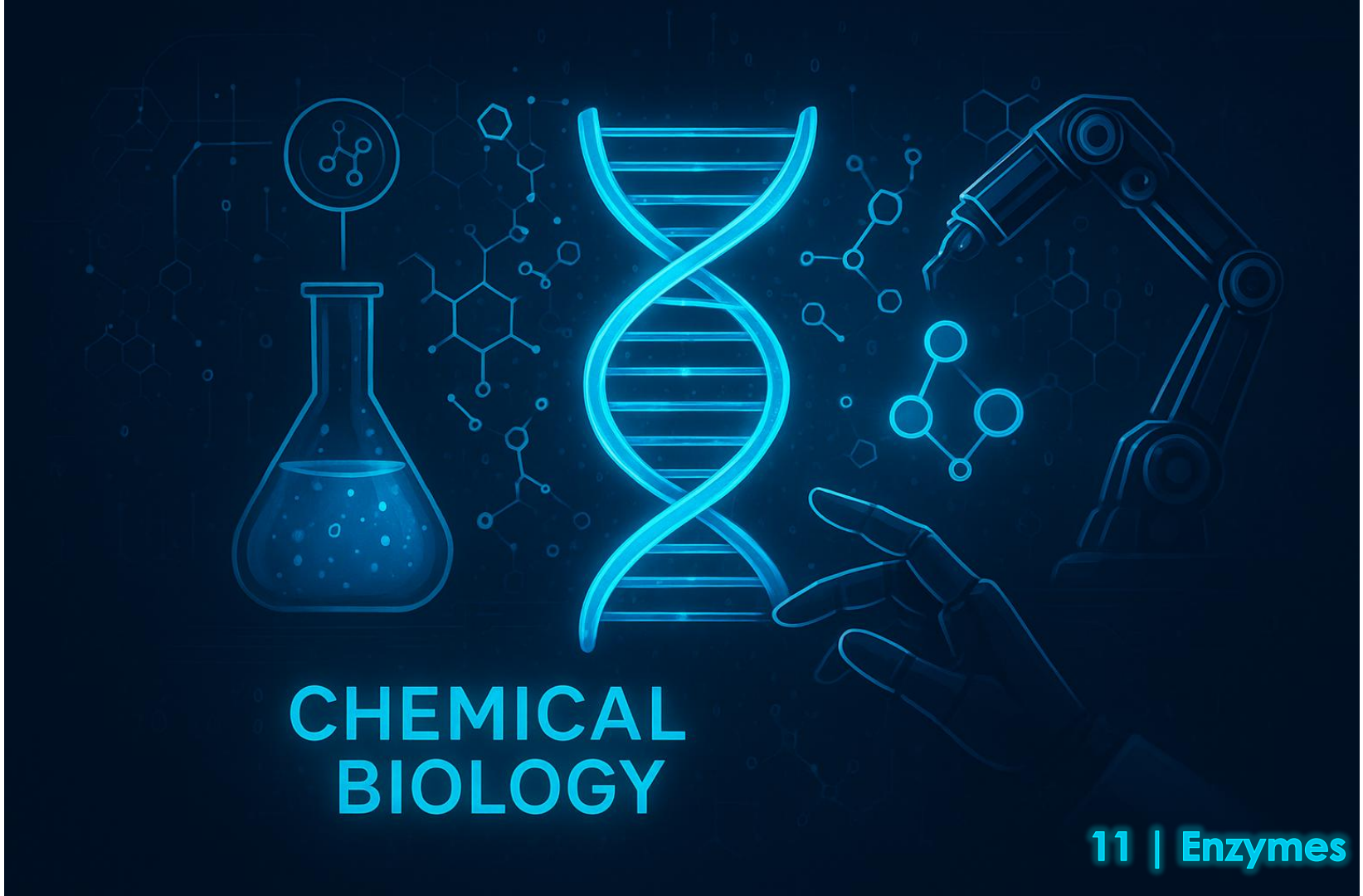

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General Course Information

- Moodle: https://go.epfl.ch/CH-313
  - Lecture slides (evening before the lecture)
  - Distributed presentation topics (assignments)
  - Forum (for questions and announcements)

- Examination (written, graded, detailed information will follow)
- Contact:
  - Moodle forum (for questions)
  - markus.jeschek@epfl.ch

