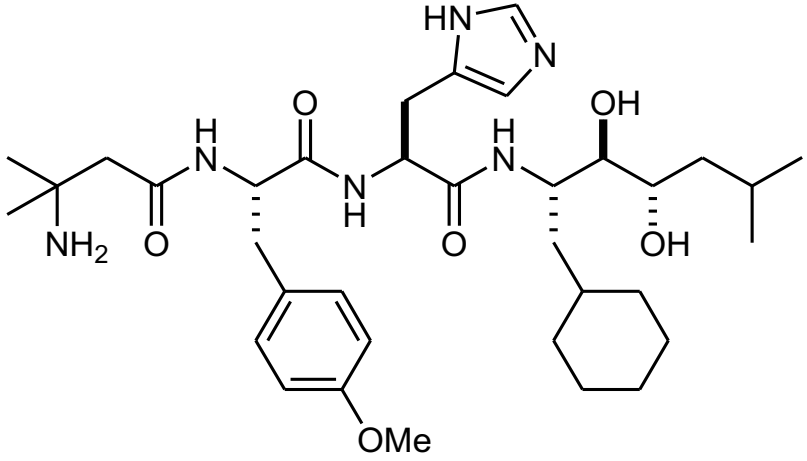




FK-906 (Fujisawa)

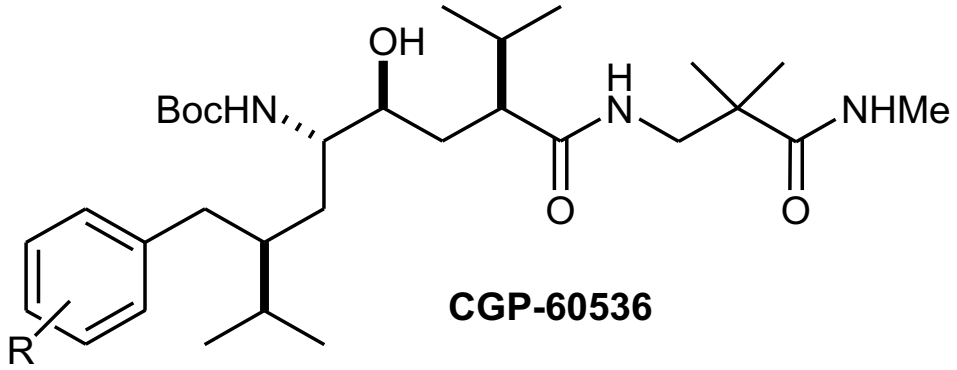


Remikiren (Roche)



Enalkiren (Abbott)

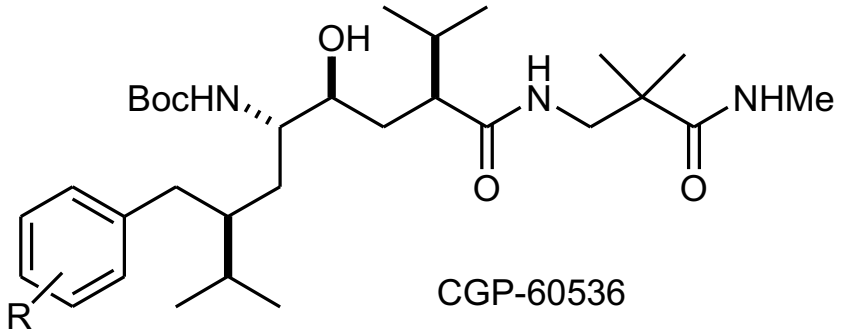
A “Designed” Renin Inhibitor



CGP-60536

CGP-60536 : J. Rahuel, V. Rasetti, J, Maibaum, H, Rueger, R. Goschke, N.C. Cohen, S. Stutz, F. Cumin, W. Fuhrer, J.M. Wood. M.G. Grutter *Chem. Biol.* **2001**, *7*, 493

The Synthesis Challenge



CGP-60536

- Four stereogenic centres
- Two isopropyl groups (2*S*, 7*S*)
- *Syn*-amino alcohol
- Innnovation, practicality, efficiency

