

# IASOC XIV (2010)

## *" Molecules, Medicine, and Us"*

**Speakers:**

**Carl Decicco (BMS, USA)**
**Terry Rosen (Amgen, USA)**
**Torsten Hoffmann (Roche, Basel)**

***Moderator and Chair*** : Stephen Hanessian
(U of Montreal and U of California, Irvine)

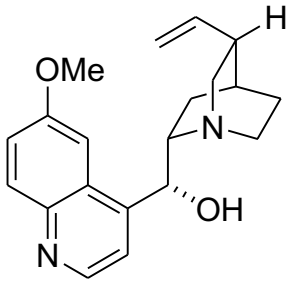
**Ischia Porto**
**Monday, September 27, Ischia**

www.newinspirations.com/(Ischia)Webb_tile.jpg

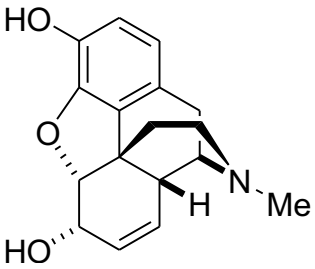
# Medicinal Chemistry Through the Ages

## From Quinine and Morphine (still in use)

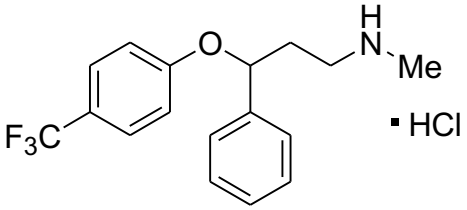
## To Prozac and Taxol



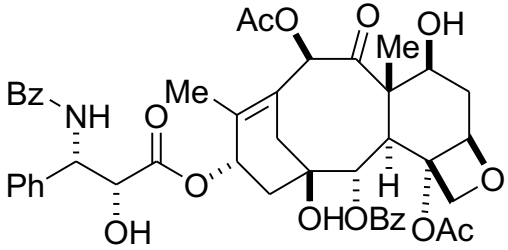

Quinine




Morphine



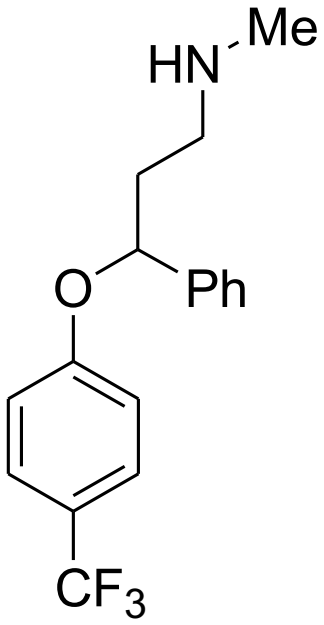

Prozac




Taxol



Vincent Van Gogh




Prozac

# DRUG DISCOVERY

## A SYNTHETIC CHEMIST'S PERSPECTIVE AND INVOLVEMENT:



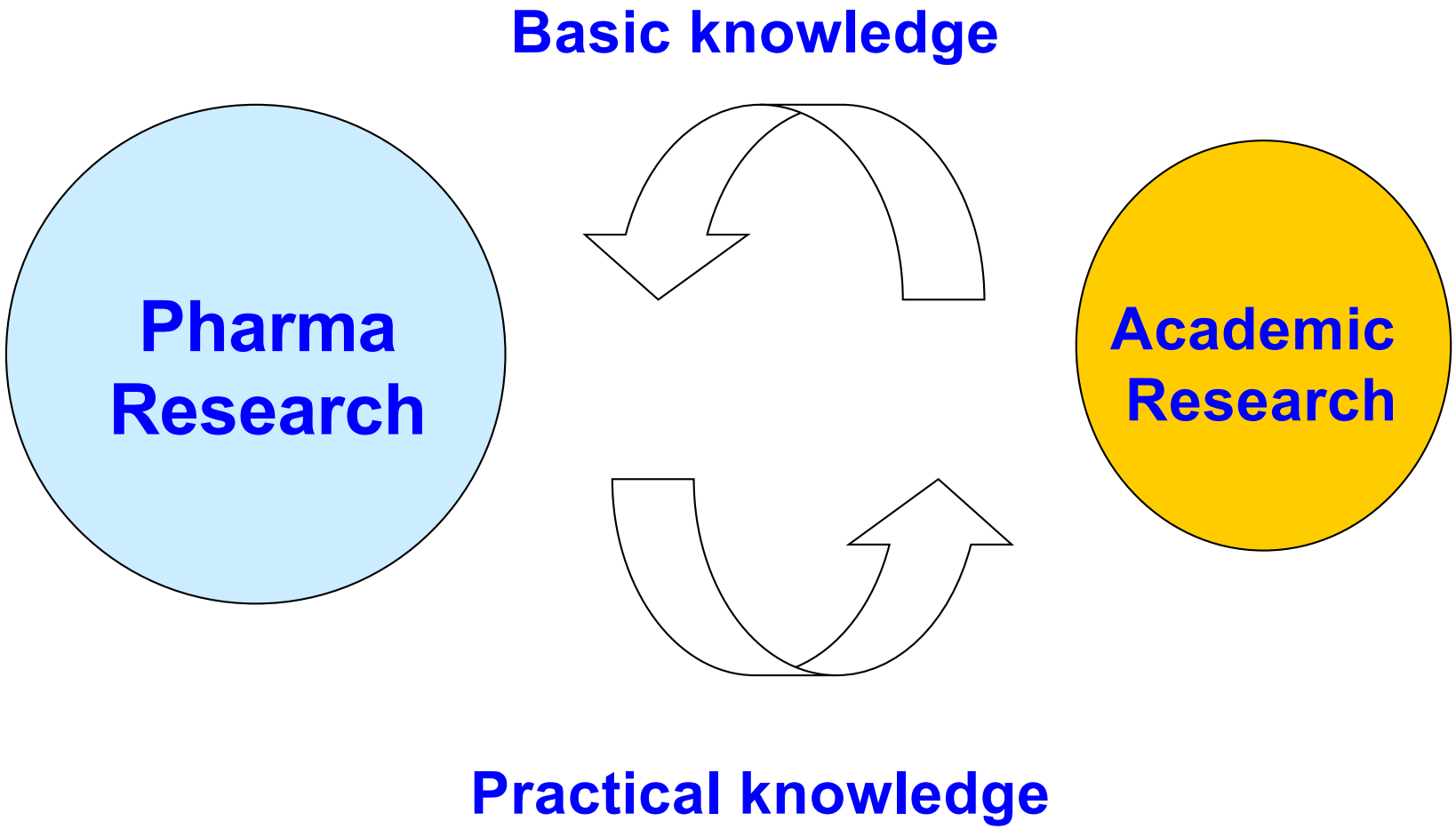

TOOLS:

INSTRUMENTAL, COMPUTATION, PHYSICO-CHEMICAL, BIOTECHNOLOGY, GENOMICS, COMPOUND COLLECTIONS AND LIBRARIES

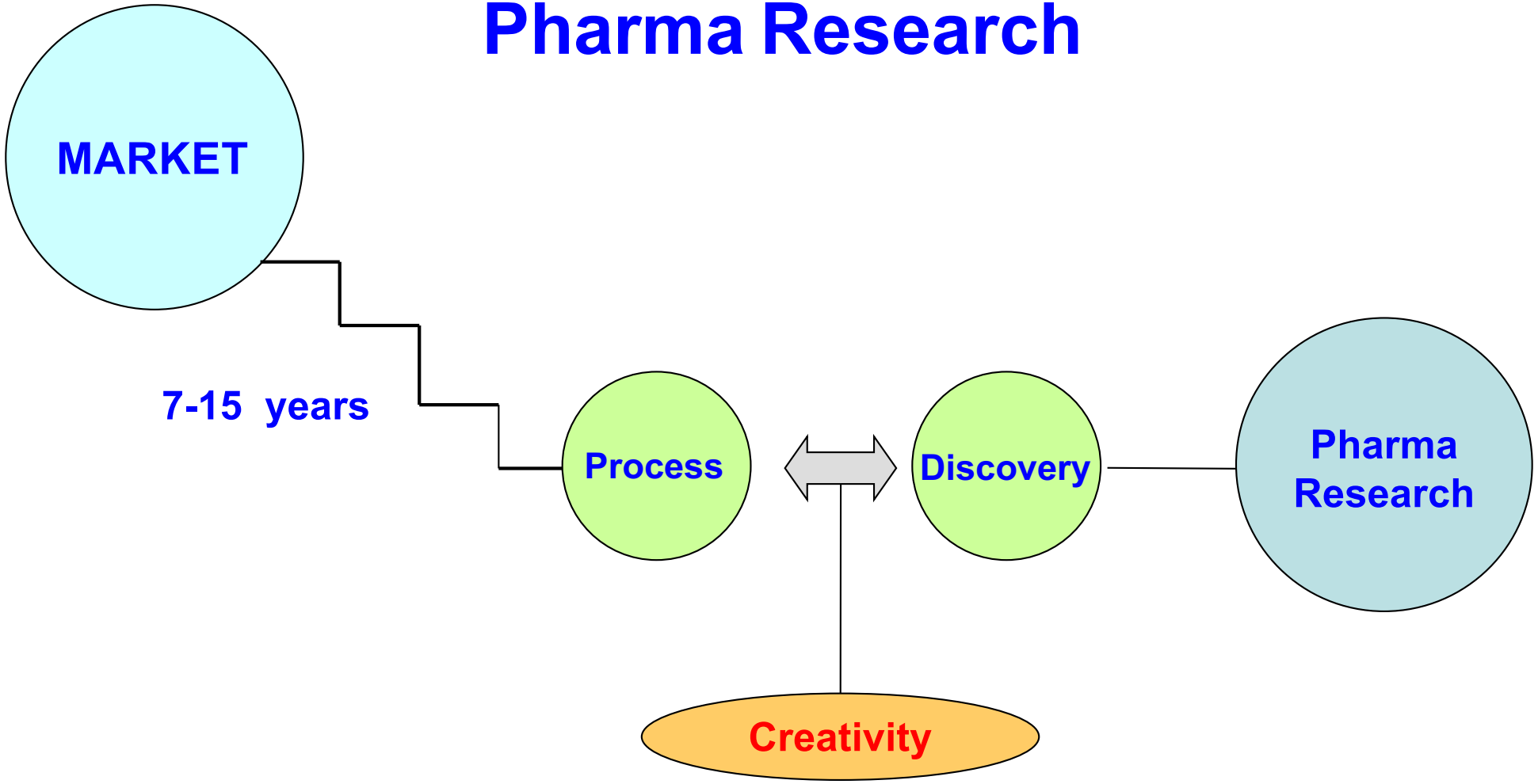
CHALLENGES:

- UNDERSTANDING INTERACTIONS AT THE MOLECULAR LEVEL (RECOGNITION, ETC
- CHEMICAL SOLUTIONS TO BIOLOGICAL PROBLEMS (DISEASE)
- BETTER DRUGS (QUALITY OF LIFE)

# Academic and Pharma Research



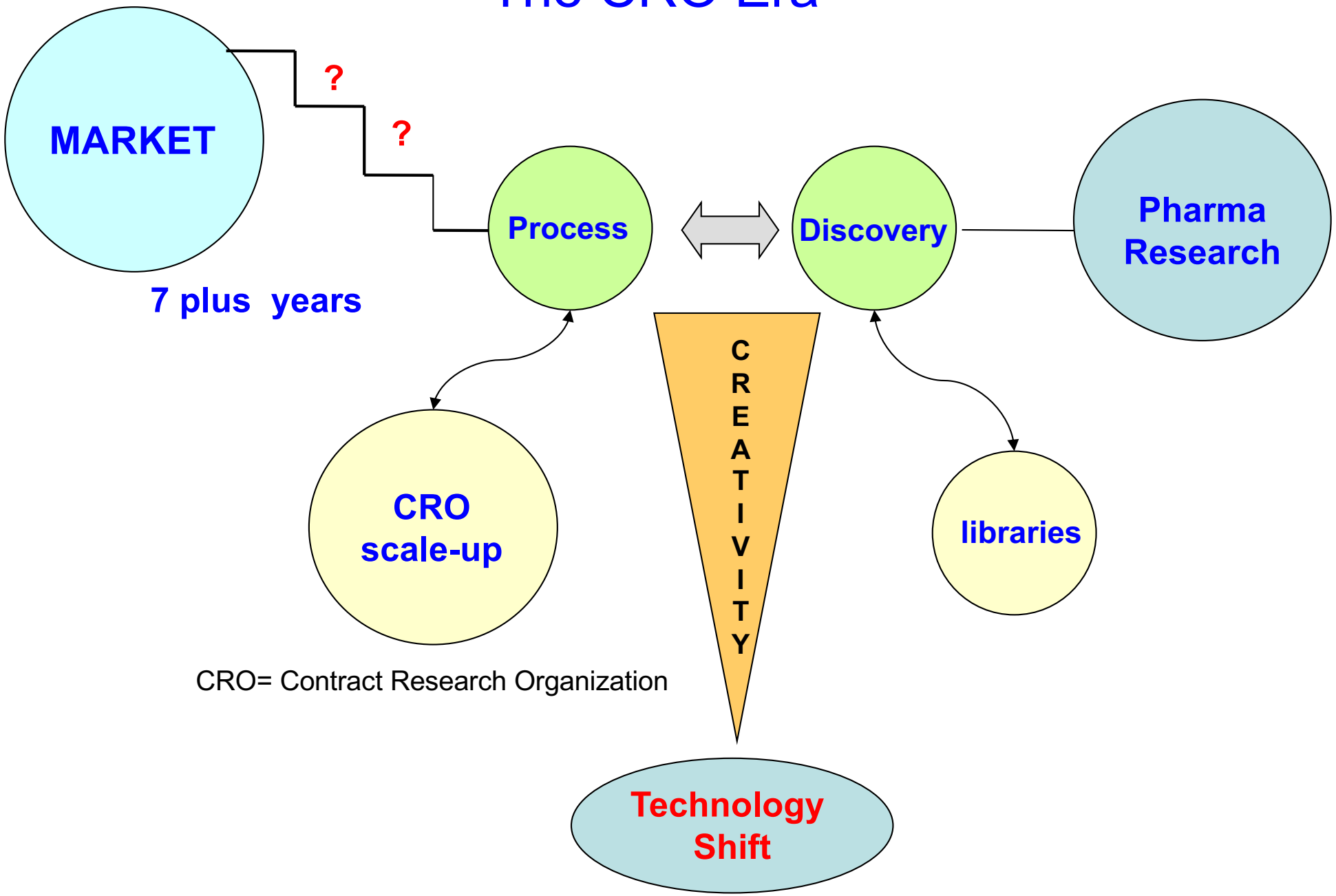
# Pharma Research




**Objectives:**

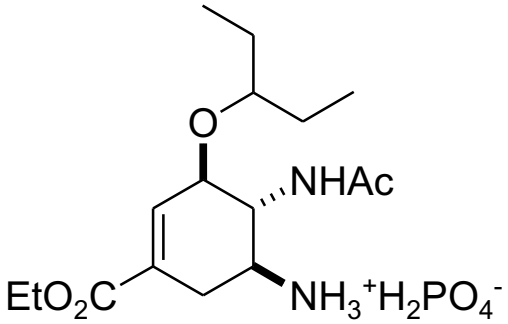
- Develop medicines for the well being of humankind
- Address unmet medical needs