- **“Concepts over details!”**
- **Interact! Ask! Discuss! Anytime!**

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Group Presentations

- Critical discussion of primary literature
- Illustrative examples for topics from the lecture

- Why?
  - Repetition of core concepts, techniques etc.
  - Presentation skills and critical discussion of research
  - Insight into current research topics

- How?
  - Two students per group
  - Assignments distributed one week before delivery of presentation (via Moodle)
  - **Send slides: markus.jeschek@epfl.ch (Mon evening before presentation)**
  - **15 min presentation (both group members should present!)** + Q&A

Tipps for Group Presentations

- Rough structure
  - Short intro on general topic
  - Main presentation according to assignment
  - Brief outlook incl. points of criticism/open questions/personal opinion as kick-starter for the discussion
- Everybody should participate in the discussion, incl. constructive(!) feedback on presentation style
- Questionnaires with different points, feedback by peers
- Typical assignment:
  - You will receive a certain topic including a related publication
  - Introduce the topic using the publication
  - present the motivation behind the research, methodology, key results (not every graph!)
  - Additional questions will be provided hinting towards central points
  - Be encouraged to look/present beyond the questions and the provided paper

Group Presentations – Schedule

#	Name1	Name2	Presentation on…	Assignment on…
1	Wininger Quentin	Jeremy	**Sep 23, 2025**	Sep 16, 2025
2	Ema	Ariane	**Sep 30, 2025**	Sep 23, 2025
3	Benjamin	Matthieu	**Oct 7, 2025**	Sep 30, 2025
4	Ivana	Ipek	**Oct 14, 2025**	Oct 7, 2025
5	Mridhula	Elodie	**Oct 28, 2025**	Oct 21, 2025
6	Abigail	Robin	**Nov 4, 2025**	Oct 28, 2025
7	Eva	Florian	**Nov 11, 2025**	Nov 4, 2025
8	Bastien	Axel	**Nov 18, 2025**	Nov 11, 2025
9	Melodie	Siolène	**Nov 25, 2025**	Nov 18, 2025
10	Nicole	Maria	**Dec 2, 2025**	Nov 25, 2025

Course Topics – Overview

- Week 1 | Introduction + DNA
- Week 2 | DNA
- Week 3 | DNA
- Week 4 | DNA
- Week 5 | DNA/RNA
- Week 6 | RNA/Translation
- Week 7 | Translation
- Week 8 | Enzymes (Zoom)
- **Week 9 | Enzymes (Zoom)**
- Week 10 | Enzymes (Zoom)
- Week 11 | Metabolism (Zoom)
- Week 12 | Engineering
- Week 13 | Engineering
- Week 14 | LSAM Intro + Exam Preparation

!Due to paternity leave the next lectures will be delivered via Zoom!

[tentative schedule]

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Zoom Info

- Week 1 | Introduction + DNA
- Week 2 | DNA
- Week 3 | DNA
- Week 4 | DNA
- Week 5 | DNA/RNA
- Week 6 | RNA/Translation
- **Week 7 | Translation**
- **Week 8 | Enzymes (Zoom)**
- **Week 9 | Enzymes (Zoom)**
- **Week 10 | Enzymes (Zoom)**
- **Week 11 | Metabolism (Zoom)**
- Week 12 | Engineering
- Week 13 | Engineering
- Week 14 | LSAM Intro + Exam Preparation

!Due to paternity leave the next lectures will be delivered via Zoom!

https://epfl.zoom.us/j/68900732223

Meeting ID: 689 0073 2223

[tentative schedule]

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Protein – Enzymes
(Kinetics)