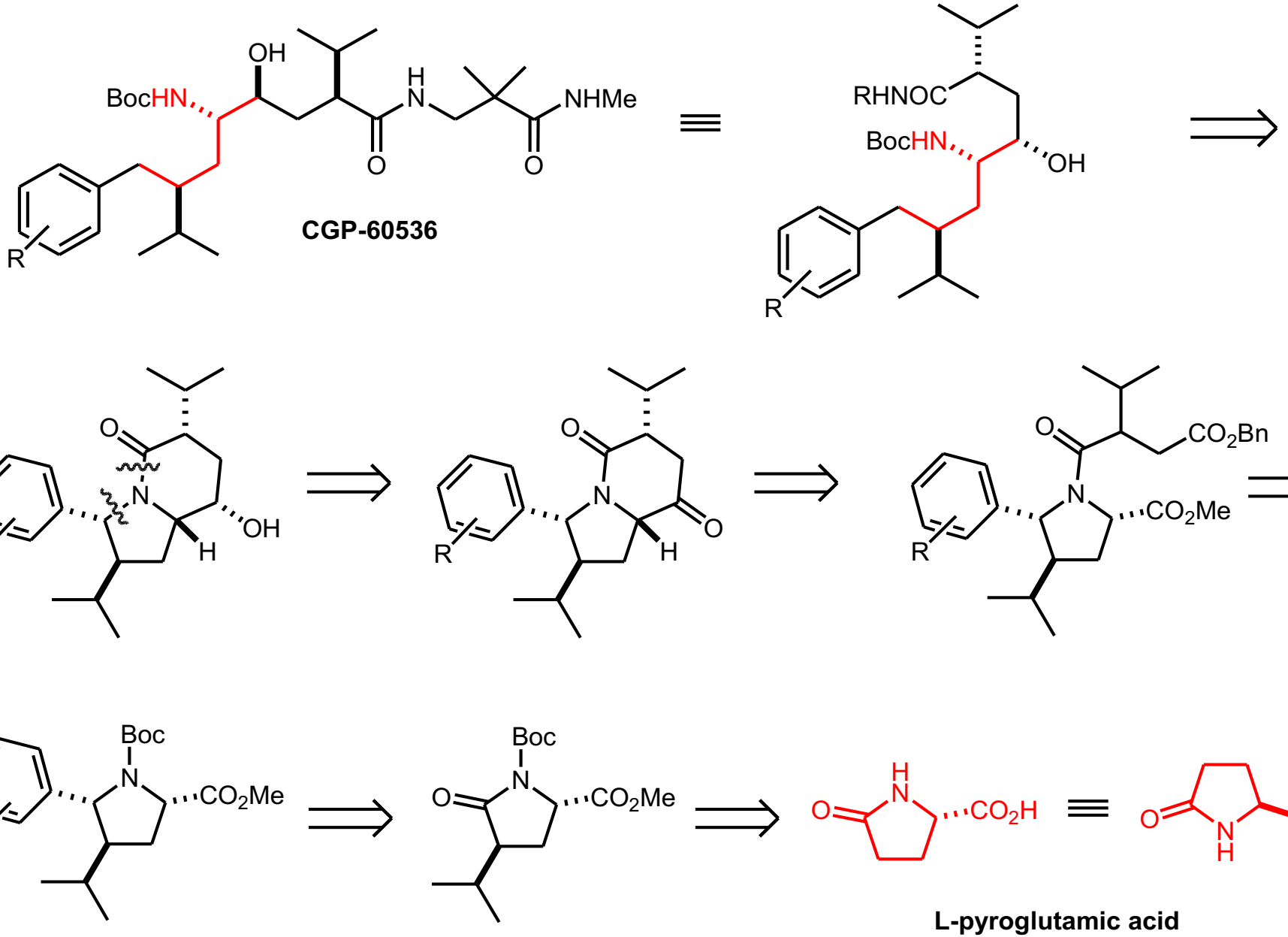
No chiral auxiliaries $

No toxic reagents ☠

Ciba Geigy Patent, EP-678503, April 7, 1995
U.S. 5,654,445 (1997)

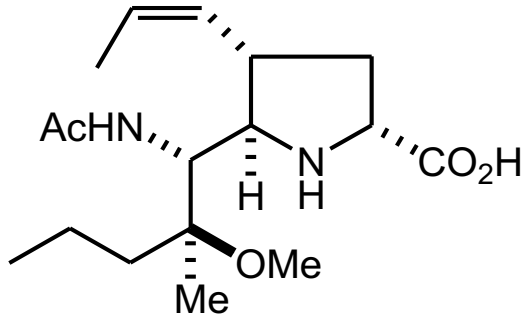
D. Sanham *et al.* Tetrahedron Lett. *41*, 10091 (2000)
J. Maibaum *et al.* Tetrahedron Lett. *41*, 10085 (2000)