# The CRO Era



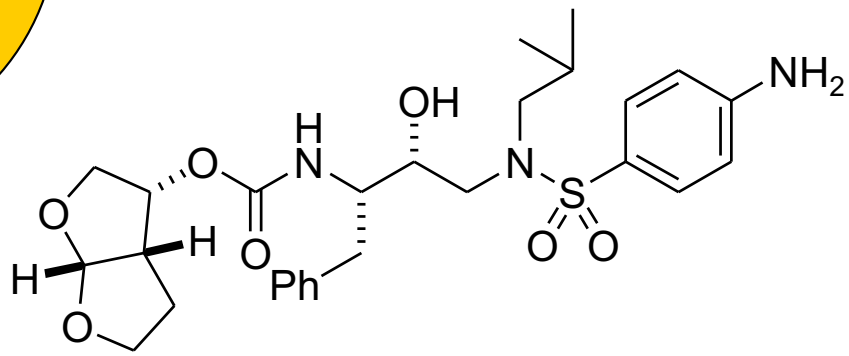

CRO= Contract Research Organization

# Academic Research




*Oseltamivir*
*(Tamiflu)*

***Corey***



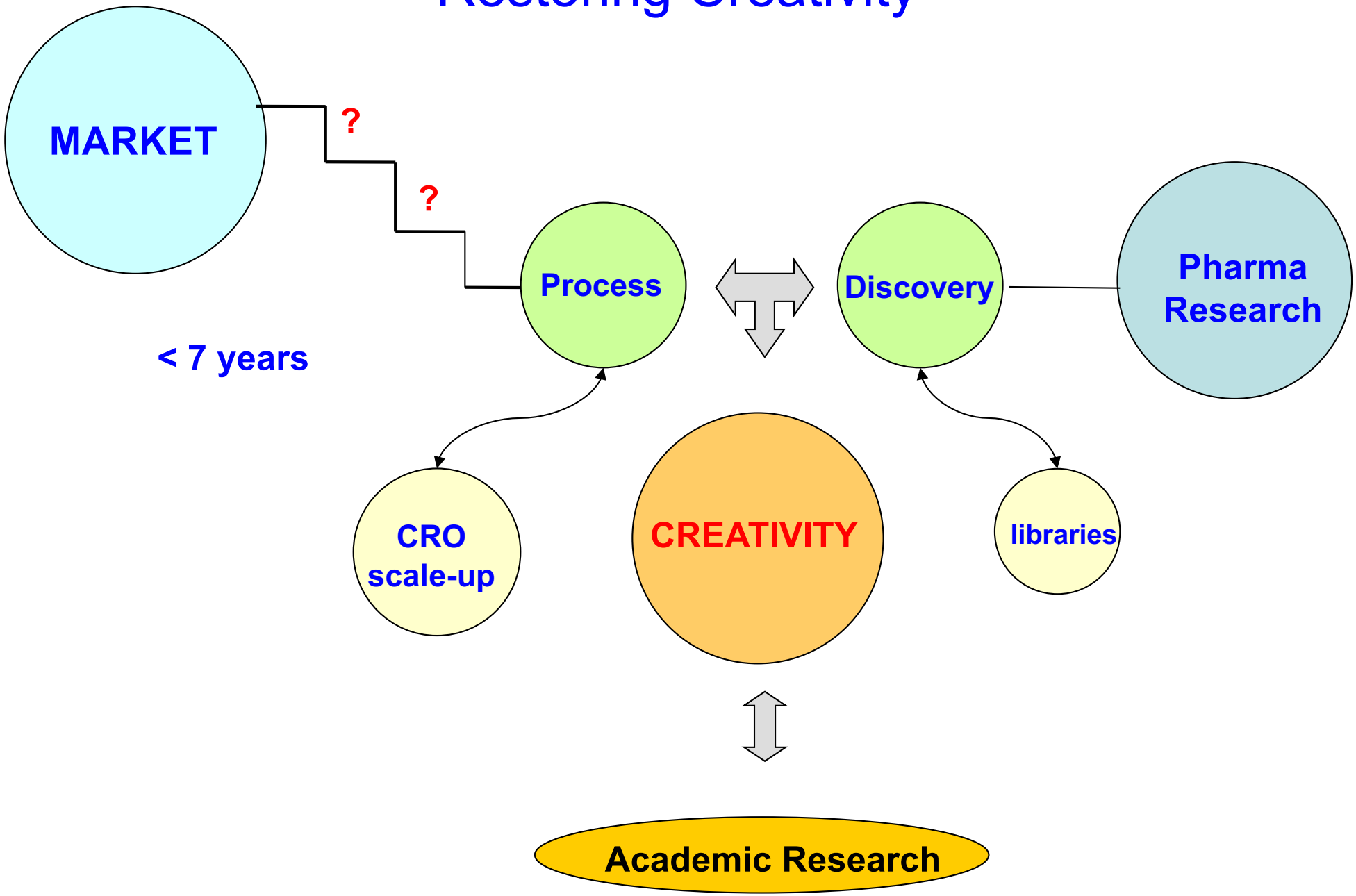

*Darunavir*
*(Presixta)*

***Ghosh***

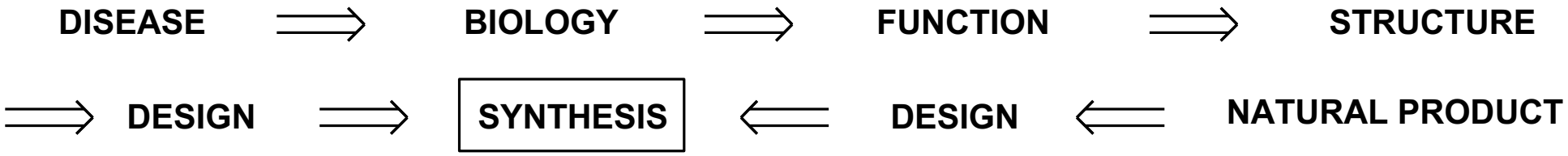
## Objectives:

- **Provide a forum to think, and to apply knowledge to address fundamental and practical problems in science**
- **Prepare young scientists for the rigors of research in industry and academia**

# Restoring Creativity



# UNIVERSITY-INDUSTRY PARTNERSHIPS




## UNIVERSITY:

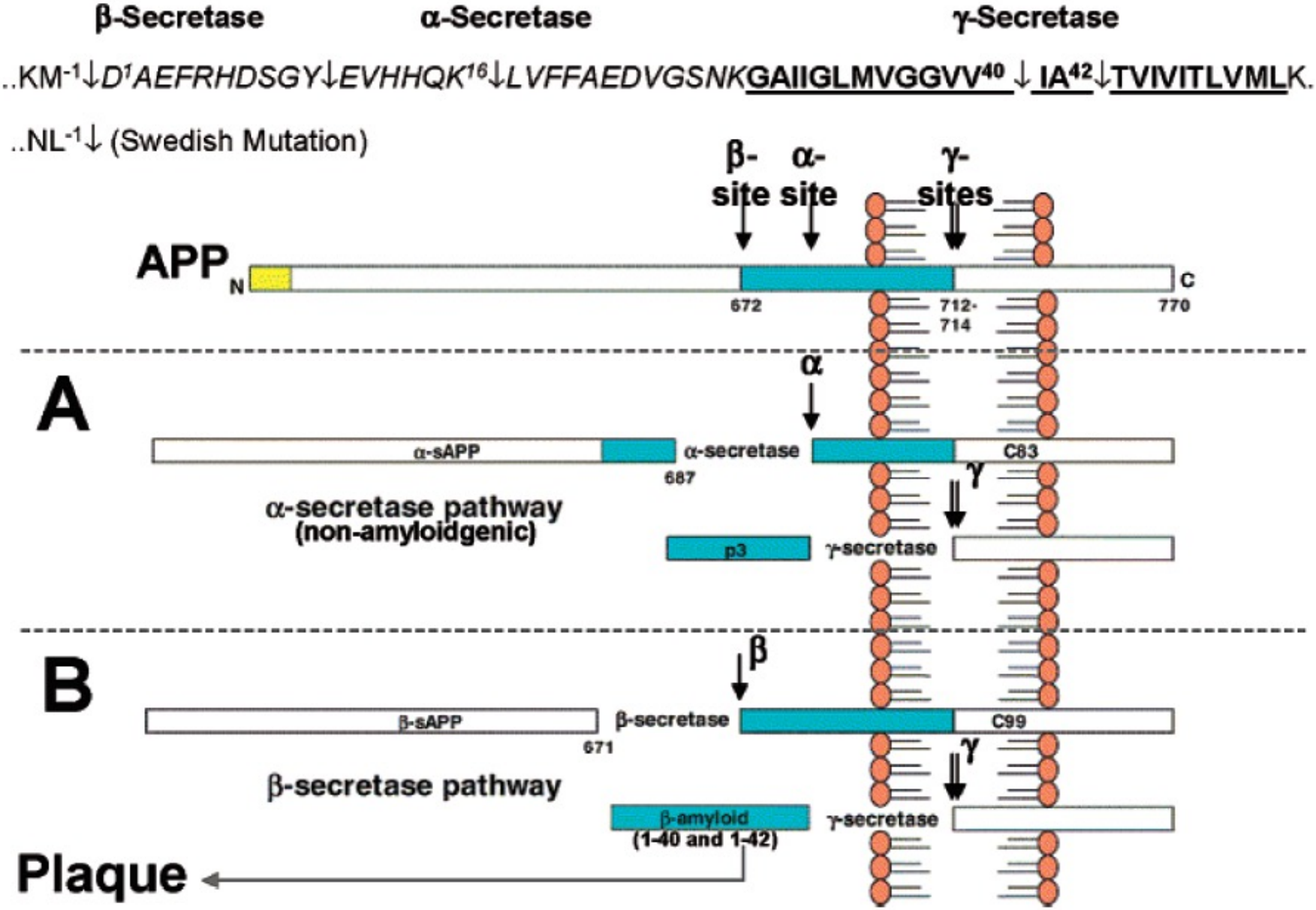
- Fundamental and "curiosity"-orientend research
- Focussed program
- Funding dictates time
- Industrial collaboration "essential"
- Publication priority

## INDUSTRY:

- Target-oriented research
- All inclusive program
- University collaboration "informative"
- Patenting priority
- *Shares and profits*

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

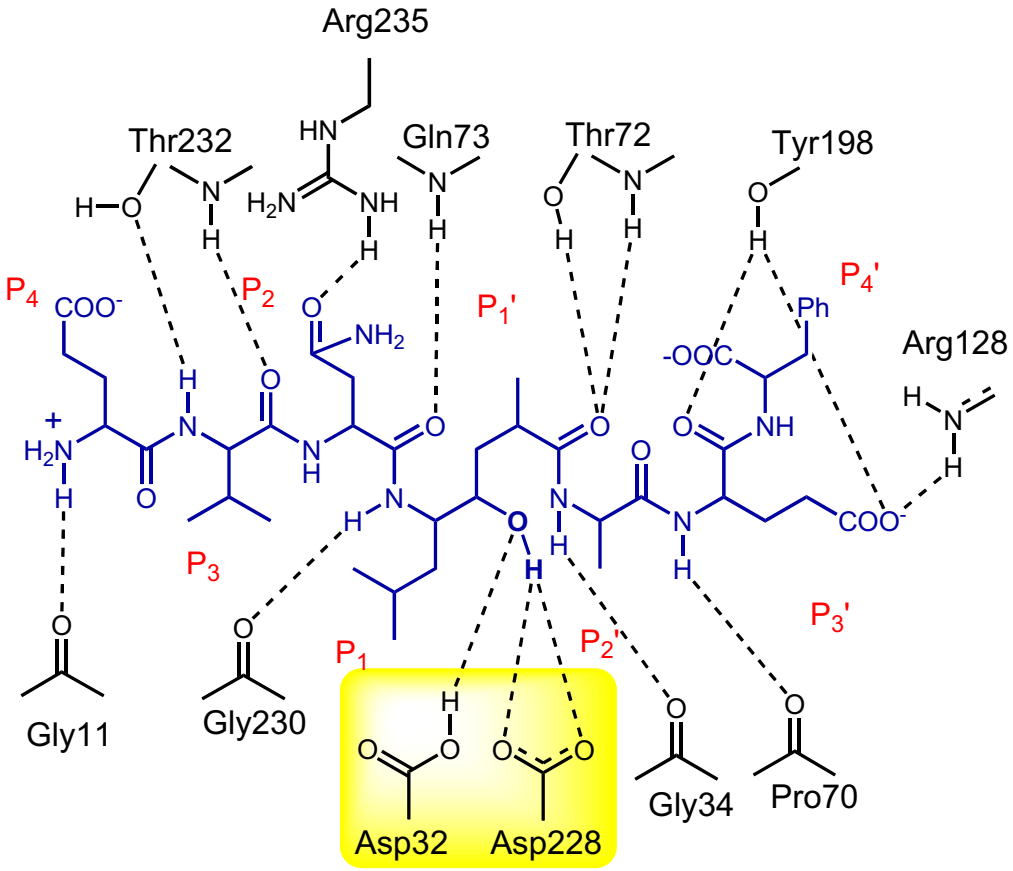
# Amyloid precursor protein processing by α, β and γ–Secretases

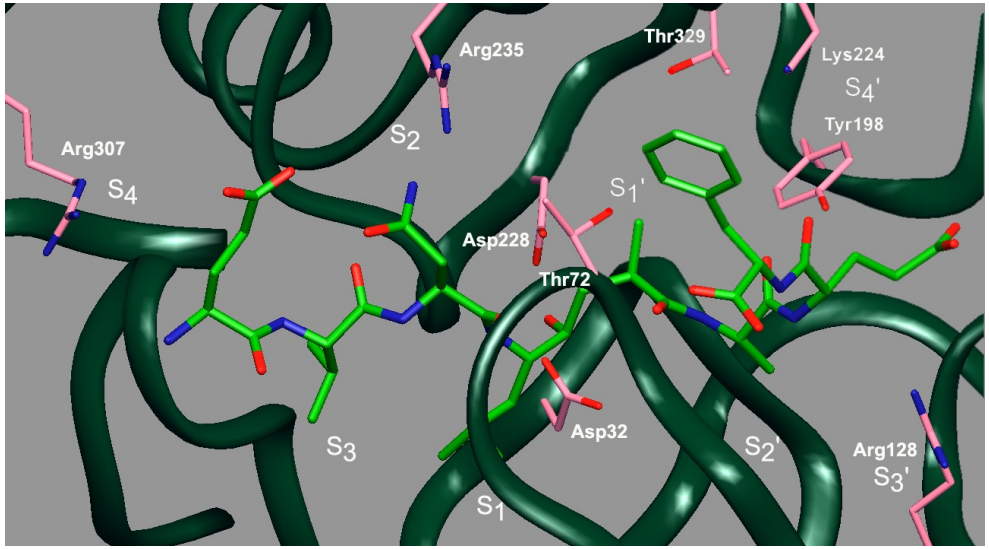


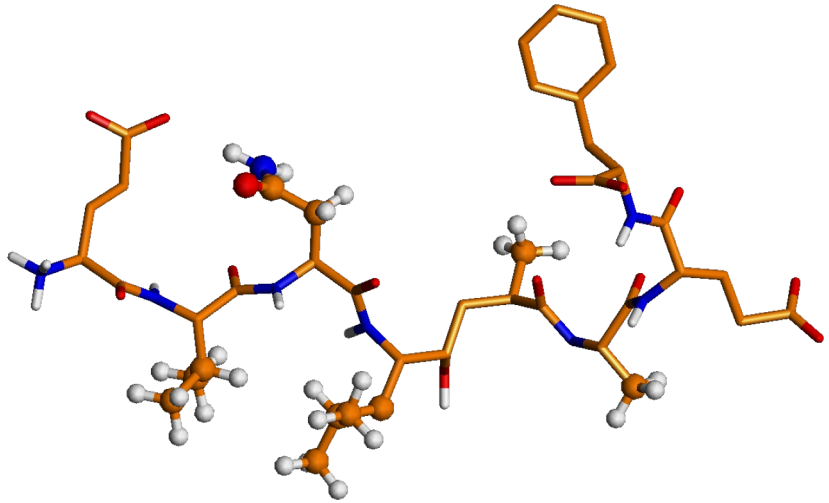

John, V.; *et al. J. Med. Chem.* **2003**, 46, 4625.