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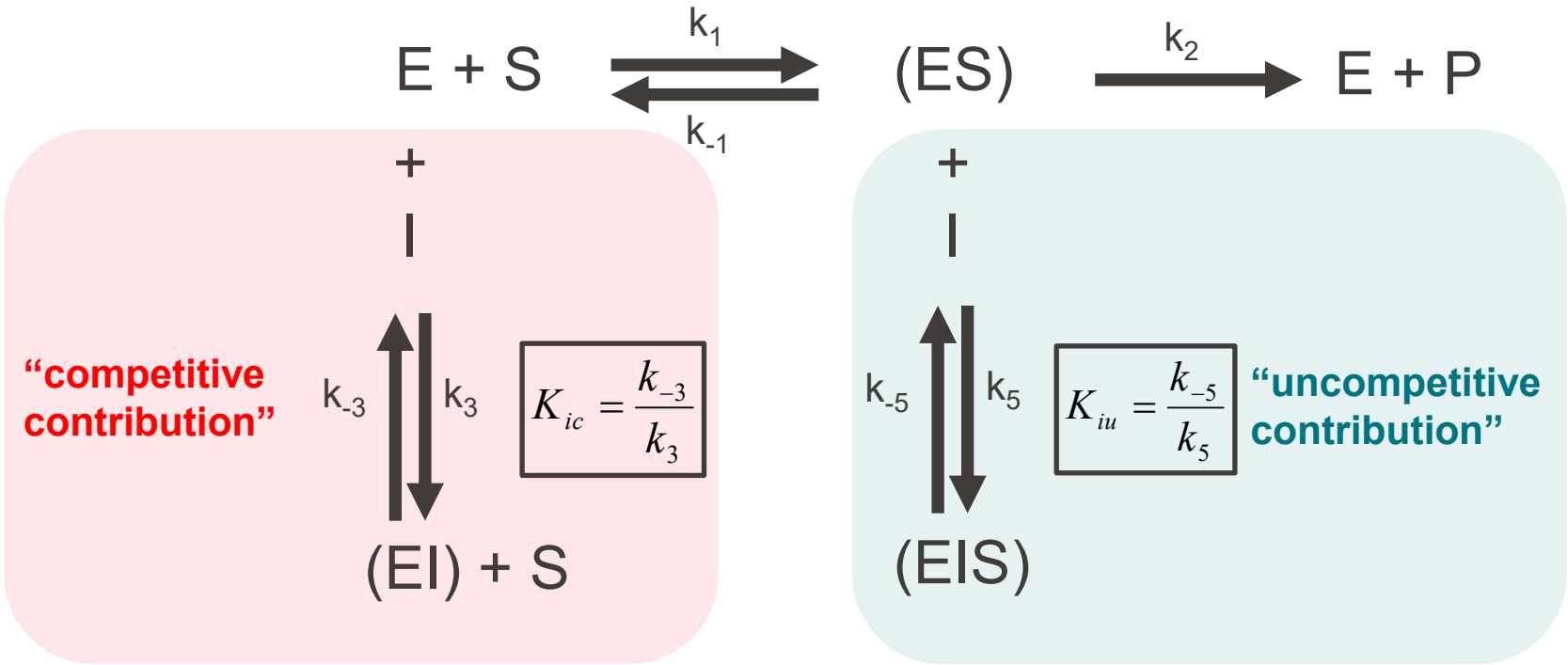
Reversible Inhibition (Expanded MM)



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Temperature Dependence

- Temperature influences both k_{cat} and K_M!
- assumption: influence on K_M is negligible (why?)
- effect on k_{cat} described by Arrhenius equation

$$v = \frac{k_{cat}(T)[E_0][S]}{K_M(T) + [S]}$$

Arrhenius equation:

$$k_{cat} = A \cdot e^{-\frac{\Delta G^{\ddagger}}{R \cdot T}}$$

- But: enzyme inactivation at high T!

$$E_{act} \xrightarrow{k_d} E_{inact}$$

$$\ln k_{cat} = \ln A - \frac{\Delta G^{\ddagger}}{R} \cdot \frac{1}{T}$$

A: frequency factor [1/s]
$\Delta G^{\ddagger}$: activation energy [J/mol]
R: gas constant, 8.314 J/(mol*K)
T: absolute temperature [K]

END OF LECTURE 10!

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Kinetics of Enzyme Inactivation

- assumption: 1st order kinetics

$$E_{act} \xrightarrow{k_d} E_{inact}$$

$$\frac{d[Eact]}{dt} = k_d \cdot [Eac_t]$$

$$[E_{act}] = [E_{act}]_0 \cdot e^{-kd \cdot t}$$

Arrhenius:

$$\ln k_d = \ln A_d - \frac{\Delta G^{\ddagger}{}_d}{R} \cdot \frac{1}{T}$$

$$t_{1/2} =$$

Q: Derive the formula for the enzyme half life $t_{1/2}$!