THE VISUAL DIALOGUE - SEEING THROUGH THE MIND'S EYE



Hanessian, S.; Claridge, S.; Johnstone, S. *J. Org. Chem.* **2002**, *67*, 4261

A Potent Influenza Neuraminidase Inhibitor

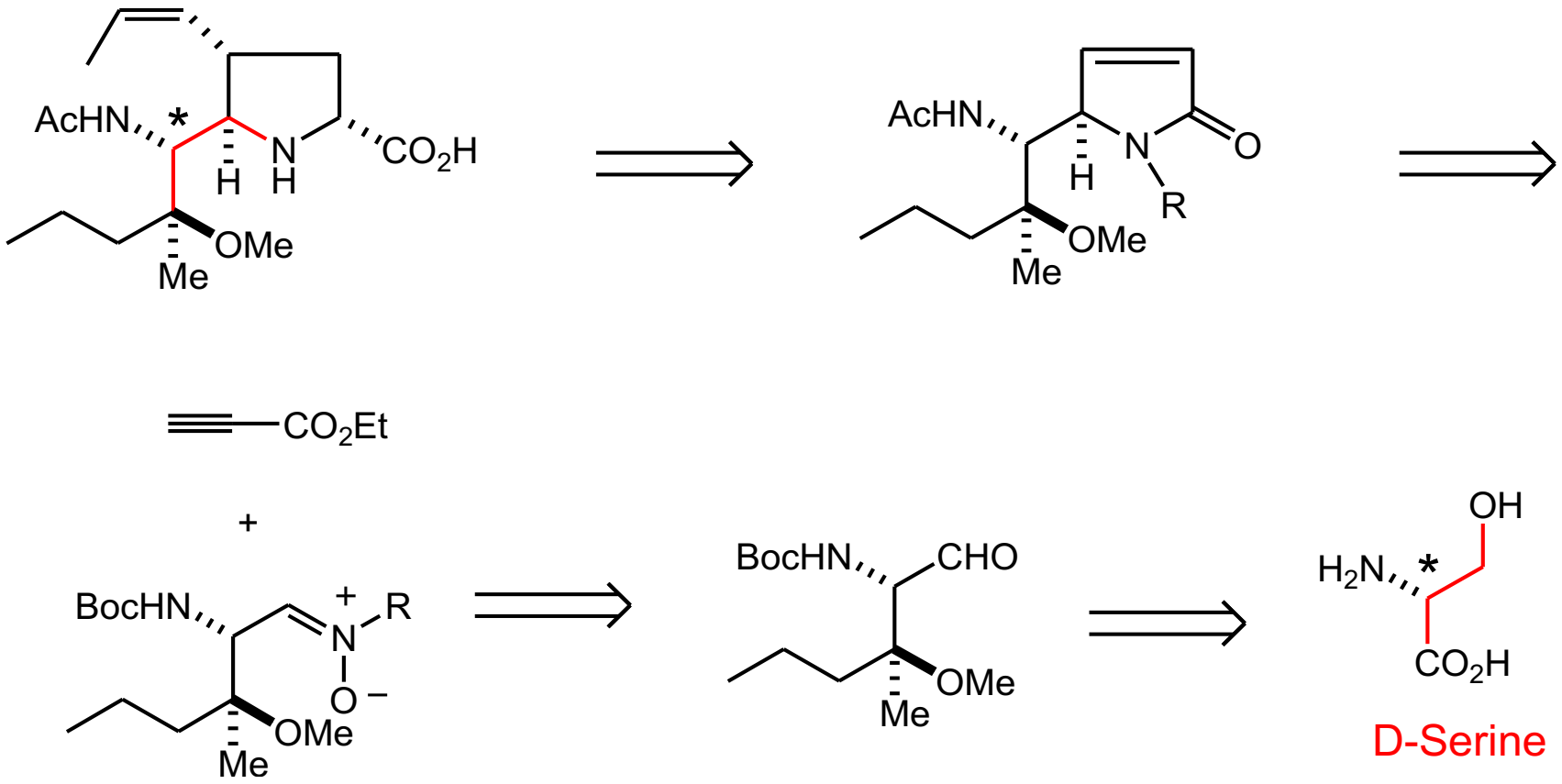


C. Maring et al. Abbott Laboratories

S. Hanessian et al. University of Montreal

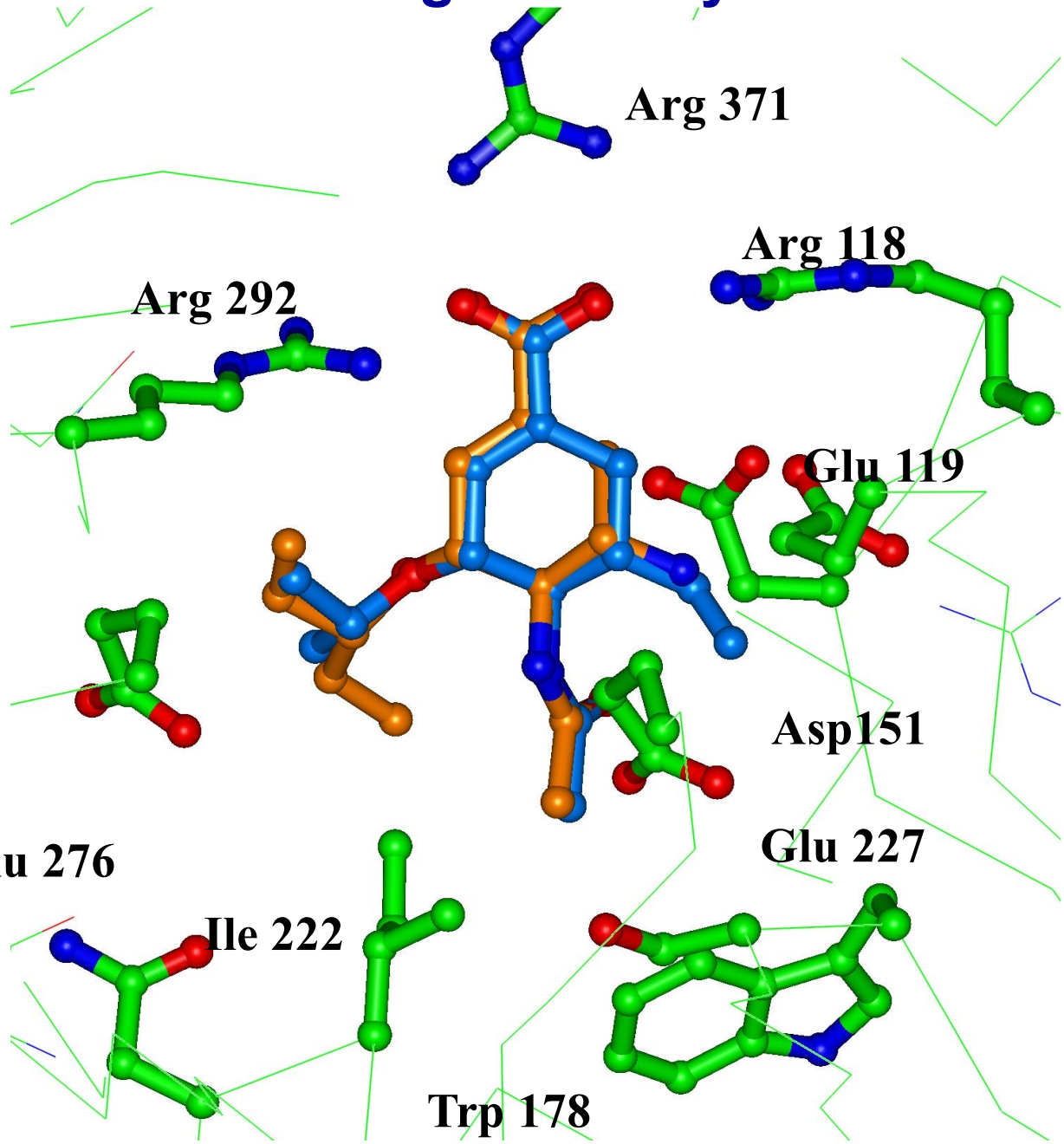
PCT WO 01/28996 A2, April 26, 2001

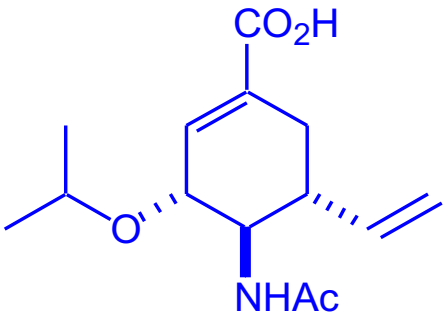
A-315675 Disconnection



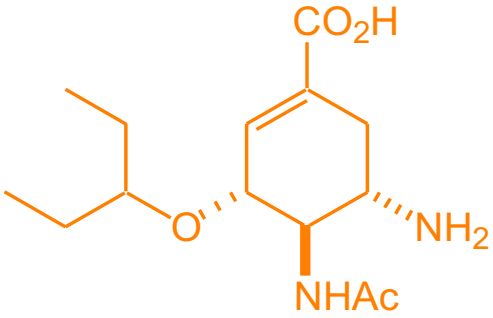
Hanessian, S.; Bayrakdarian, M.; Luo, X. *J. Am. Chem. Soc.* **2002,** *124*, 4716