# OM99-2 / β-Secretase (BACE 1) Complex

*Novartis (Basel) Pharma collaboration*

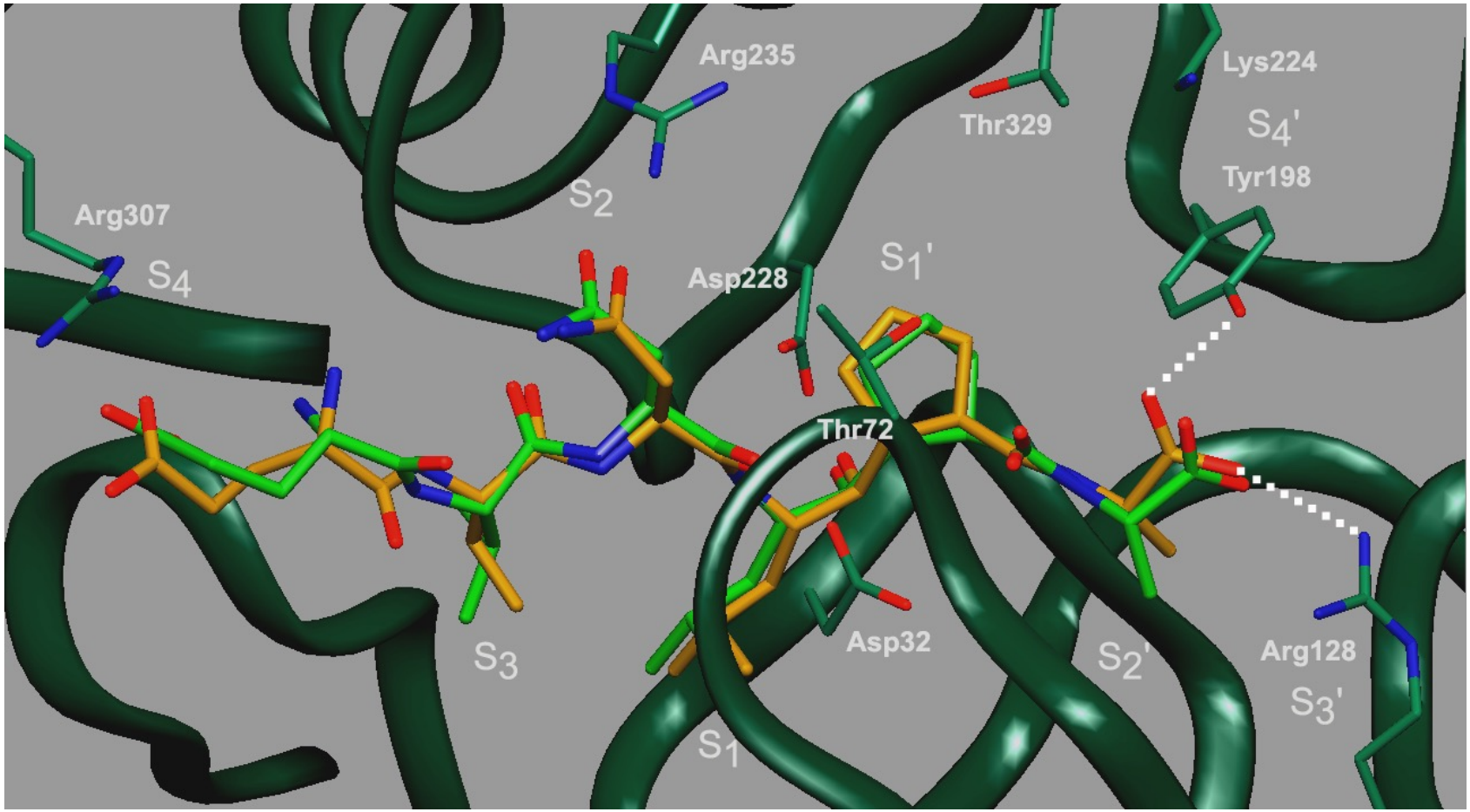


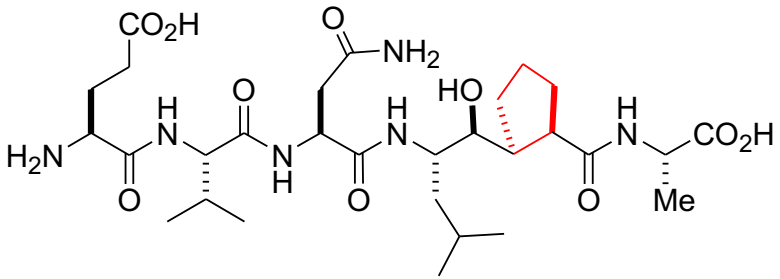



Tang, J.; *et al*. *Science* **2000**, *290*, 150

# X-Ray co-crystal structure with BACE1




Superposition of modeled (green) and crystallized (orange) conformations.

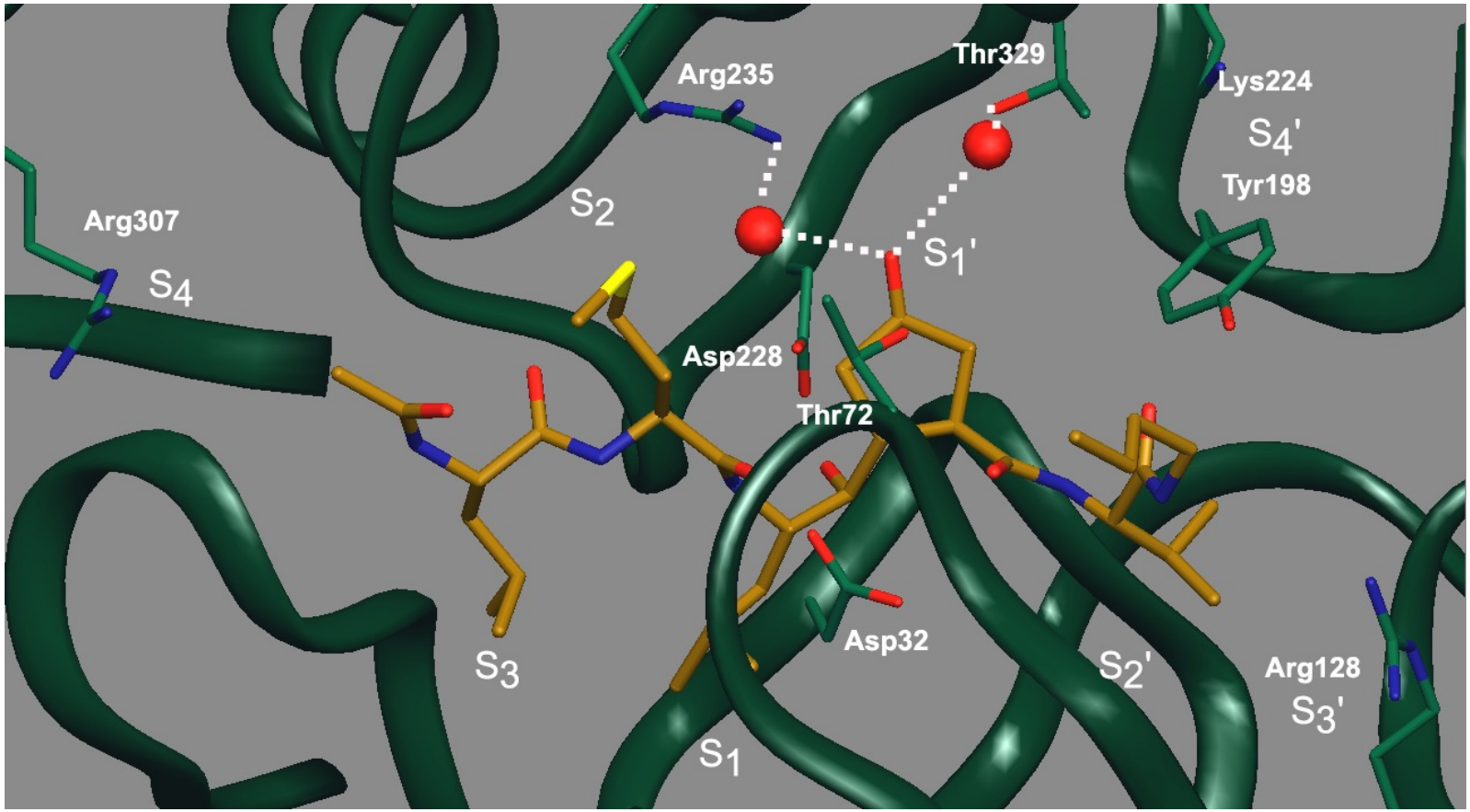



$IC_{50}$= 39nM (BACE 1)

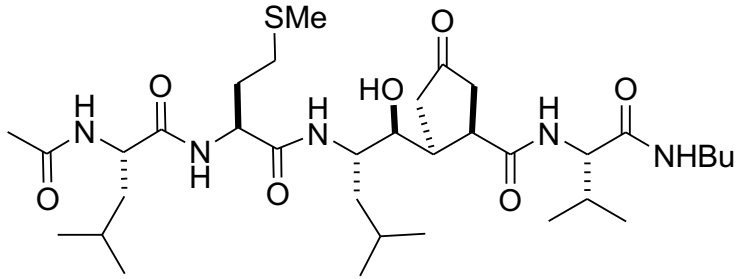
$IC_{50}$= 6030 (Cathepsin D)

*with* Yun, H; Hou, Y; Yang, G; Bayrakdarian, M; Therrien, E; Moitessier, N; and Novartis Basel groups *J.Med.Chem*. **2005**, *48*, 5175

# X-Ray co-crystal structure with BACE1



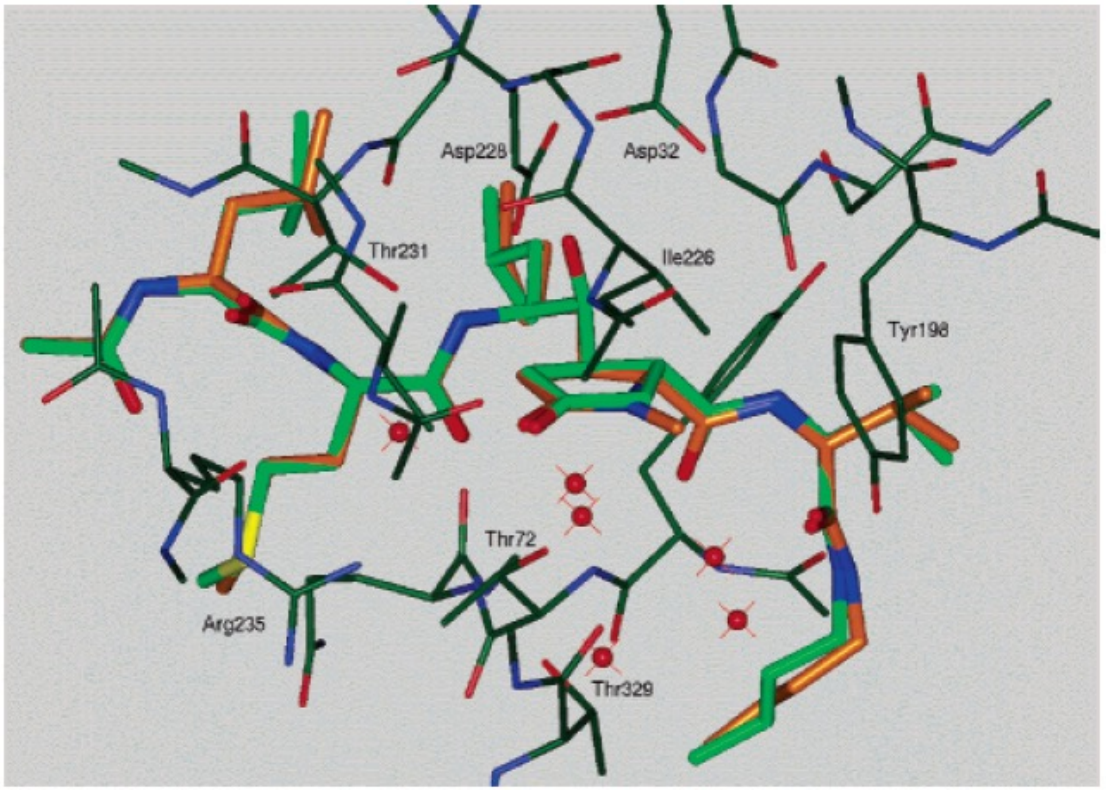

Co-crystal structure with BACE1. The carbonyl oxygen of the CP occupies the site of the central water molecule and forms a bifurcated H-bond with the other flanking water molecules (red spheres). Arg235 is displaced from its original position to accommodate the H-bonding with one water molecule.

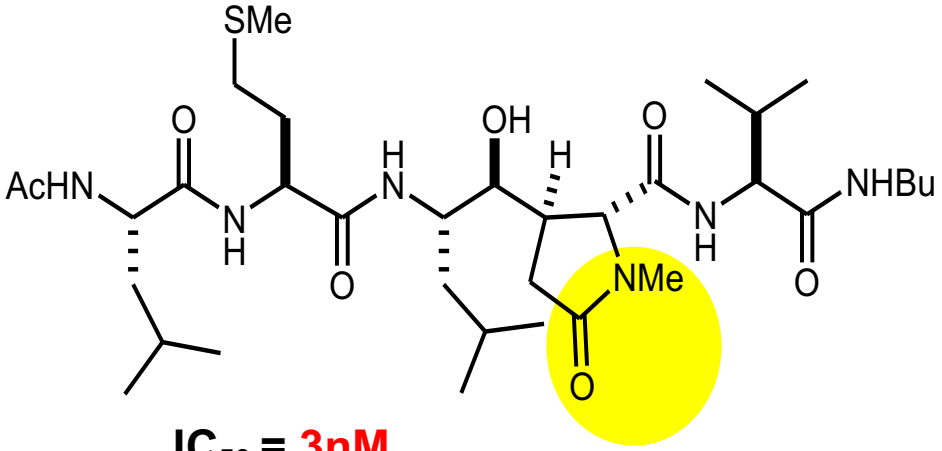



**$IC_{50}$ = 20nM**

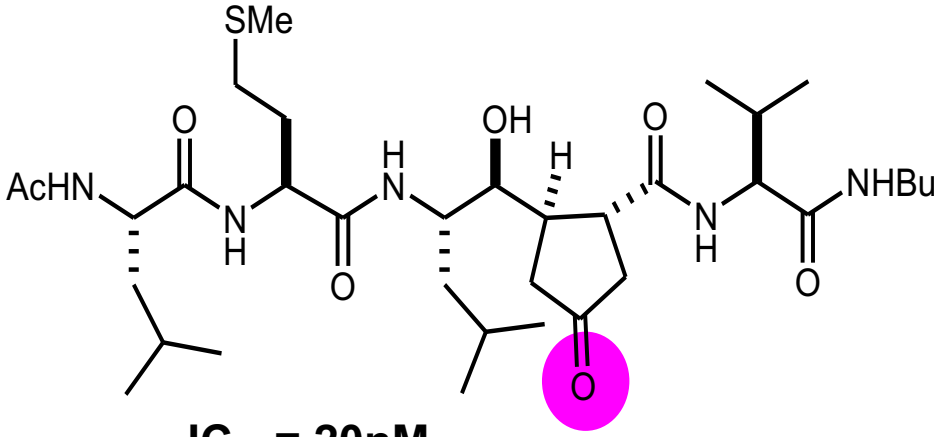
*with* Yun, H.; Hou, Y.; Tintelnot-Blomley, M. *J. Org. Chem*. **2005**, *70*, 6746