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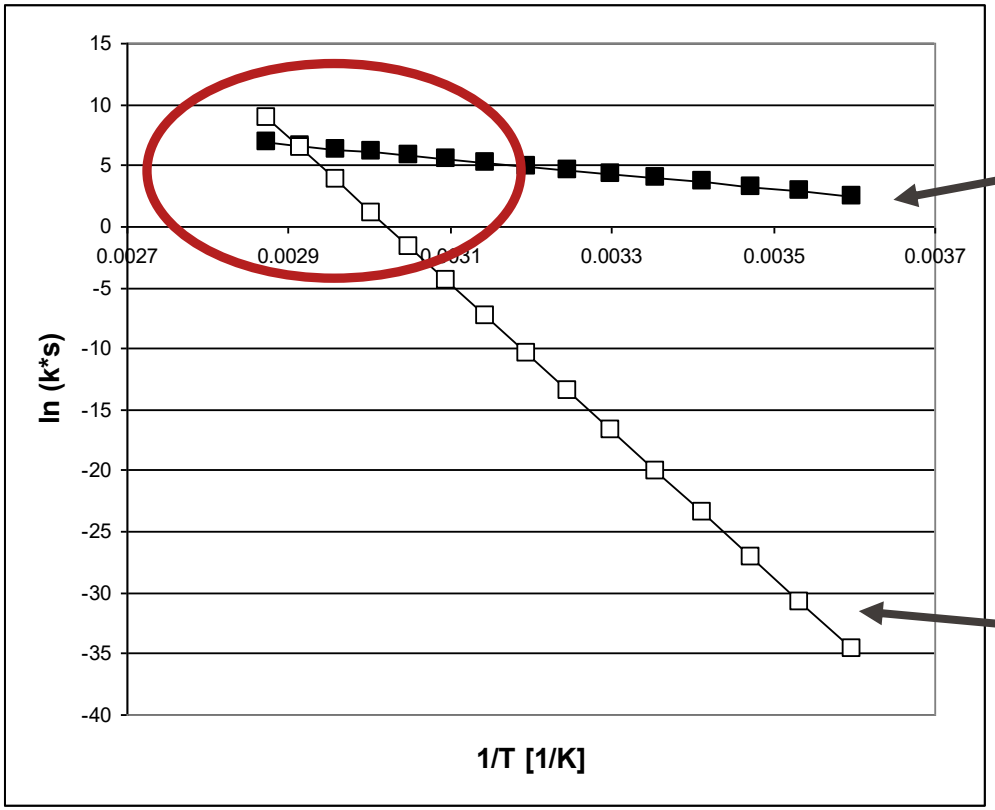
Temperature Dependence



Typical $\Delta G^{\ddagger}$:

- **enzymatic reaction: ~10-100 kJ/mol**
- **thermal enzyme inactivation: ~200-500 kJ/mol**

"reaction":

$$\ln k_{cat} = \ln A - \frac{\Delta G^{\ddagger}}{R} \cdot \frac{1}{T}$$

→ There has to be a T_{opt}!

"inactivation":

$$\ln k_d = \ln A_d - \frac{\Delta G^{\ddagger}{}_d}{R} \cdot \frac{1}{T}$$

Q: Name reasons other than T for enzyme inactivation!

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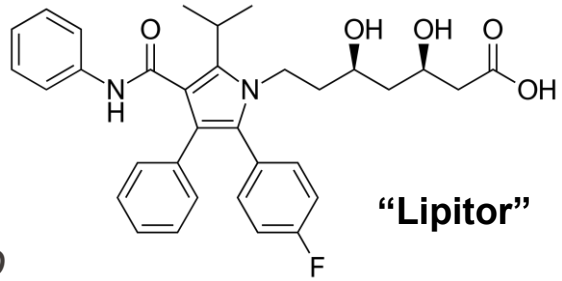
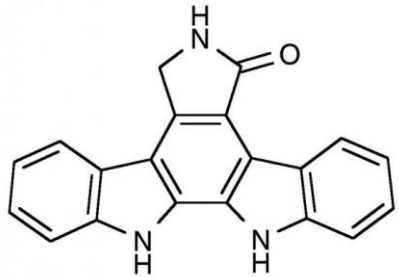
Competitive Inhibitor Drugs

- Structural similarity to substrates
- Rather straight-forward design
- Can be outcompeted by natural substrate *in vivo*

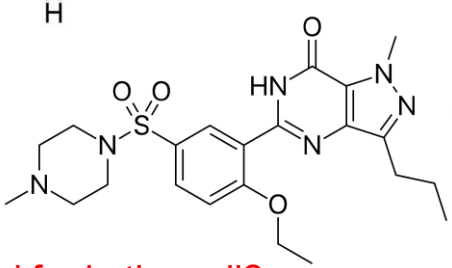


“Lipitor”

- Examples:
  - Atorvastatin (“Lipitor”)
  - Staurosporine aglycone
  - Sildenafil (“Viagra”)



Staurosporine aglycone



“Viagra”

Q: How can the effect of a competitive inhibitor be compensated for in the cell?