A New Paradigm in Enzyme Inhibitor Design





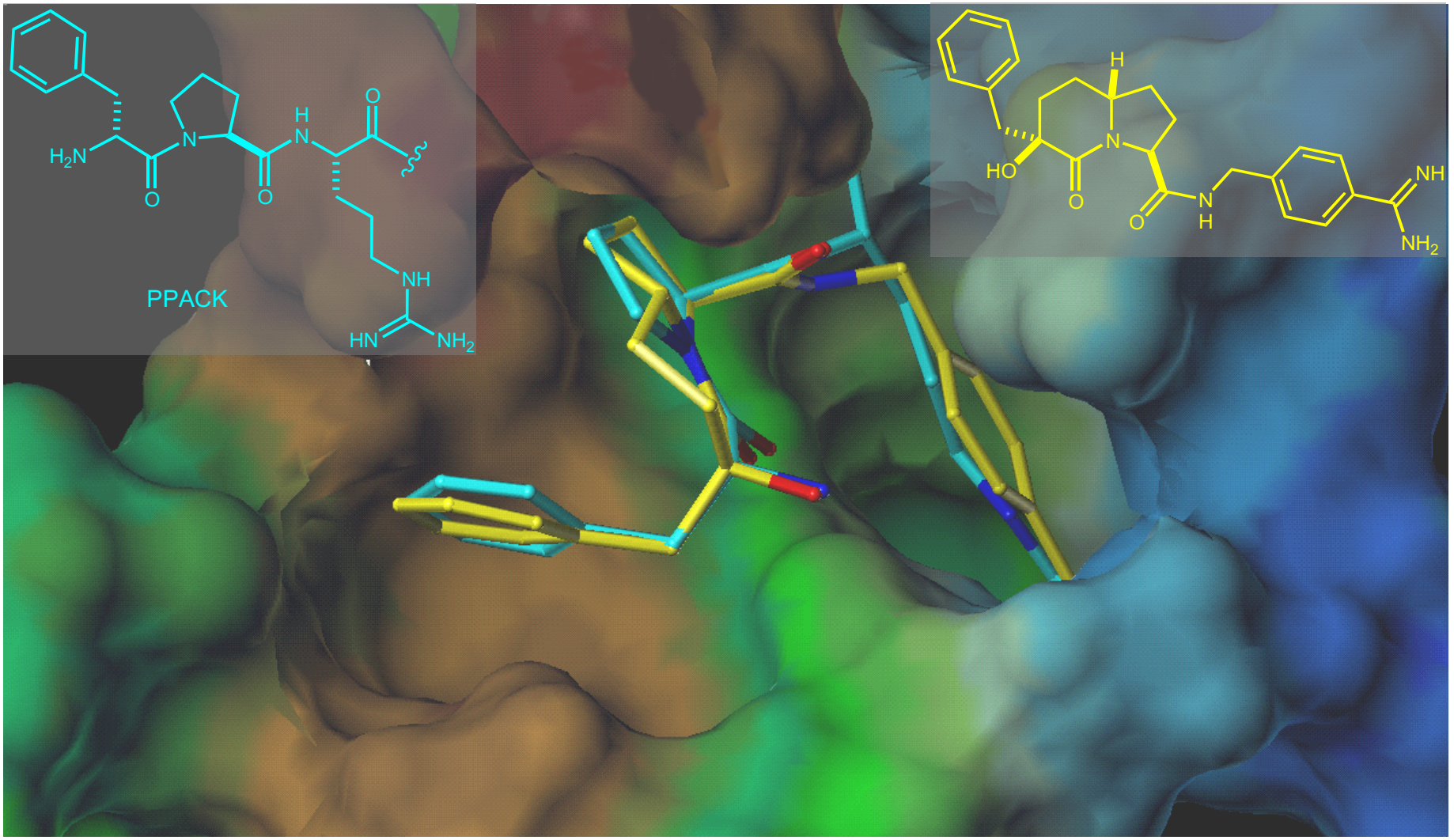
45 nM



GS-4071

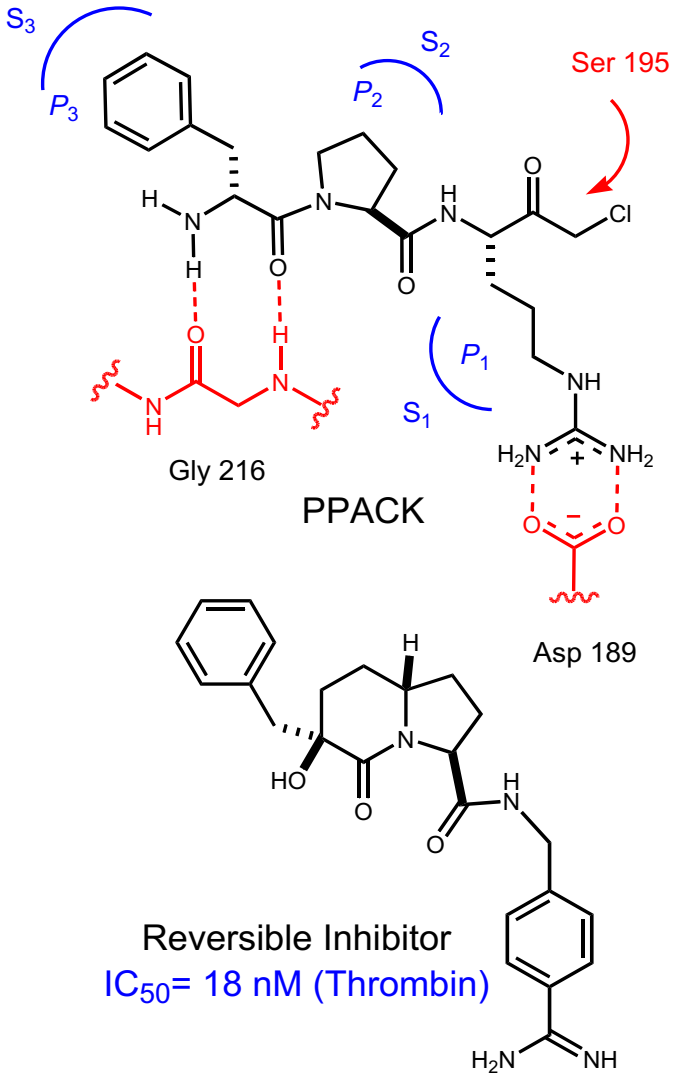
Hanessian, S.; Wang, J.; Montgomery, D.; Stoll, V.; Stewart, K. D.; Kati, W.; Maring, C.; Kemp, D.; Hutchins, C.; Laver, W. G. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3425

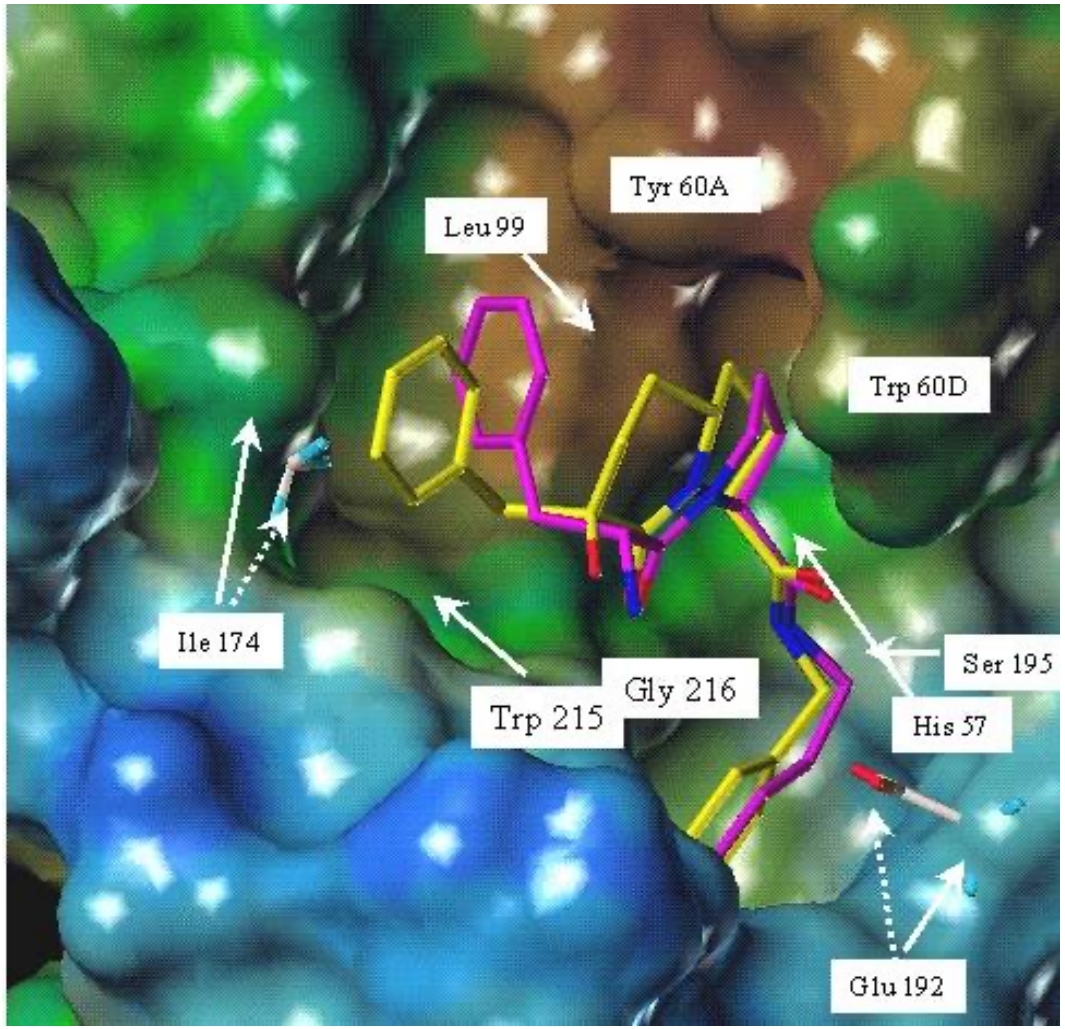
D-Phe-Pro-Arg and a “Designed” Constrained Mimetic