# Structure-based design: ketone to lactam



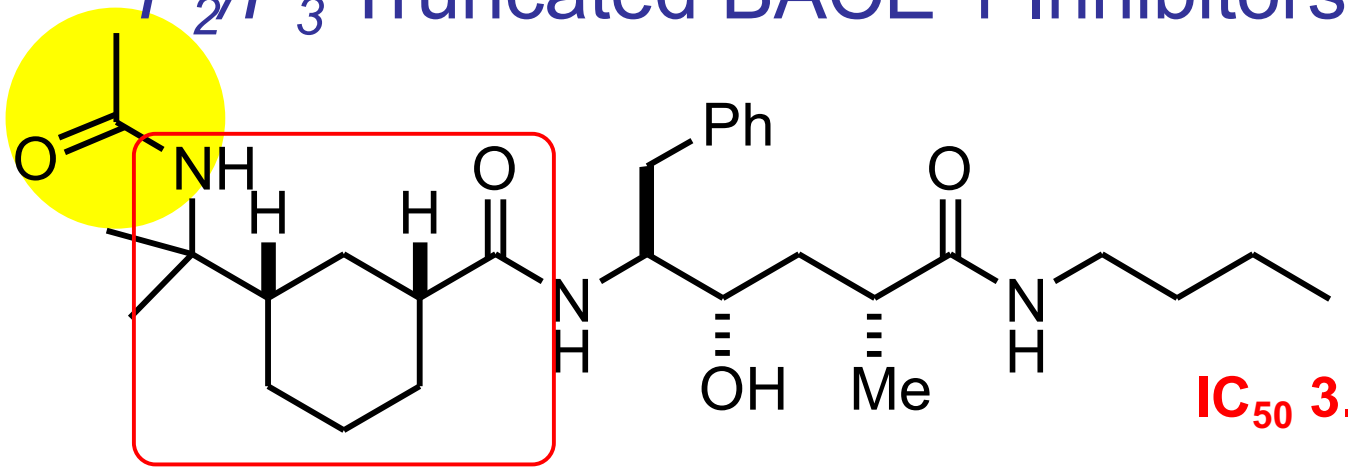

**$IC_{50}$ = 3nM**




**$IC_{50}$ = 20nM**

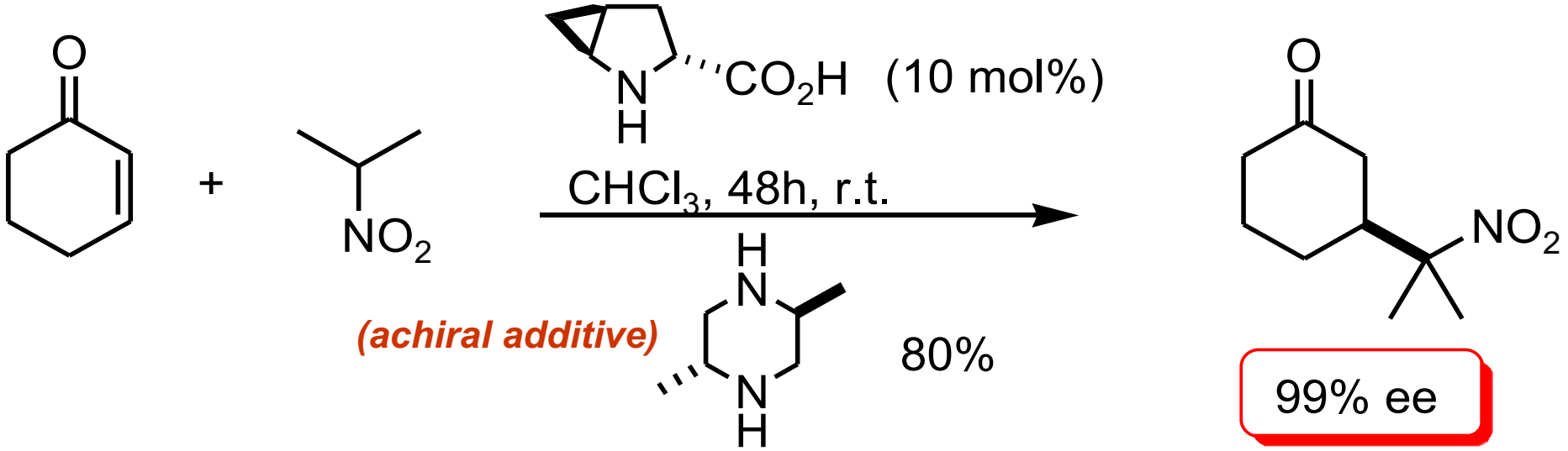
*with* Yun, H.; Hou, Y.; Tintelnot-Blomley, M. *J. Org. Chem*. **2005**, *70*, 6746

# $P_2/P_3$ Truncated BACE 1 Inhibitors




$IC_{50}$ 3.74 μM

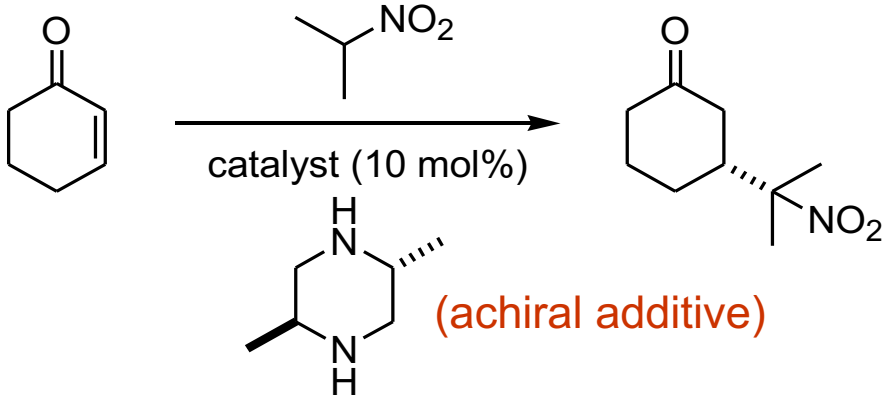
***X-Ray co-crystal with BACE1 shows wrong orientation of amide***



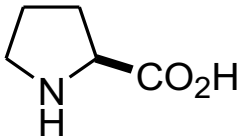
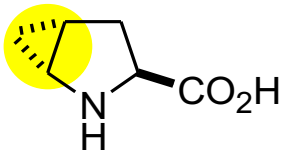
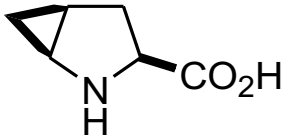
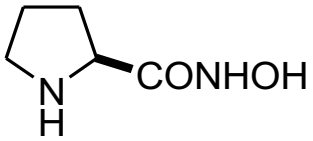
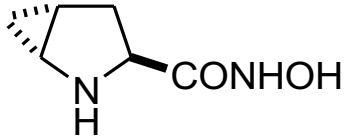

*with* Maji, D.K.; Govindan, S.; Matera, R.; Tintlenot-Bromley, M. *J.Org.Chem.* **2010**, *75, 2861;*
Shao, Z.; Betschart, C.; Rondeau, J-M.; Neumann, U.; Tintelnot-Bromley, M. *Bioorg. Med. Chem. Lett*. **2010,** *20,* 1924;

*with* Shao, Z.; Warrier, J. S. *Org. Lett*. **2006**, *8*, 4787; Pham, V. *Org.Lett*. **2000**, *2*, 2975

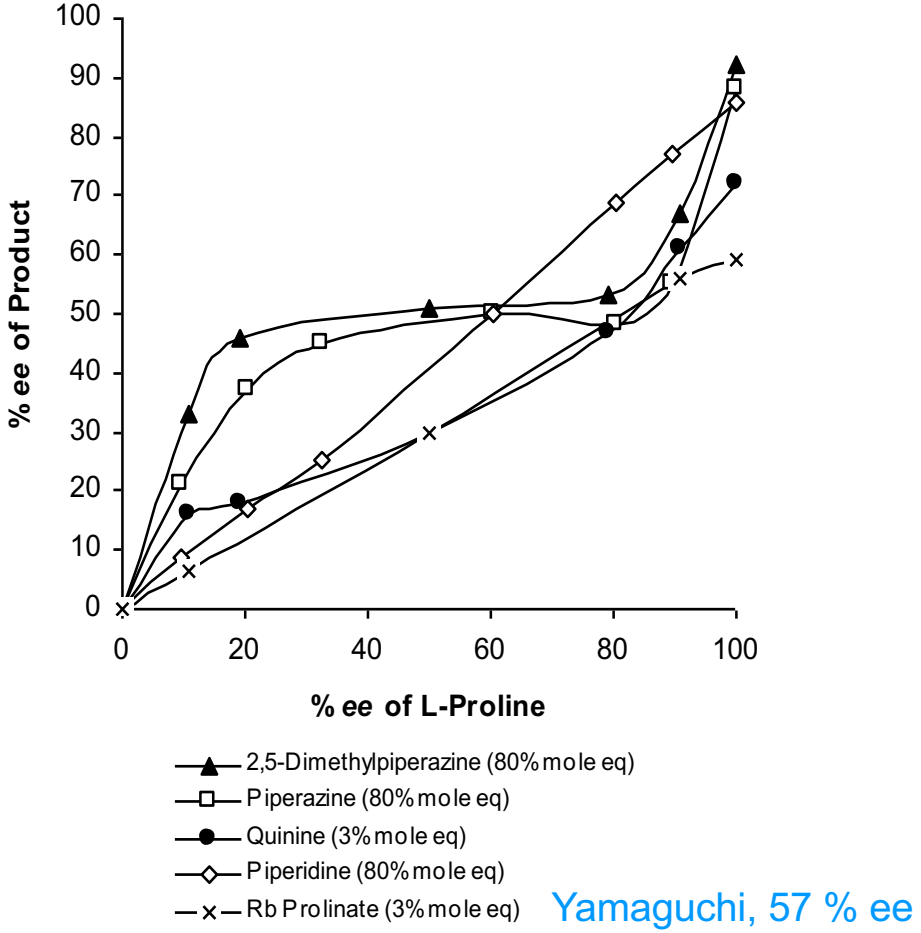
# Metal-free, organocatalytic nitroalkane Michael addition




(achiral additive)

| catalyst | ee (%) | yield (%) |
|---|---|---|
|  | 89 | 83 |
|  | 99 | 92 |
|  | 75 | 52 |
|  | 75 | 78 |
|  | 81 | 65 |

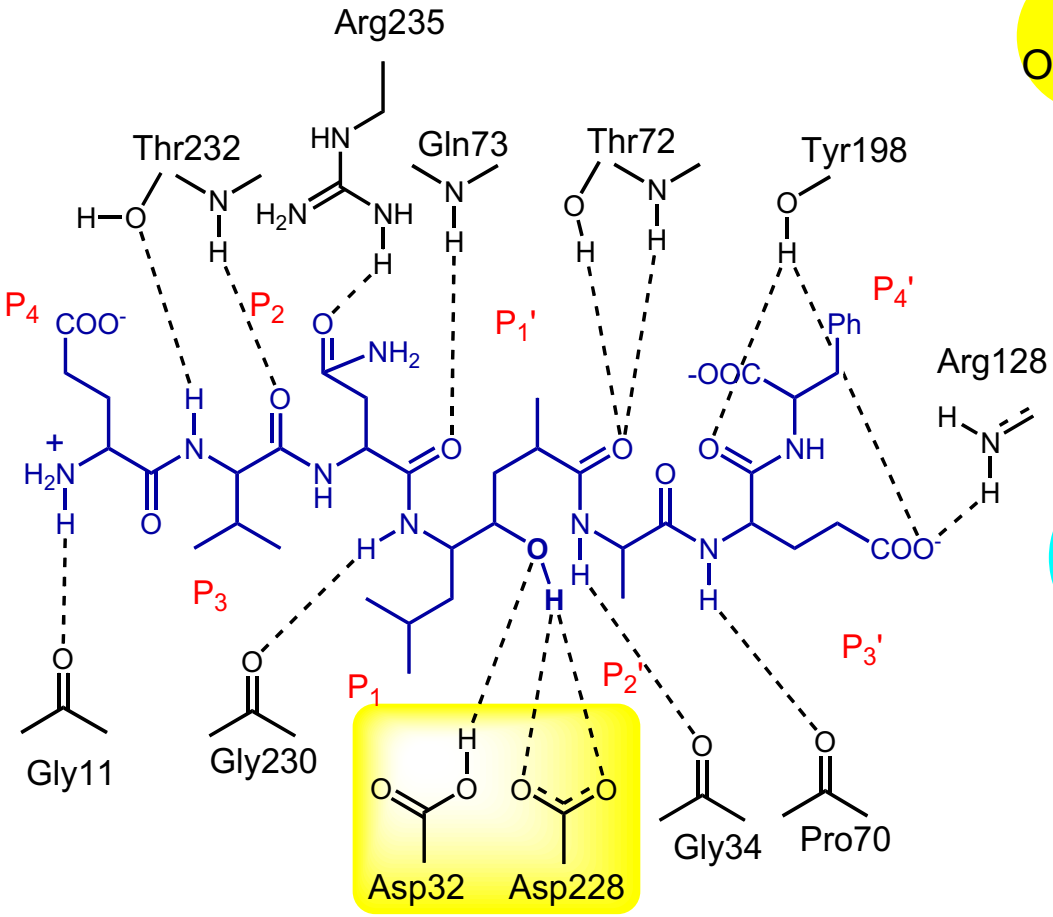
Non-linear effects in the addition of 2-nitropropane to 2-cyclohexenone



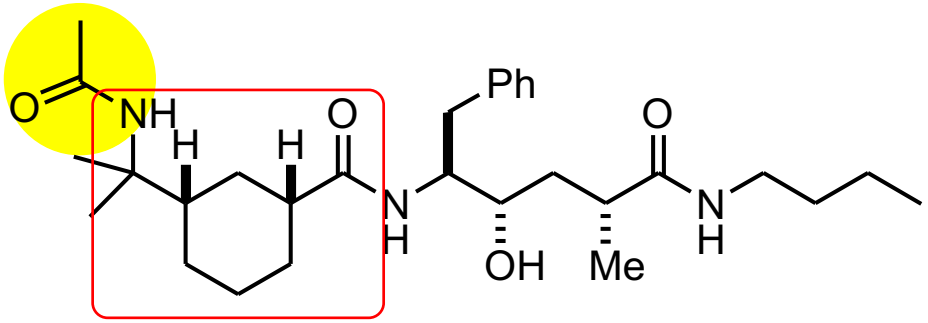

Yamaguchi, 57 % ee

*with* Pham, V. *Org. Lett.* **2000**, *2*, 2975-2978

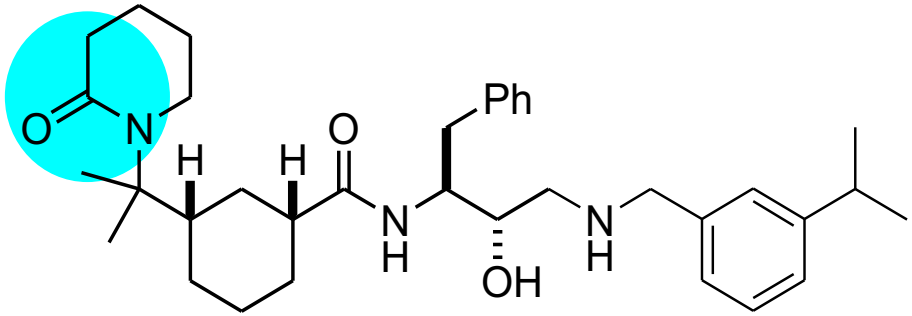
# From Tang's heptapeptide to a *'designed'* minimally peptidic low nM inhibitor