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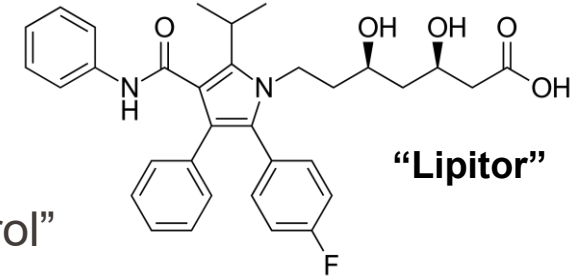
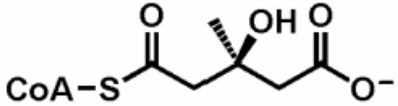
Atorvastatin ("Lipitor")

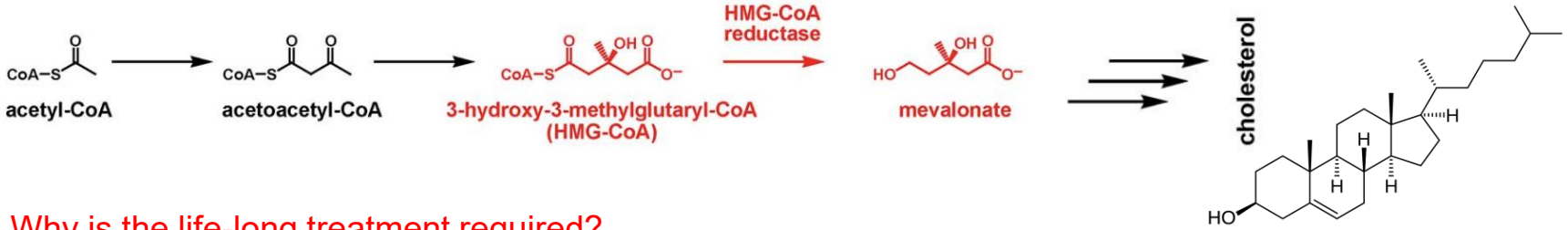
- Statin for oral treatment of cardiovascular diseases
- Reduces cholesterol biosynthesis → reduced levels of low-density lipoprotein (LDL) = "bad cholesterol"
- Inhibitor of HMG-CoA reductase (liver)
- WHO list of "essential medicines"
- Life-long treatment required!



"Lipitor"



HMG-CoA



Q: Why is the life-long treatment required?

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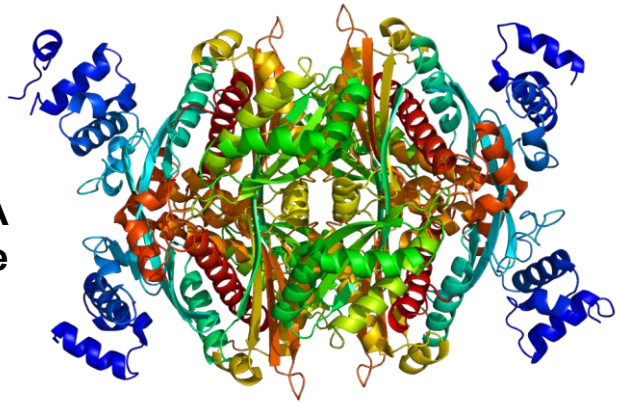
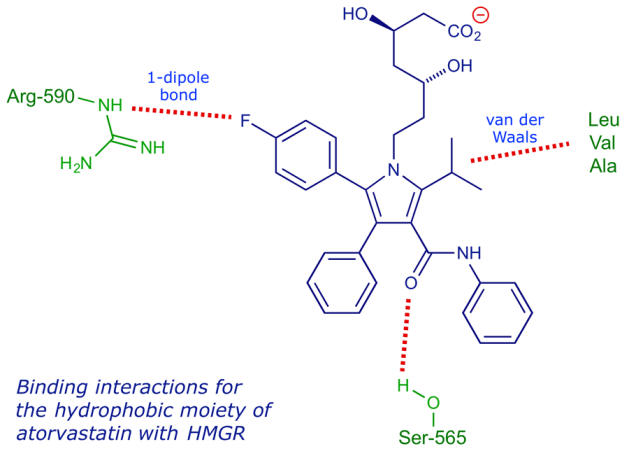
HMG-CoA Reductase Inhibition