Hanessian, S.; Balaux, E.; Musil, D.; Olsson, L-L.; Nilsson, I. *Bioorg. Med. Chem. Lett.* **2000**, *10,* 243.

X-Ray Co-Crystal of Thrombin with Prototypical Inhibitor

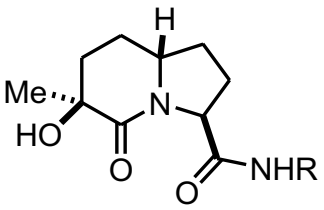




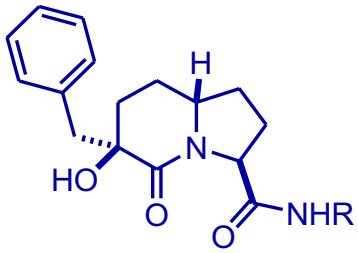
PPACK in pink, Inhibitor in yellow

Hanessian, S.; Balaux, E.; Musil, D.; Olsson, L-L.; Nilsson, I.
Bioorg. Med. Chem. Lett. **2000**, *10,* 243.

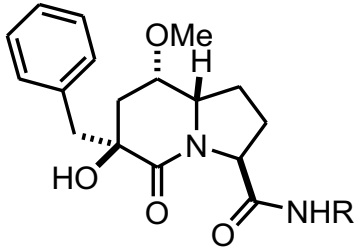
Biological Results



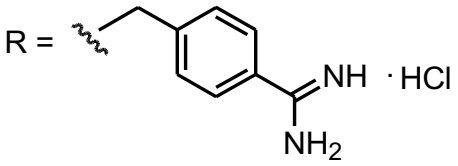
thrombin: 270 nM
factor VII: >10 000 nM

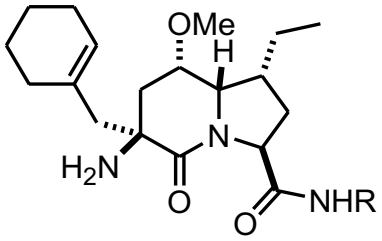


thrombin: 18 nM
factor VII: 1 100 nM

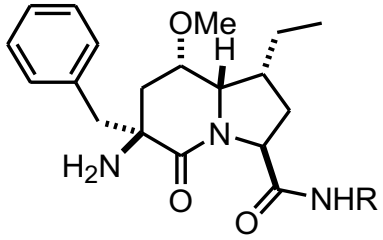


thrombin: 110 nM
factor VII: 520 nM

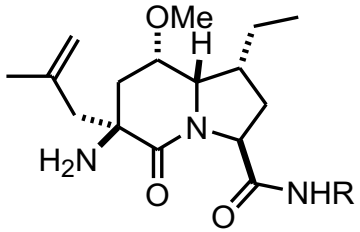




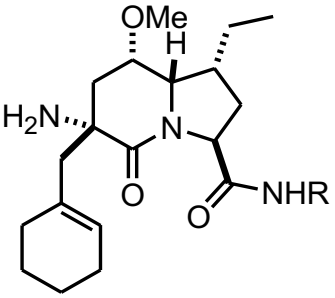
thrombin: 170 nM
factor VII: 4 600 nM



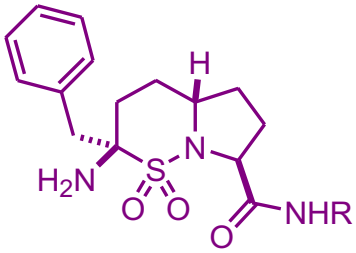
thrombin: 210 nM
factor VII: 420 nM



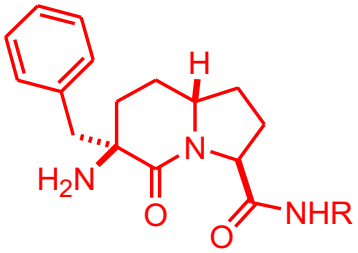
thrombin: 380 nM
factor VII: 3 600 nM



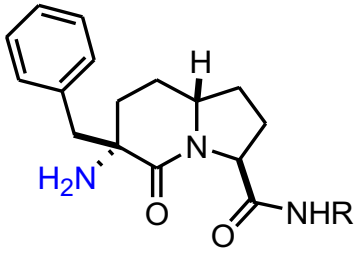
thrombin: 7 200 nM
factor VII: 109 000 nM