Tang's OM99-2
$IC_{50}$ 1-2 nM



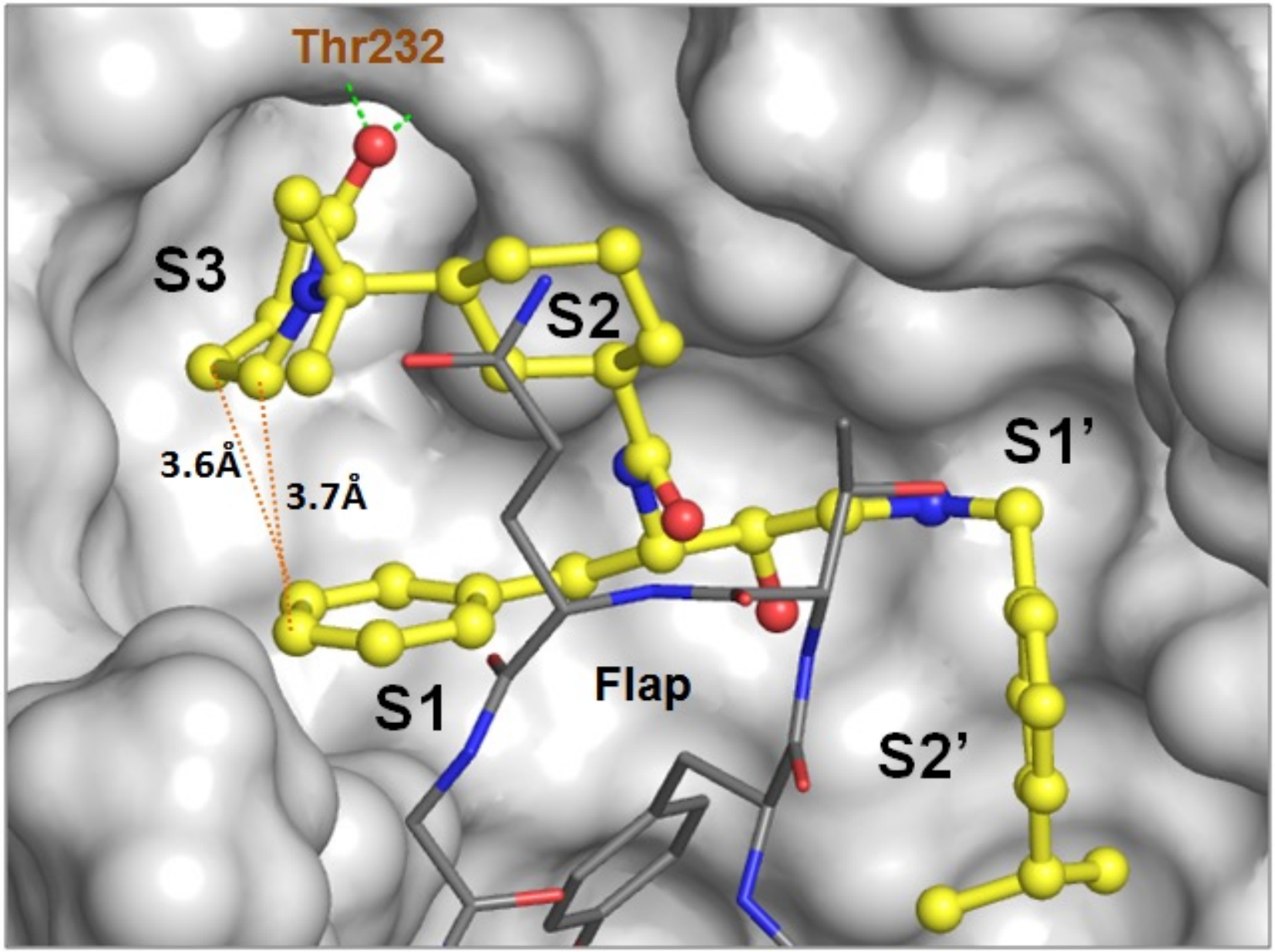

**$IC_{50}$ 3.74 uM**




Synthetic prototype
$IC_{50}$ **2-3 nM**

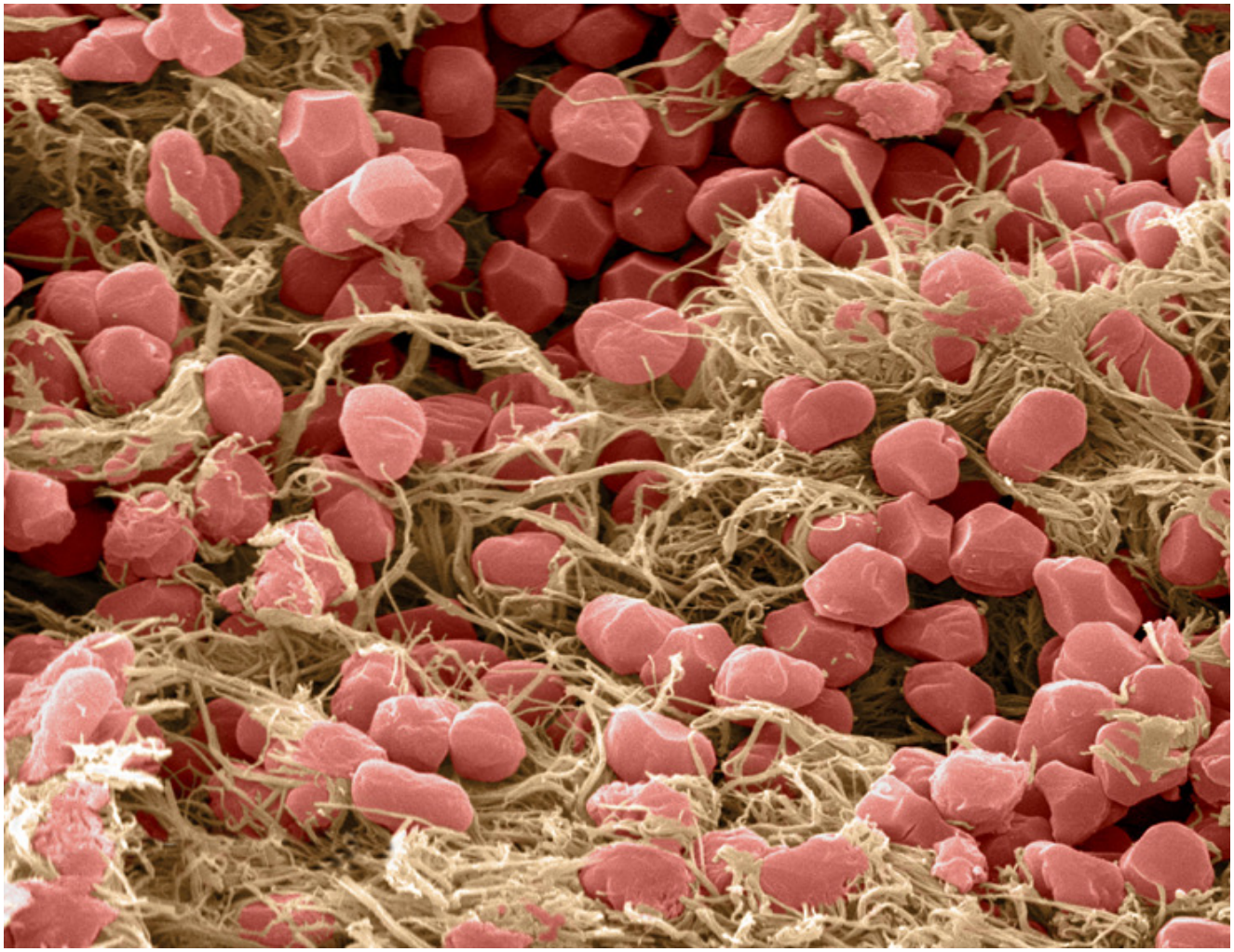

*with* Maji, D.K.; Govindan, S.; Matera, R.; Tintlenot-Bromley, M. *J.Org.Chem.* **2010***,* 75*, 2861;* Shao, Z.; Betschart, C.; Rondeau, J-M.; Neumann, U.; Tintelnot-Bromley, M. *Bioorg. Med. Chem. Lett*. **2010,** *20***,** 1924.

# *X-ray co-crystal structure with BACE 1*



*AstraZeneca (Sweden) collaboration*

# Thromboembolic Diseases

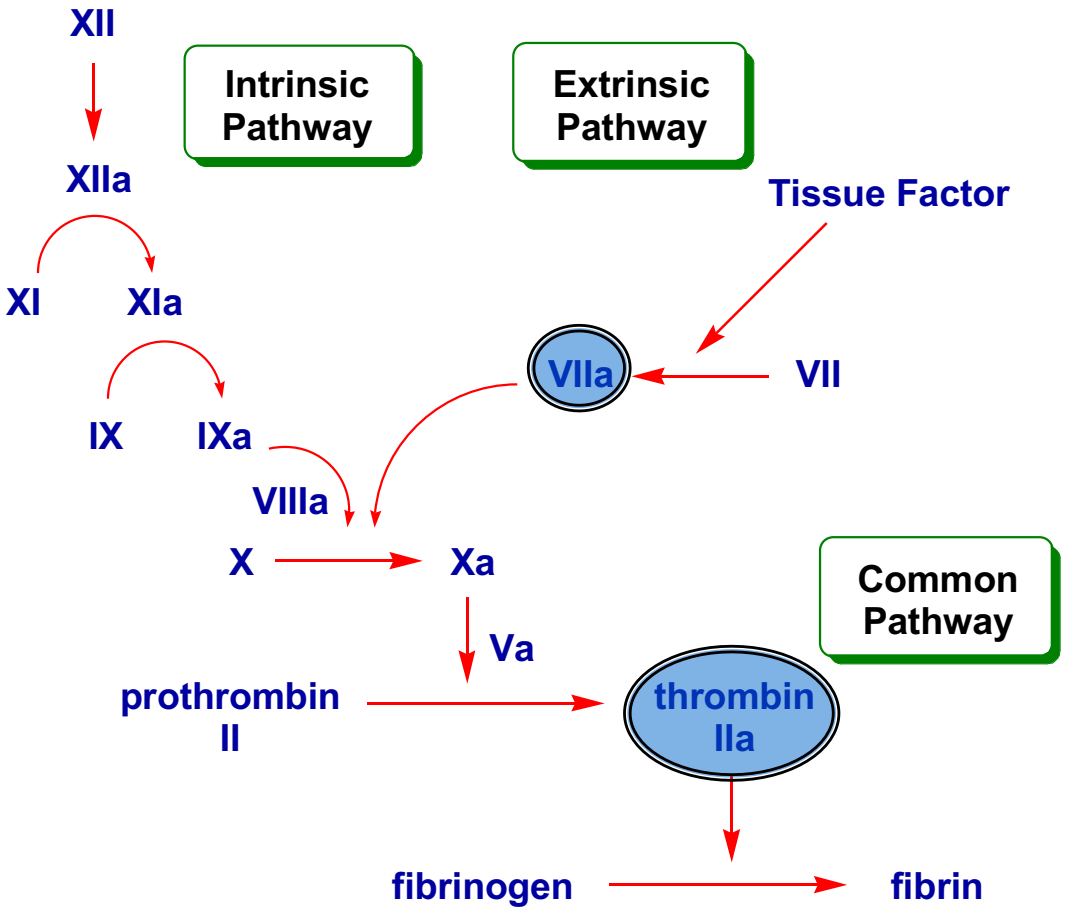


- The major cause of morbidity and mortality in the world

# Thrombin and Factor VIIa

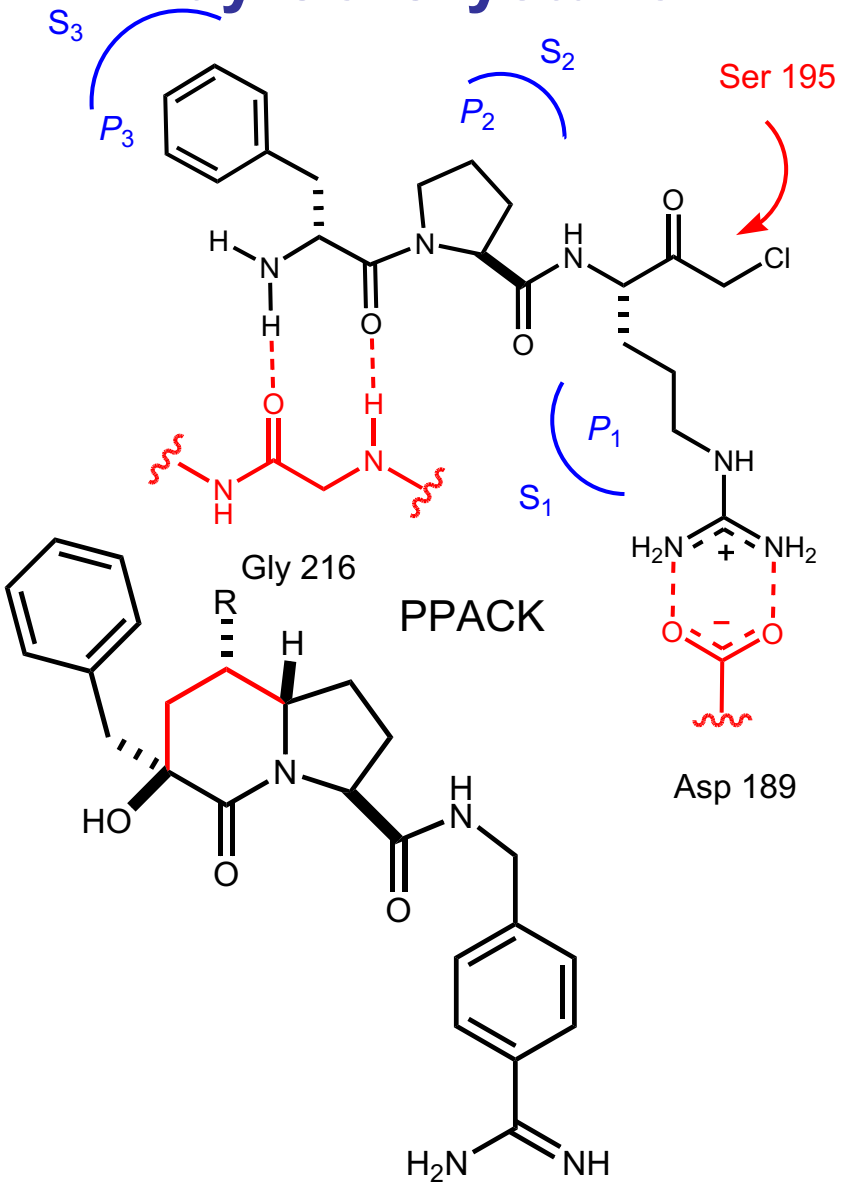
*AstraZeneca collaboration*

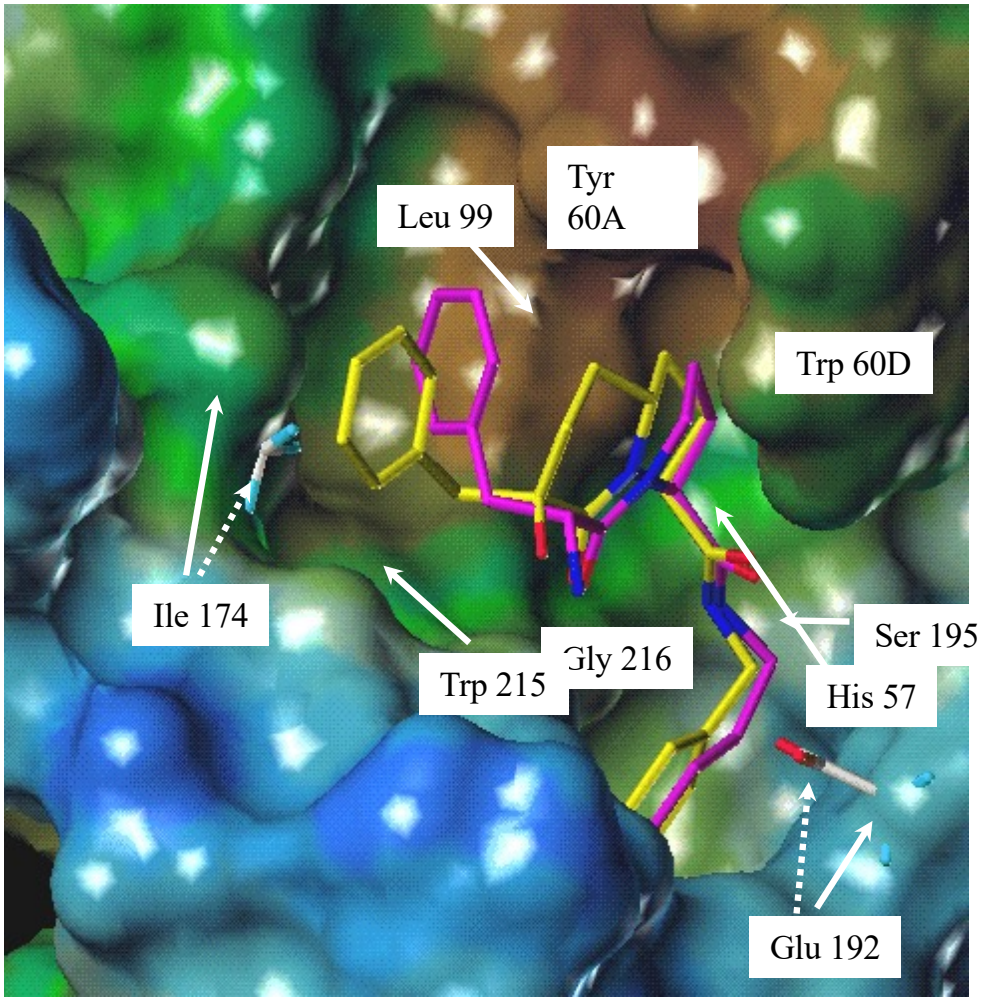
- Members of the family of serine proteases
- Thrombin holds central position in the final steps of the blood coagulation cascade
- Factor VIIa holds a major role in the extrinsic pathway
- They both regulate hemostasis
- Lead to the conversion of Fibrinogen to Fibrin
- Stimulate platelet aggregation
- Current treatments → side effects




Reviews:
*Clin. Appl. Thrombosis/Hemostasis* ***2001****, 7*, 195-204
*Am. Heart J.* **2001**, *142*, S3-8
*Exp. Opin. Invest. Drugs* **2001**, *10*, 845-864
*Current Medicinal Chemistry* **1998**, *5*, 289-304