thrombin: 494 nM



thrombin: 4.7 nM



thrombin: 2 550 nM

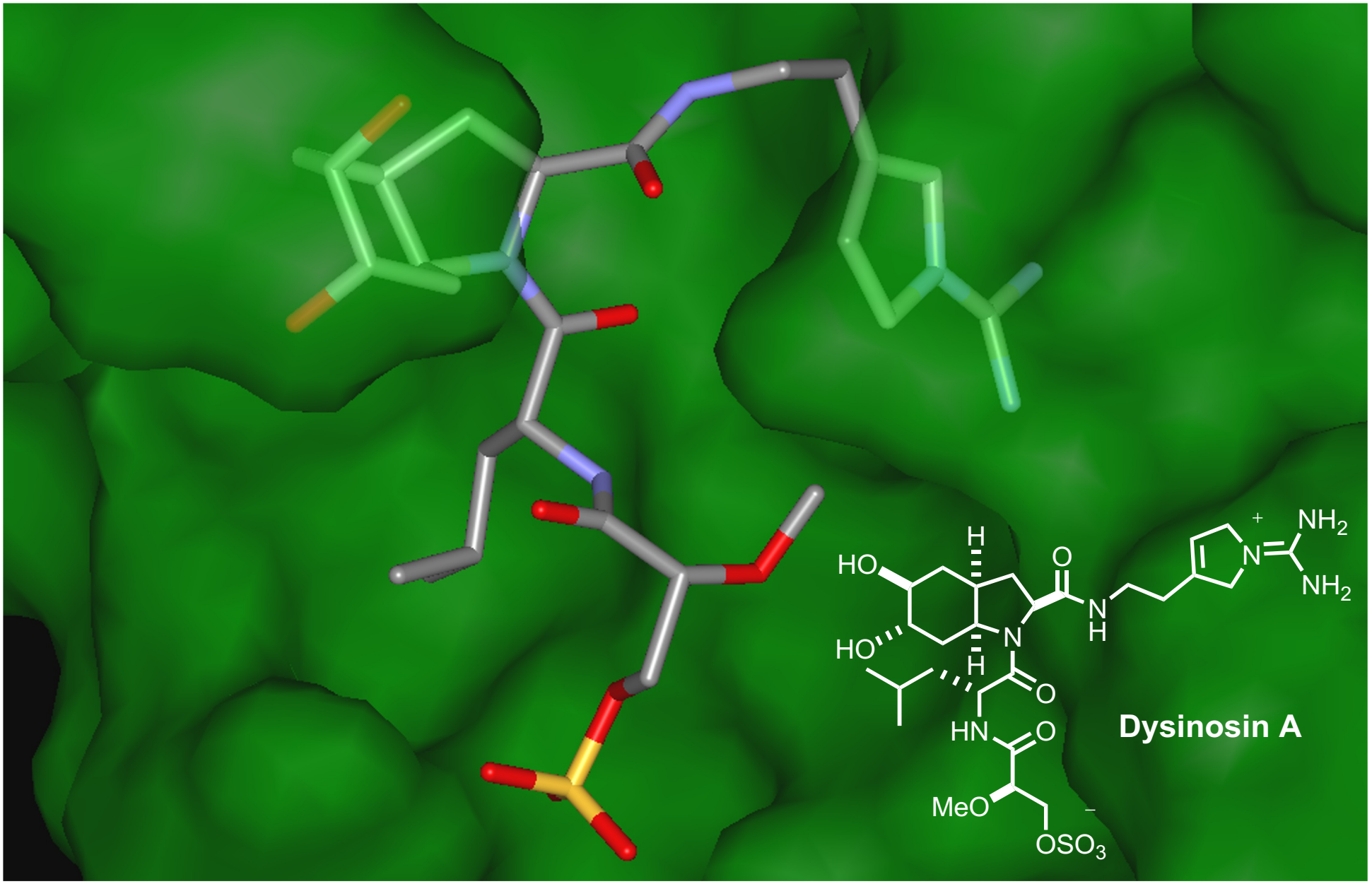
Hanessian, S.; Balaux, E.; Musil, D.; Olsson, L-L.; Nilsson, I. *Bioorg. Med. Chem. Lett.* **2000**, *10,* 243
Hanessian, S.; Therrien, E.; Granberg, K.; Nilsson, I. *Bioorg. Med. Chem. Lett.* **2002** *12*, 2907.

Dysinosin A – A Novel Aeruginosin

- New marine natural product
- Isolated from a new genus and species of sponge of the family *Dysidea sp*, Lizard Island, North Queensland, Australia
- Potent inhibitor of blood coagulation cascade Factor VIIa
- Inhibitor of serine protease thrombin
- Structure determined by ^{1}H, ^{13}C NMR
- Absolute stereochemistry deduced from an X-ray co-crystal structure with thrombin

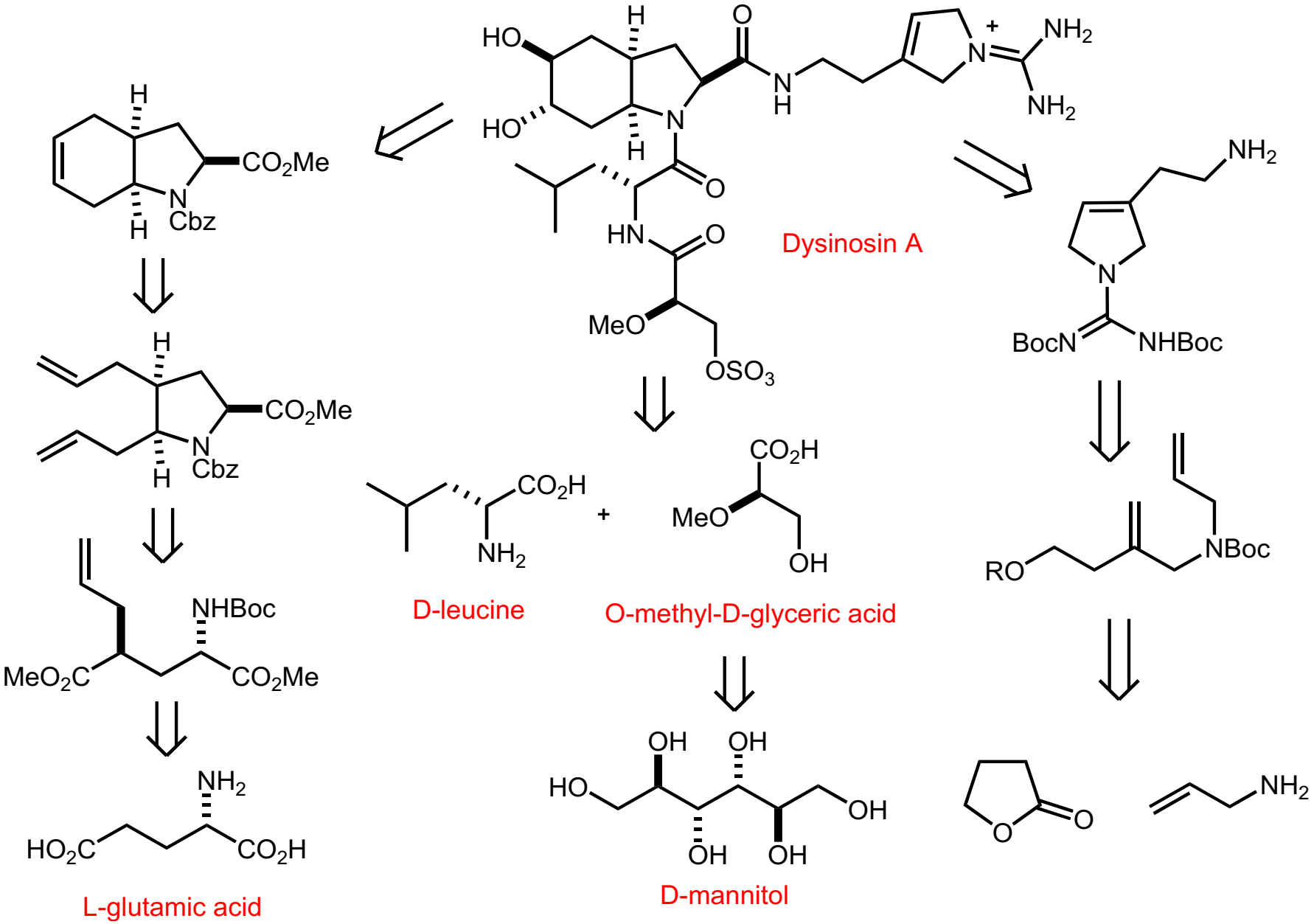
Carroll, A. R.; Pierens, G.; Fechner, G.; Almeida Leone, P.; Ngo, A.; Simpson, M.; Hooper, J. A.; Bostrom, S.-L.; Musil, D.; Quinn, R. J.; *J. Am. Chem. Soc.* **2002**,*124*, 13340. AstraZeneca R&D Griffith University, Brisbane, Australia.

X-ray Co-crystal Structure of Dysinosin A with Thrombin



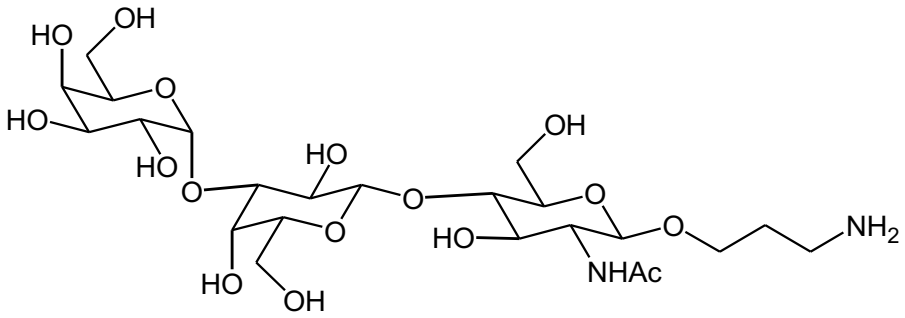
Carroll, A.-R.; Quinn, R. *et al. J. Am. Chem. Soc.* **2002**,*124*, 13340

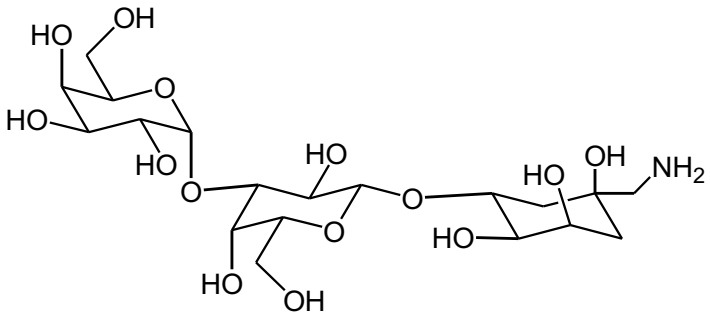
Disconnections of Dysinosin A

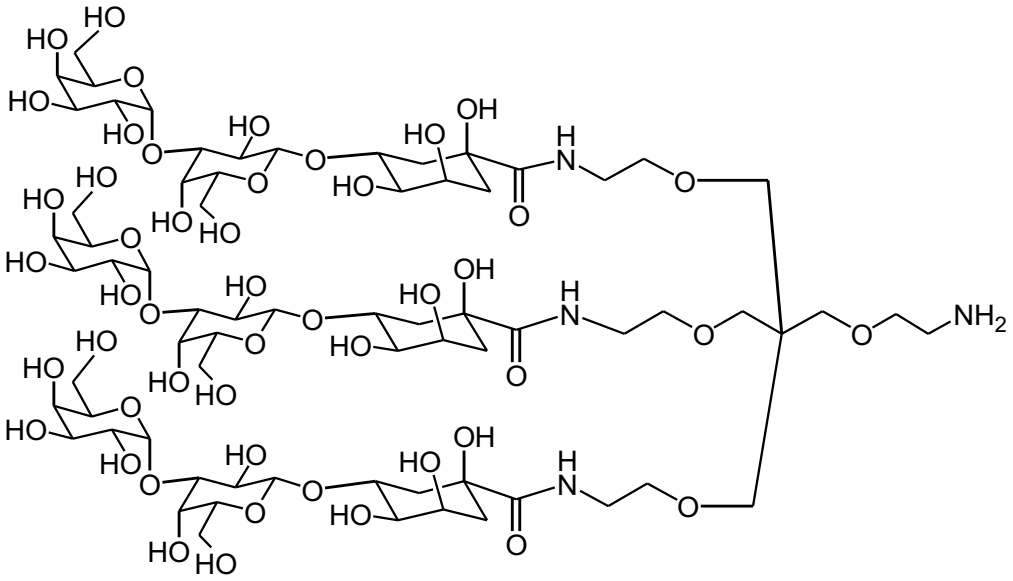


Hanessian, S.; Margarita, R.; Hall, A.; Johnstone, S.; Tremblay, M.; Parlanti, L. *J. Am. Chem. Soc.* **2002**, *124*, 13342

Synthesis of Gal Determinant Epitopes, Their Glycomimetic Variants, and Trimeric Clusters – Relevance to Tumor Associated Antigens and to Discordant Xenografts