# X-Ray Co-Crystal of Thrombin with Prototypical Inhibitor




PPACK in pink, Inhibitor in yellow

R = H

$IC_{50}$ thrombin: **18 nM**

$IC_{50}$ factor VIIa: 1 100 nM

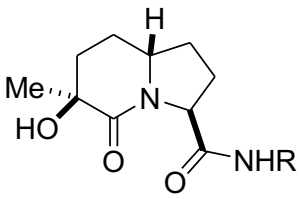
R = OMe

$IC_{50}$ thrombin: 110 nM

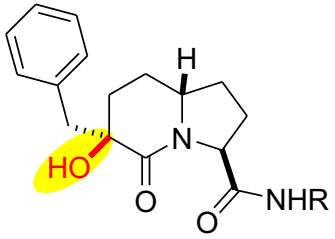
$IC_{50}$ factor VIIa: 520 nM

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

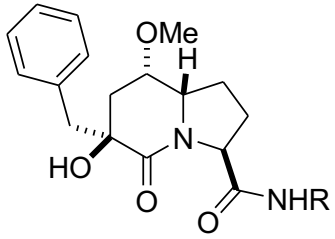
# Small Molecule Thrombin Inhibitors



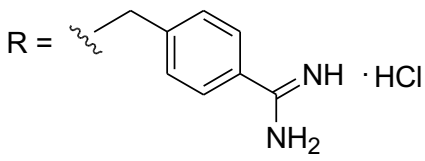

thrombin: 270 nM
factor VII: >10 000 nM

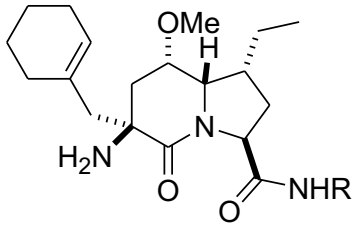



thrombin: 18 nM
factor VII: 1 100 nM

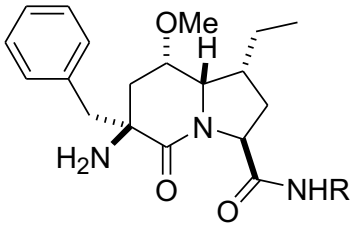



thrombin: 110 nM
factor VII: 520 nM

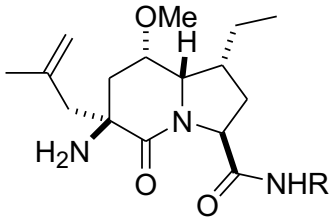


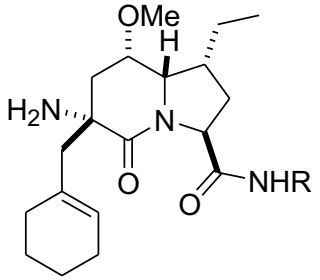

thrombin: 170 nM
factor VII: 4 600 nM



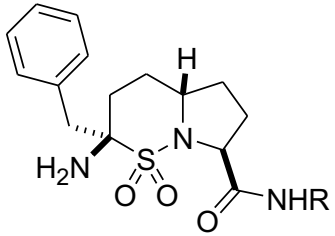

thrombin: 210 nM
factor VII: 420 nM



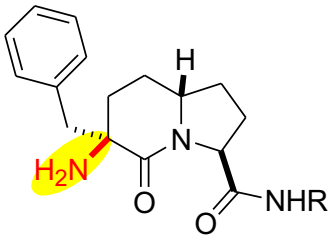

thrombin: 380 nM
factor VII: 3 600 nM



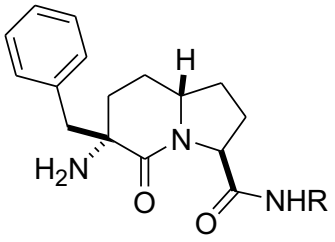

thrombin: 7 200 nM
factor VII: 109 000 nM




thrombin: 494 nM



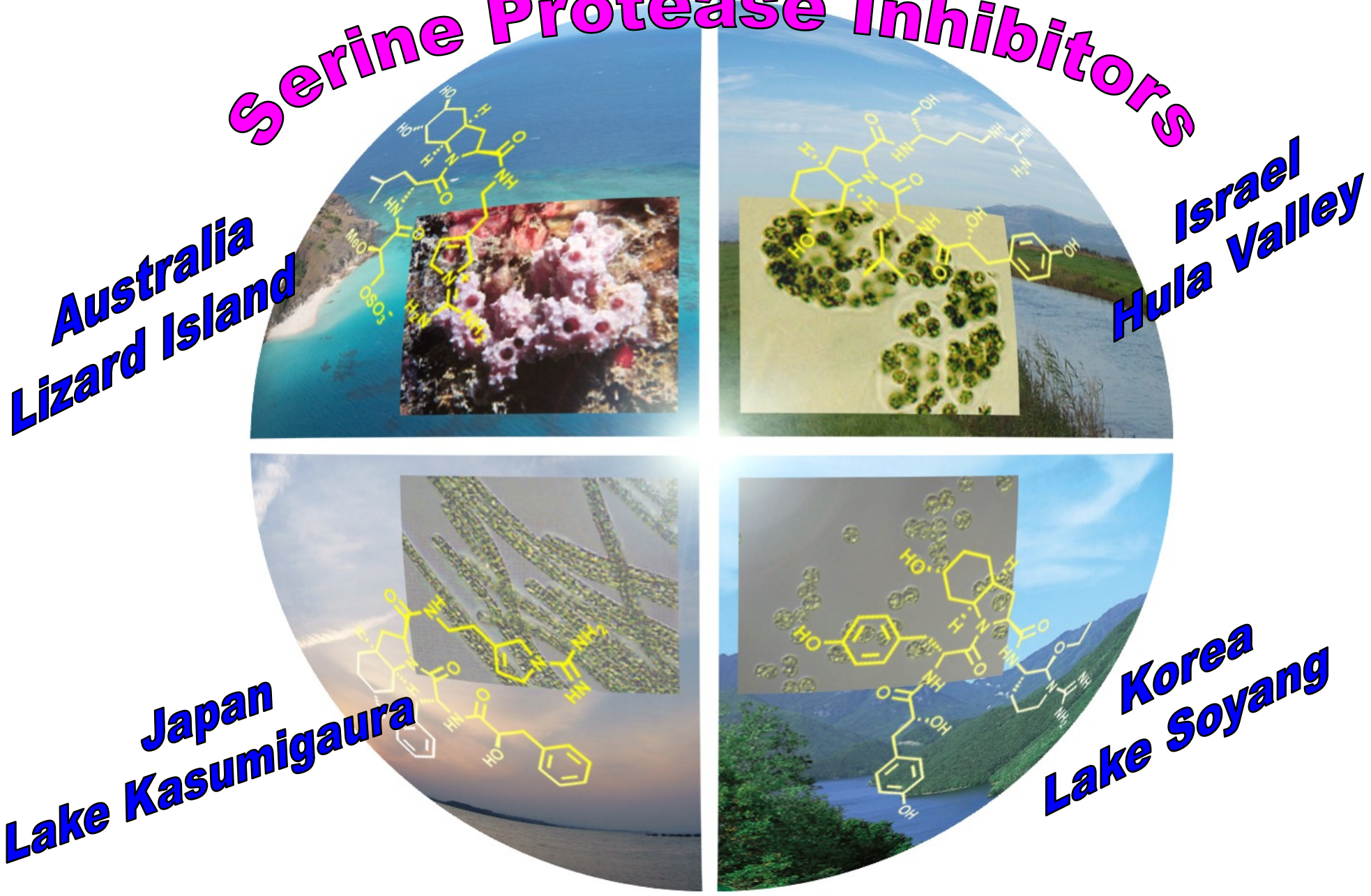

**thrombin: 4.7 nM**




thrombin: 2 550 nM

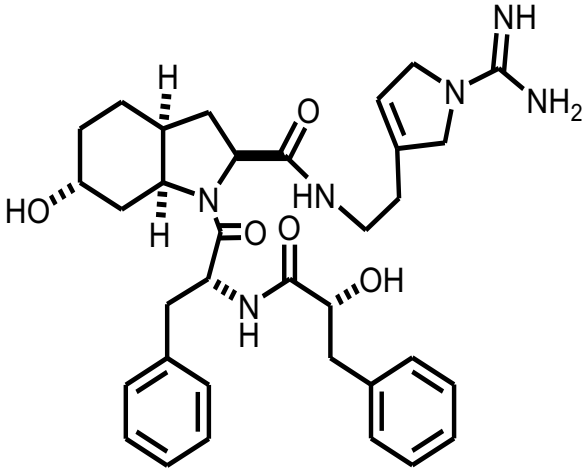
with E. Balaux, D. Musil, L.-L. Olsson, I. Nilsson, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 243;
with E. Therrien, K. Granberg, I. Nilsson, *Bioorg. Med. Chem. Lett.* **2002** *12*, 2907

# Aeruginosins: Serine Protease Inhibitors

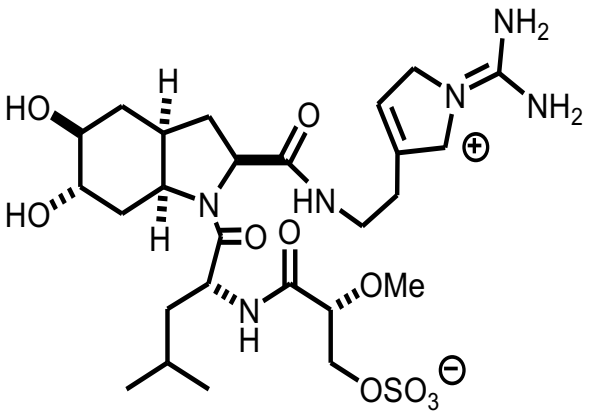



Review: *"Chemistry and Biology of the Aeruginosin Family of Serine Protease Inhibitors"*
K. Ersmark, J. R. Del Valle, S. Hanessian, *Angew. Chem. Int. Ed.* **2008,** *47,* 1202

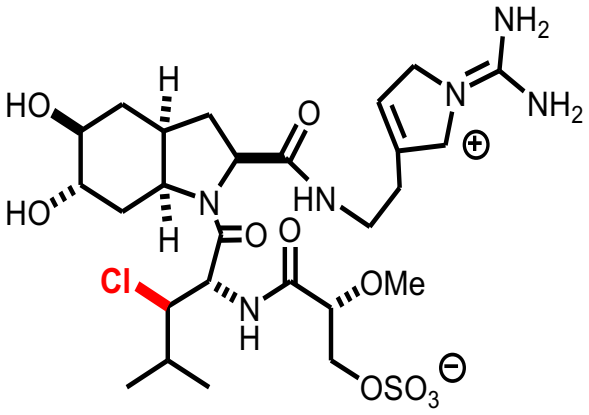
# The "*Magic*" Chlorine Atom?



*Oscillarin*



*Dysinosin A*

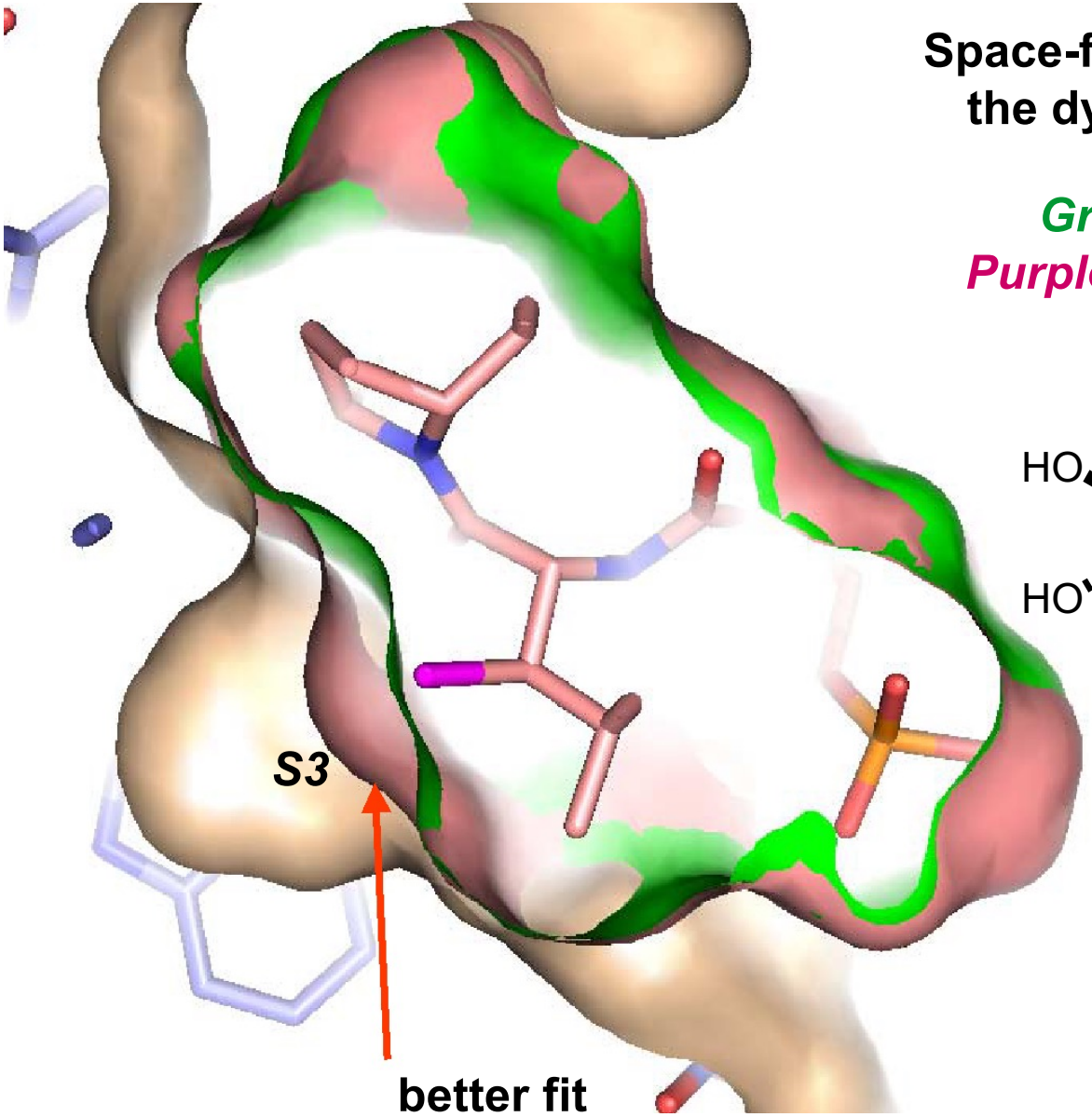


*"Chlorodysinosin A"*

| $IC_{50}$ | | | |
|---|---|---|---|
| Thrombin | 28 nM | 46 nM | 5.7 nM |
| Factor VIIa | 3.9 μM | 326 nM | 39 nM |
| Factor Xa | - | 5 μM | 1.5 μM |
| Factor XIa | - | 18 nM | 4 nM |

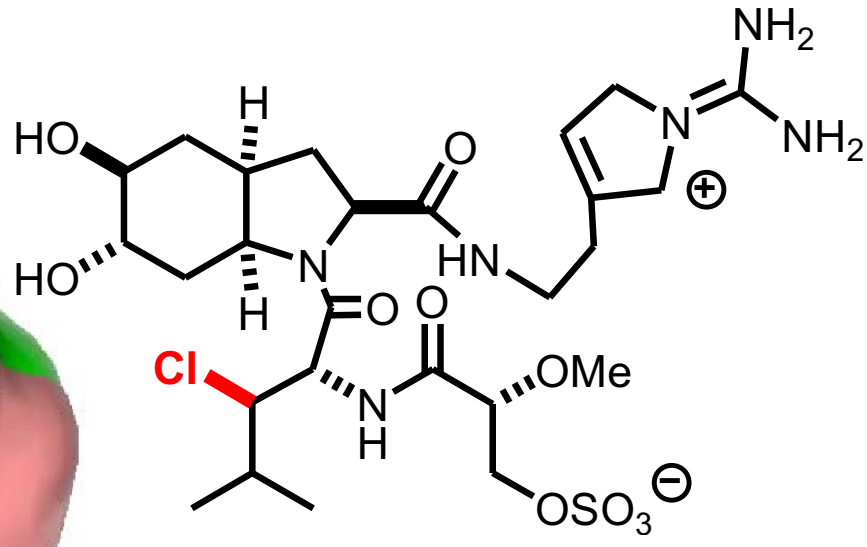
with J. R. Del Valle, Y. Xue, N. Blomberg, *J. Am. Chem. Soc.* **2006**, *128*, 10491; *J. Am.Chem. Soc*. **2004**, *126*, 6064; *J. Am. Chem. Soc*. **2002**, *124*, 13342