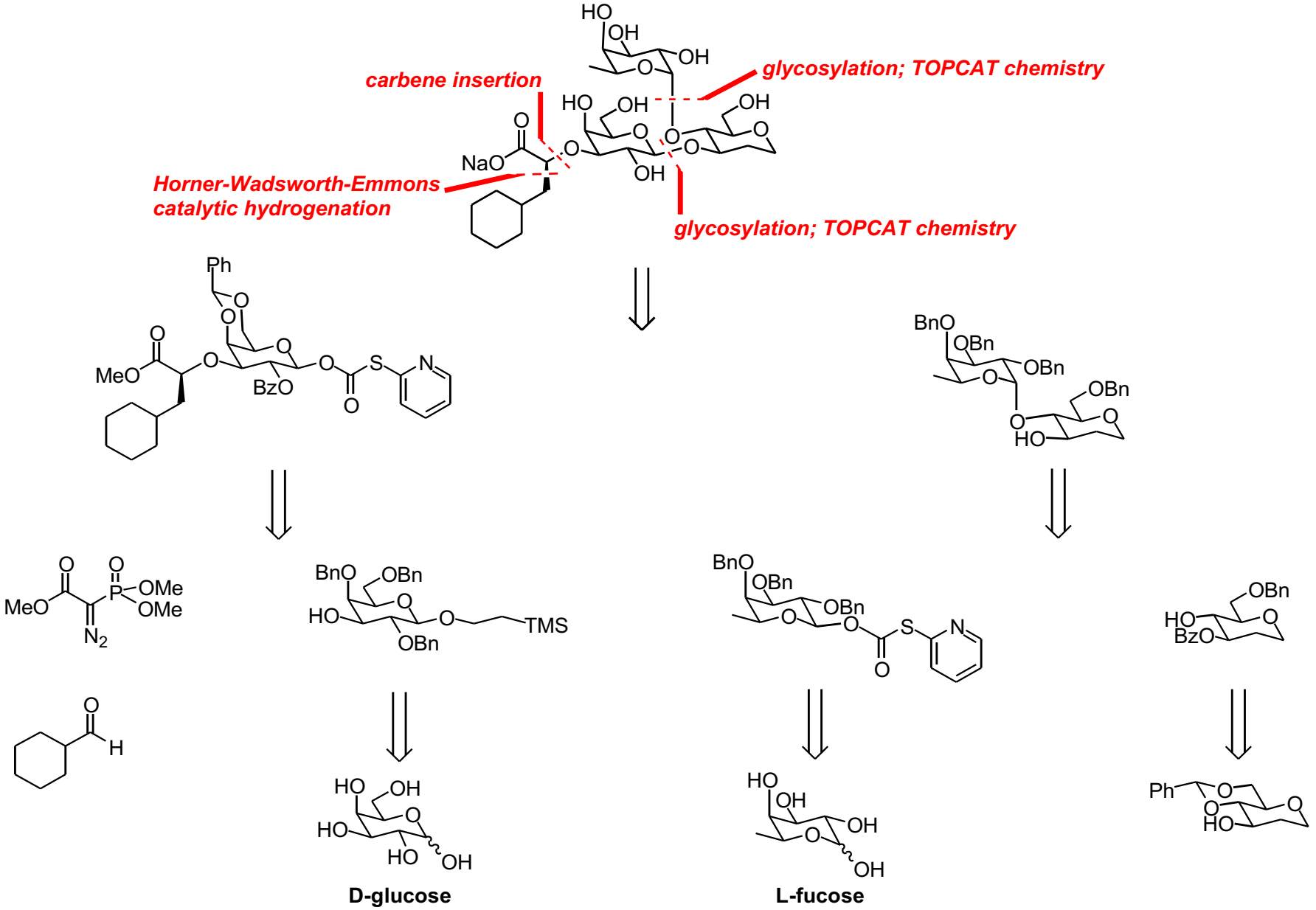






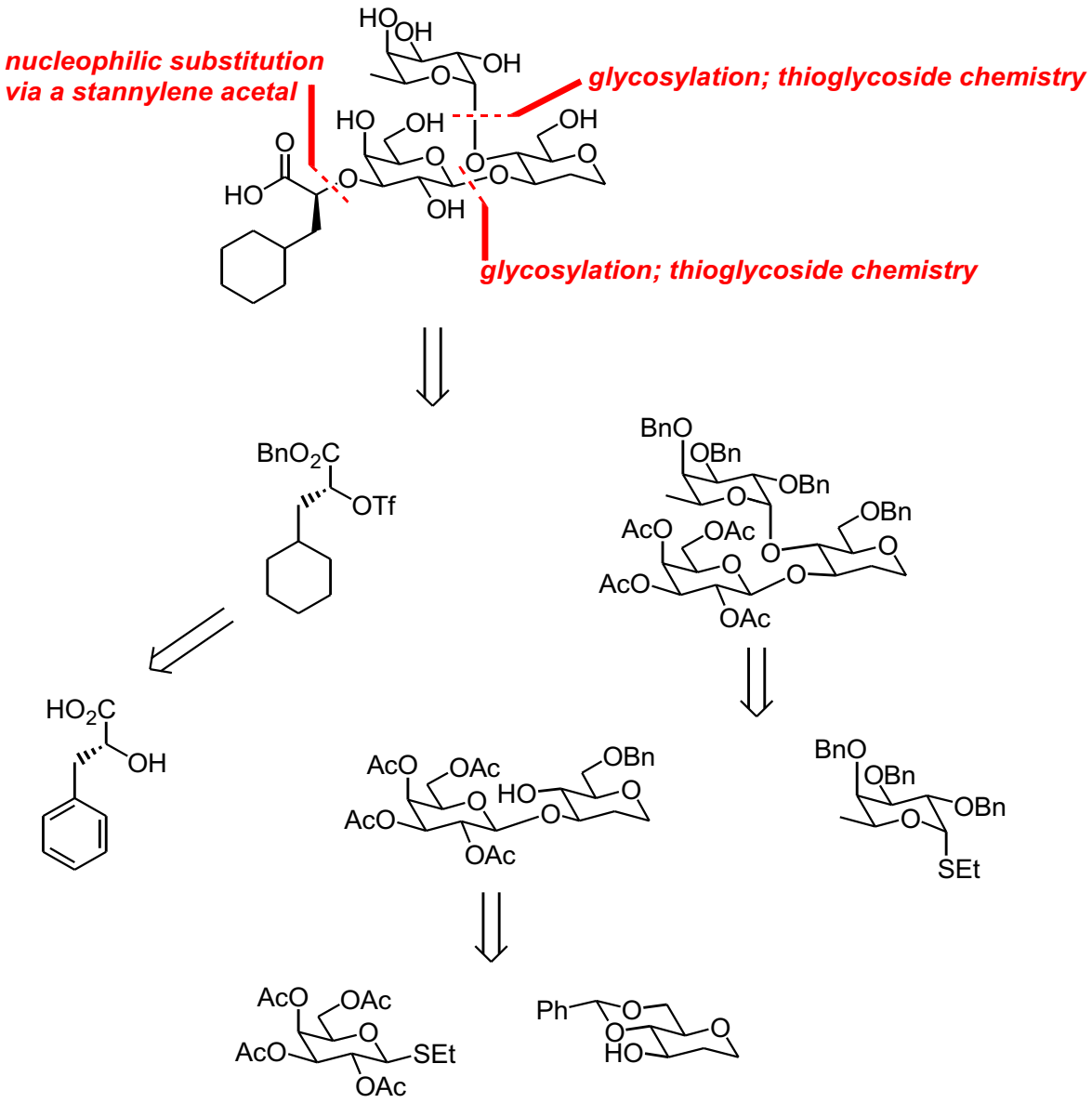
Hanessian, S.; Huynh, H. K.; Reddy, G. V.; Duthaler, R. O.; Katopodis, A.; Streiff, M. B.; Kinzy, W.; Oehrlein, R. *Tetrahedron* **2001**, *57*, 3281

Disconnections



Hanessian, S.; Mascitti, V.; Rogel, O. *J. Org. Chem.* **2002**, *67*, 3346.

Novartis Approach



Thoma, G.; Kinzy, W.; Bruns, C.; Patton, J. T.; Magnani, J. L.; Bänteli, R. *J. Med. Chem.* **1999**, *42*, 4909

« Therapeutics is the pouring of a drug of which one knows nothing into a patient of whom one knows less »

Voltaire (1694-1778)