# Topochemical Effect

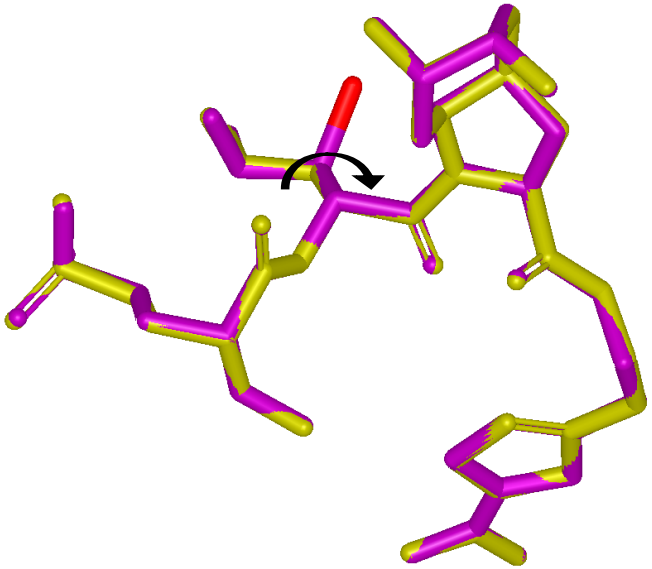



**Space-filling structural comparison of the dysinosins bound to thrombin**

***Green contour = Dysinosin A***
***Purple contour = ChlorodysinosinA***

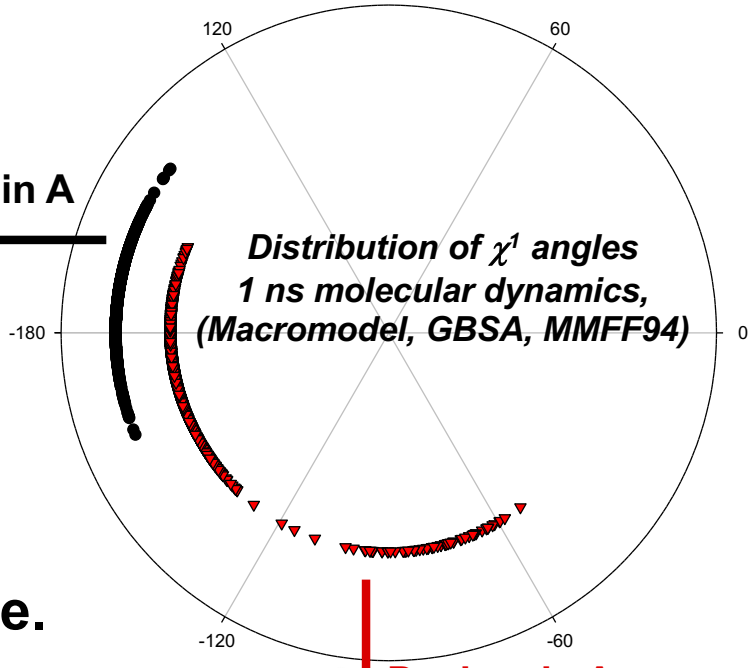


# Conformational Effects

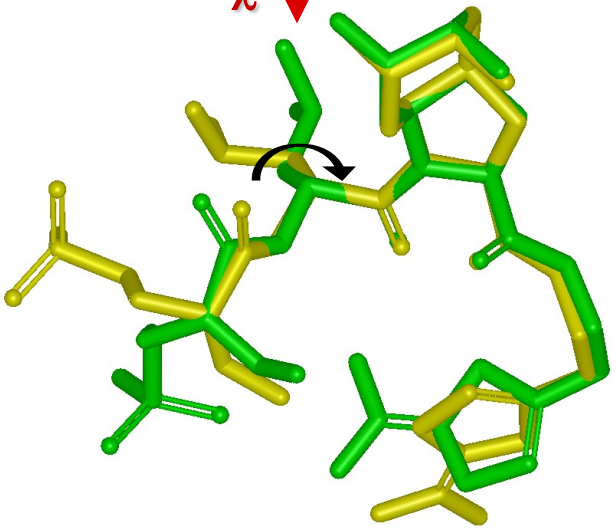


Chlorodysinosin A

$\chi^1$

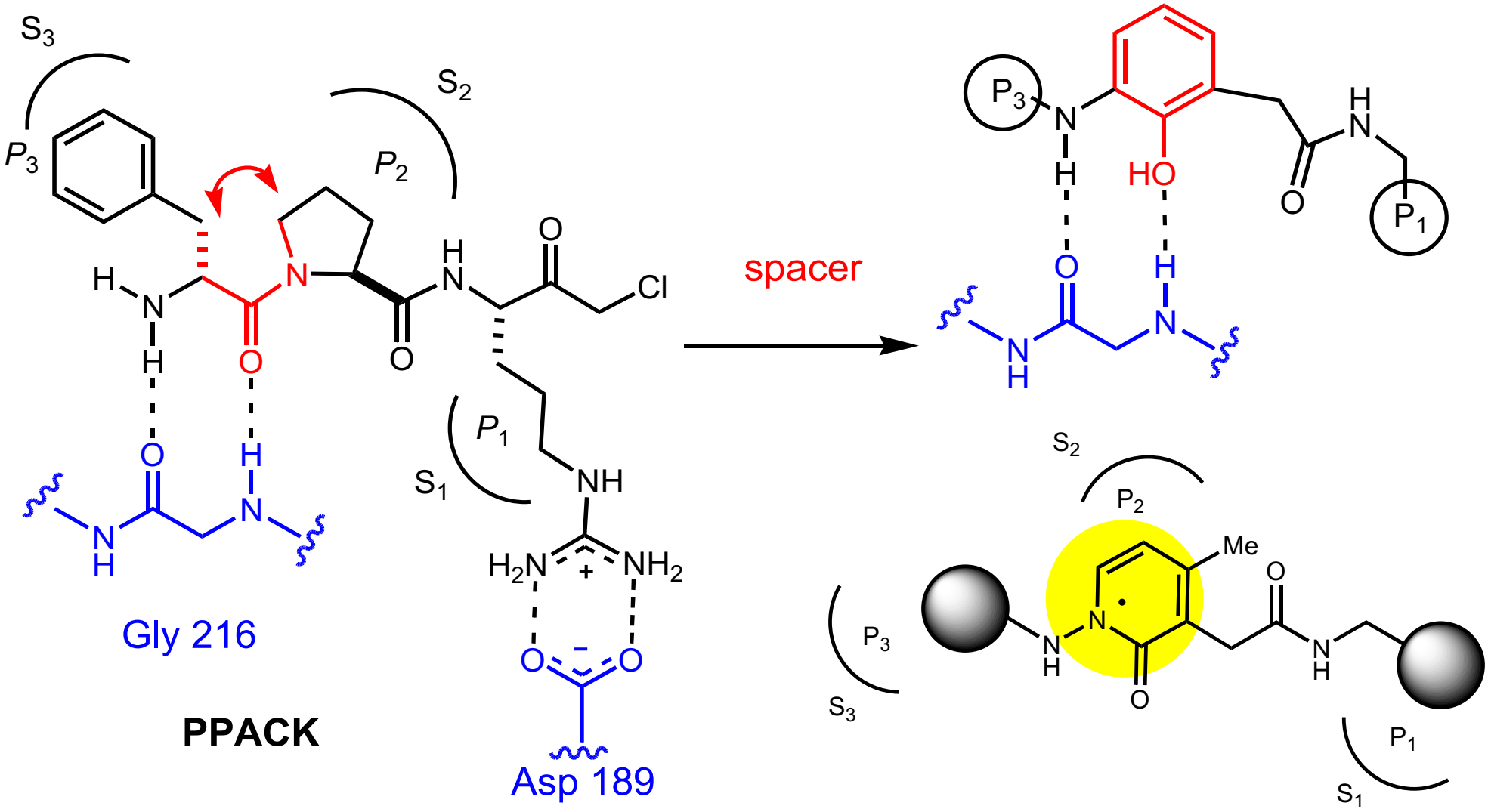



$\chi^1$ Dysinosin A



- 3-Cl substituent restricts the $\chi^1$ angle.
- 3-Cl increases lipophilicity and hydrophobic interaction with the enzyme pocket.
- 3-Cl fills the S3 site with release of water from the enzyme pocket (an entropic gain).

# Novel *P2* 2-Pyridone Spacers for Thrombin Inhibition

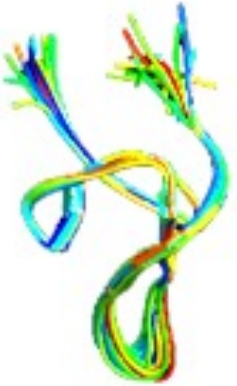



with W. A .L .van Otterlo, M. Bayrakdarian, E. Therrien, I. Nilsson, J. Petersen, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1032

***From a marine sponge…***

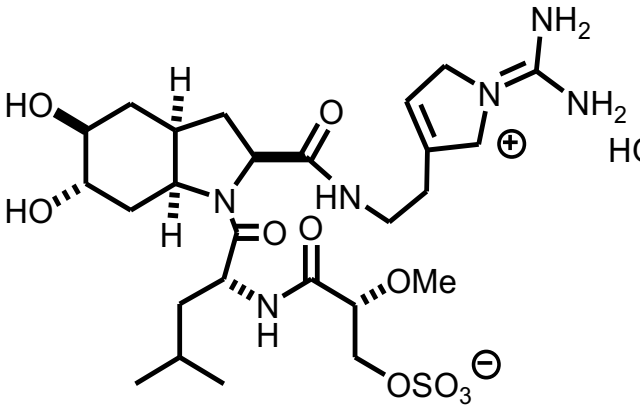


***and saliva from leeches….***



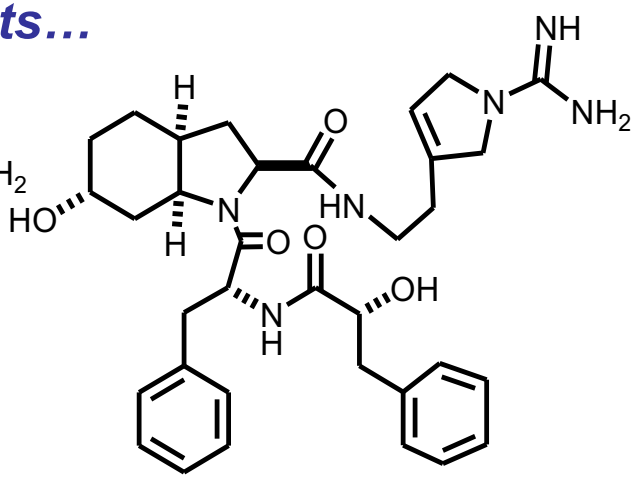
***(hirudin)***

***To novel natural products…***



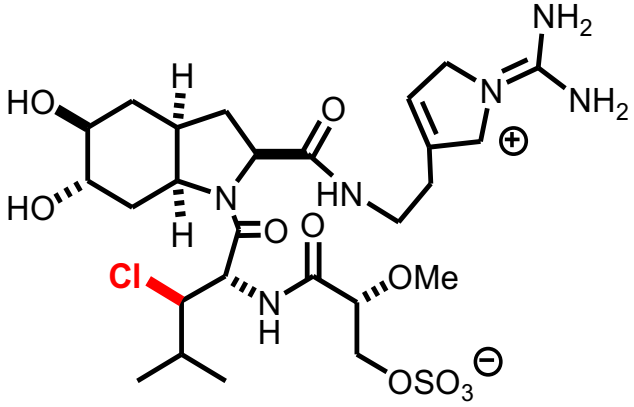
Dysinosin A

*46 nM*



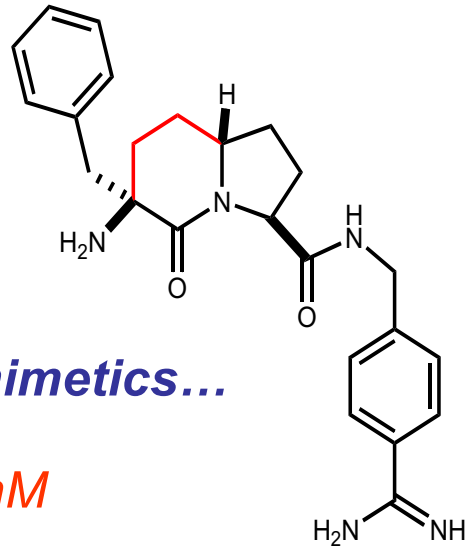
Oscillarin

*28 nM*



Chlorodysinosin A

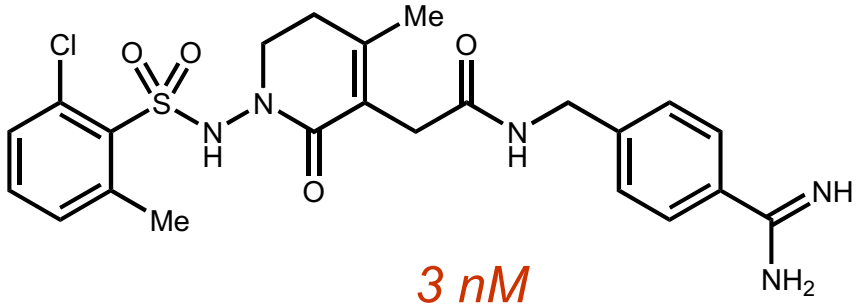
*5.7 nM*



***To peptidomimetics…***

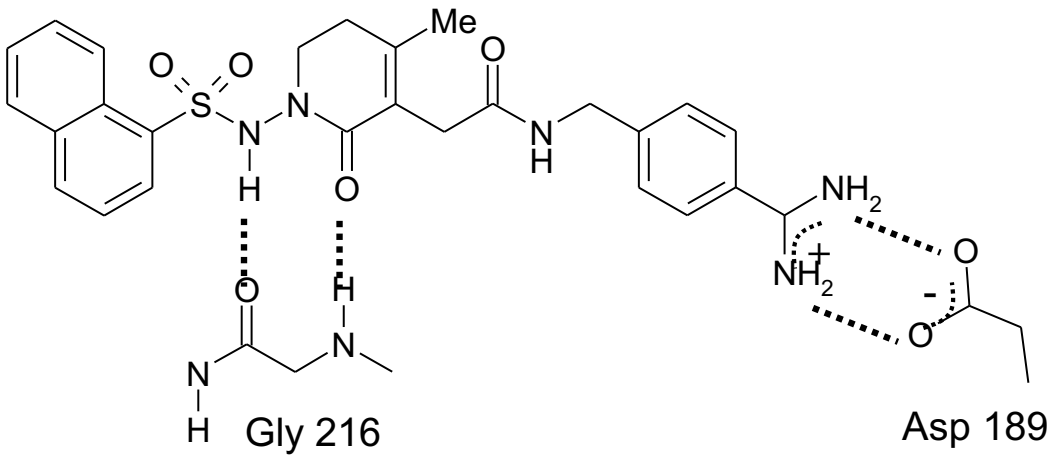
*4.7 nM*

***And to achiral, potential drug prototypes….***



*3 nM*

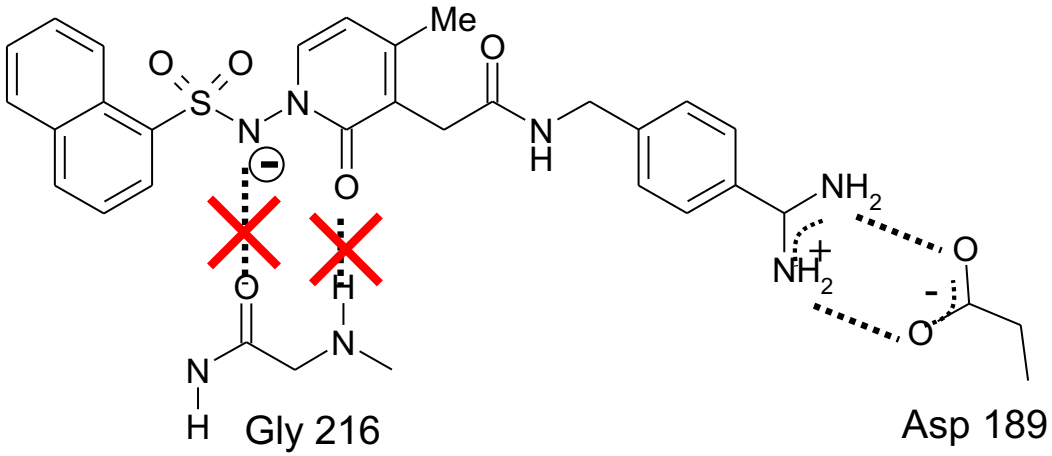
# Comparative Thrombin Inhibitory Activities




$IC_{50}$= ***26 nM***

*pKa= 8.2*

*Dihydropyridone series*



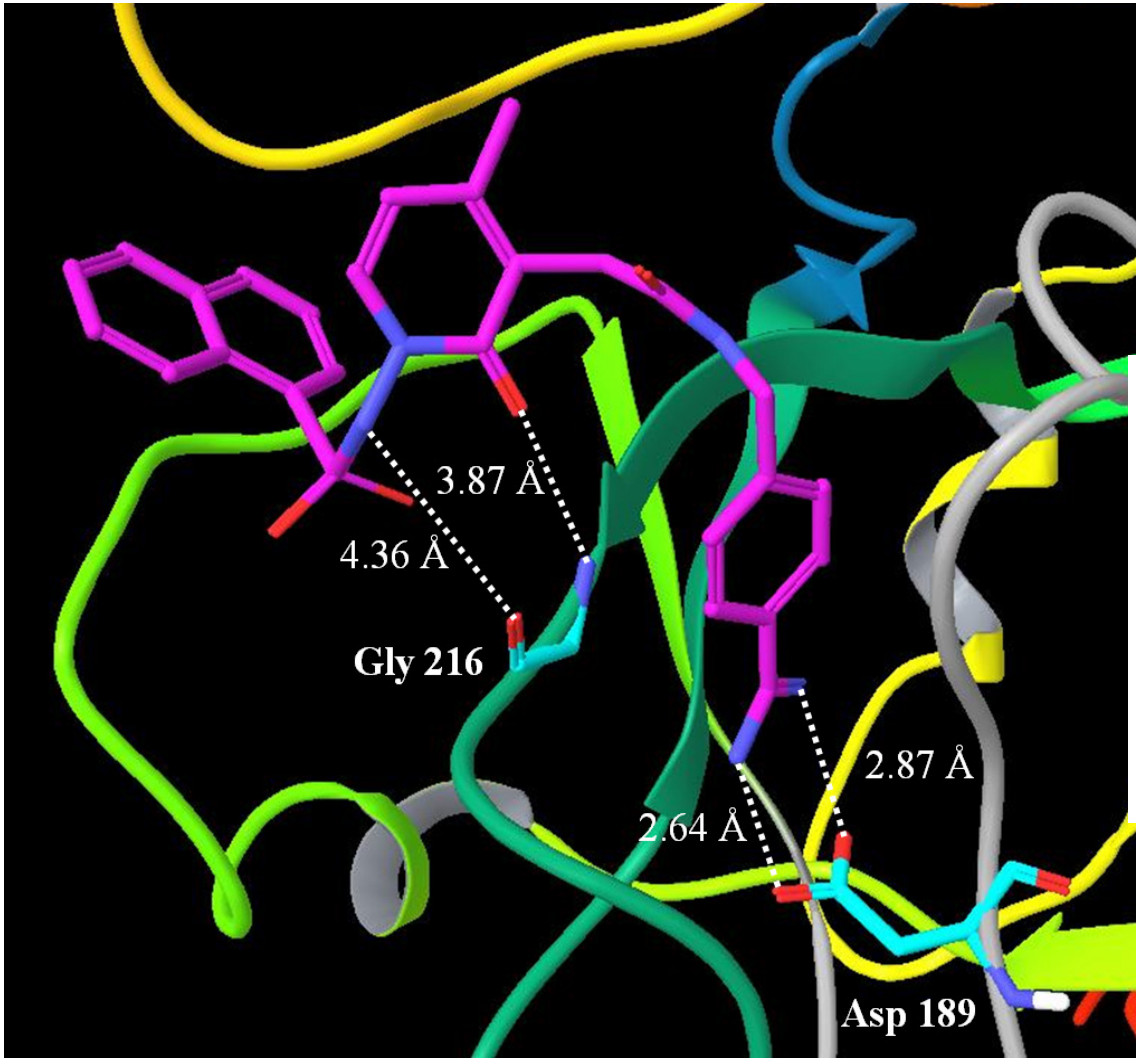

$IC_{50}$= *1240 nM*

*pKa= 5.8*

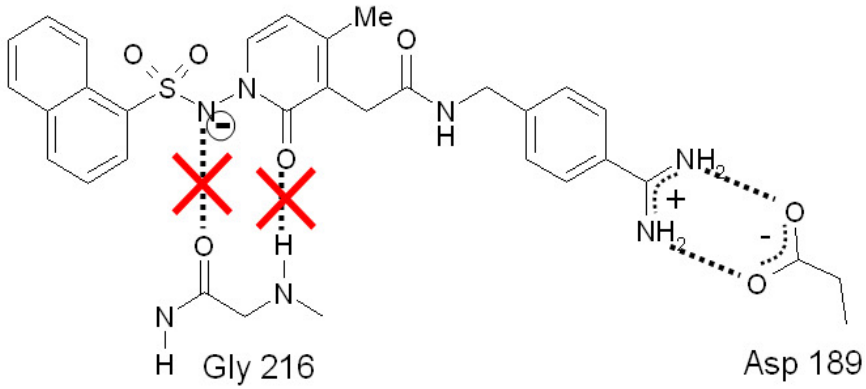
*Pyridone series*

*with* Therrien, E.; van Otterlo, W.; Xue, Y.; Gustafsson, D.; Nilsson, I.; Fjellström, O. *Bioorg. Med. Chem. Lett.* **2009**, *19,* 5429

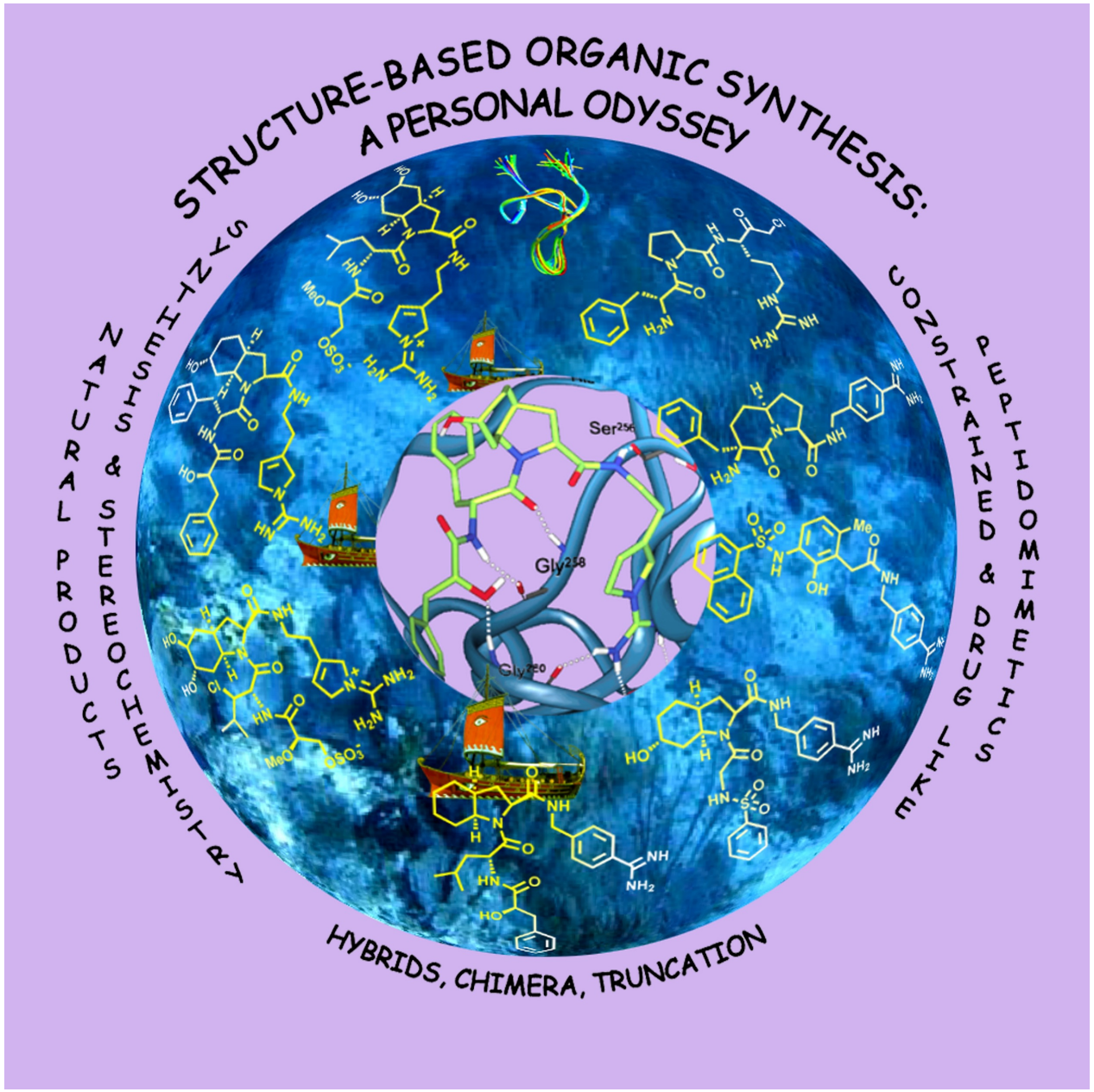
# Co-crystal Structure of the *Weakly* Active Pyridone Analog with Thrombin




*No antiparallel H-bonding*
*Only salt bridge with Asp*




Thrombin $IC_{50}$ = *1240 nM*



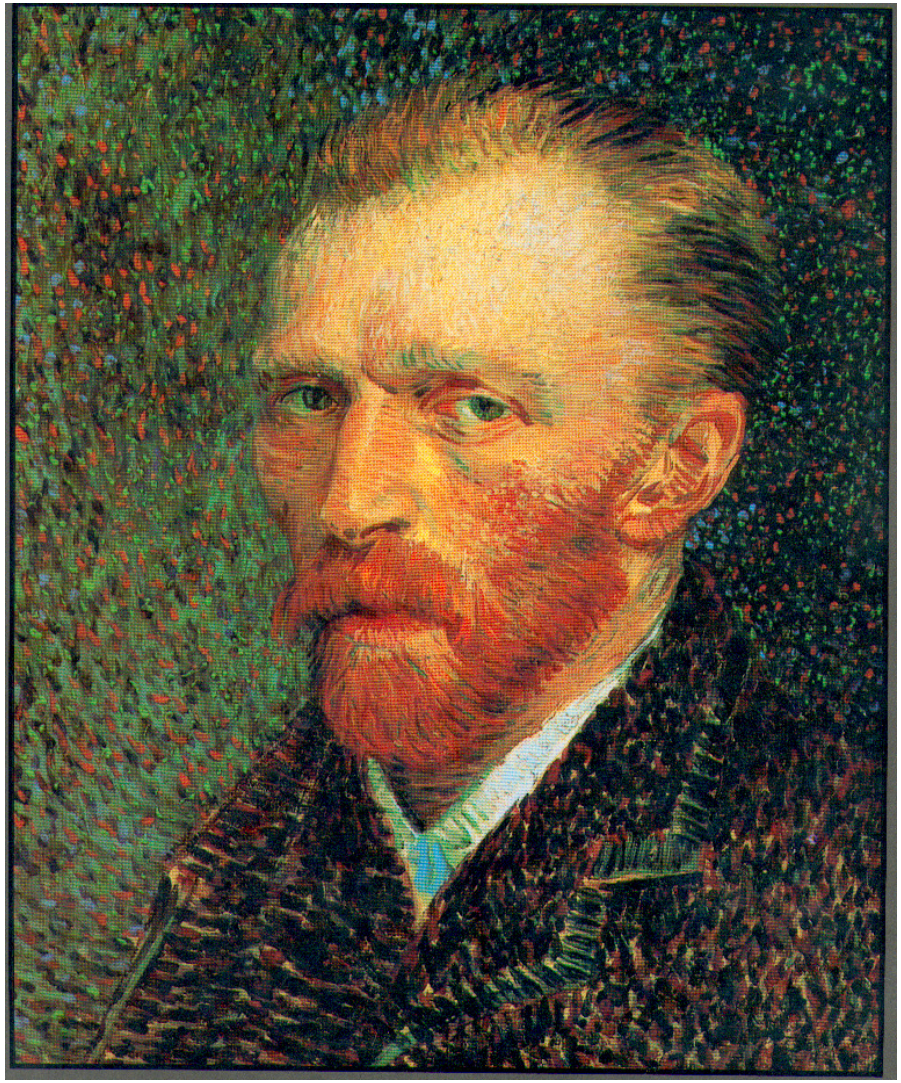

S. Hanessian, *Chem.Med.Chem.* **2006**,*12*,1300-1330.

# ACKNOWLEDGMENTS

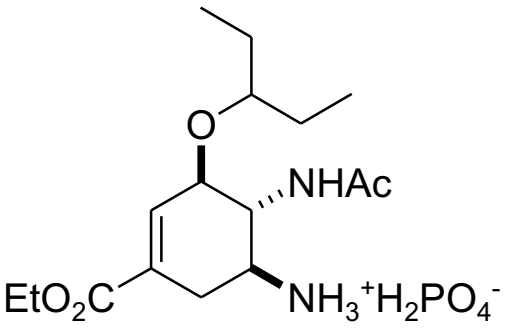

- NSERC *(Canada)*
- FQRNT *(Québec)*
- AstraZeneca *(Molndal, Sweden) Collaboration. (1990-2006) 15 publications; 2 patent applications*
- Novartis *(Basel) Collaboration(1988-2006).14 publications; 1 patent application*
- *University of Montreal*
- *University of California, Irvine*

“For the great things are not done by impulse, but by a series of small things brought together”

Vincent Van Gogh (1888)

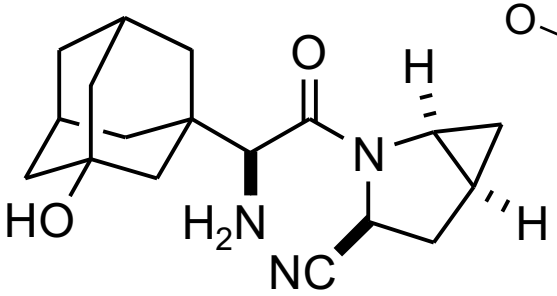


# Academic Research



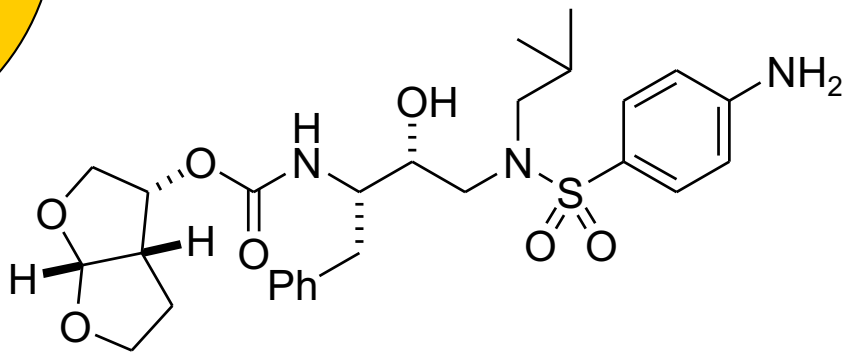

*Oseltamivir*
*(Tamiflu)*

***COREY***




*Onglyza*
*(Type II diabetis)*

***BMS***




*Darunavir*
*(Presixta)*

***Ghosh***

## Objectives:

- **Provide a forum to think, and to apply knowledge to address fundamental and practical problems in science**
- **Prepare young scientists for the rigors of research in industry and academia**