HMG-CoA reductase

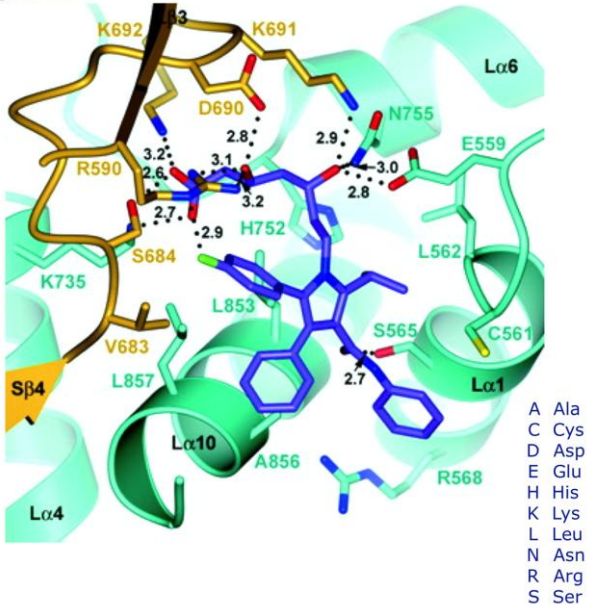




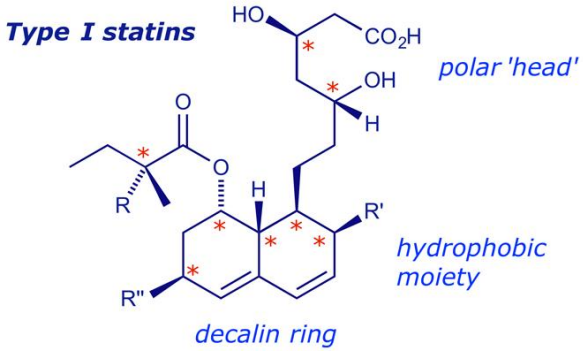
Binding interactions for the hydrophobic moiety of atorvastatin with HMGR

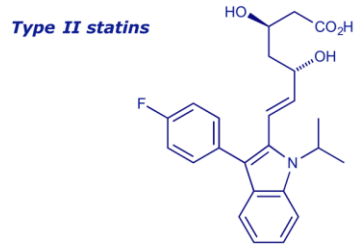
Istvan and Deisenhofer, *Science*, 2001, **292**, 1160

Figure 4E



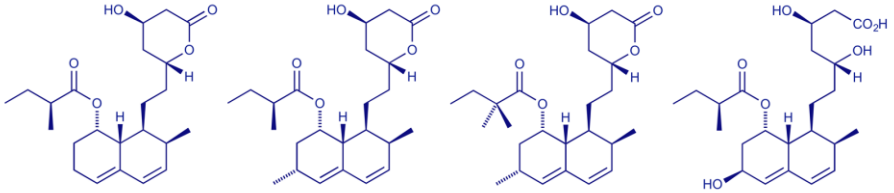
Statins – Overview





Fluvastatin
IC_{50} 28 nM

Cerivastatin
IC_{50} 10 nM

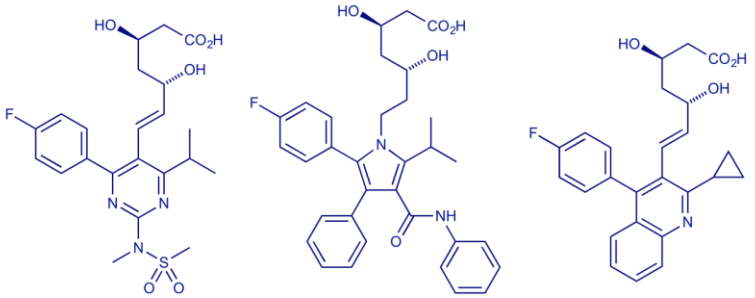


Compactin (mevastatin)
IC_{50} 23 nM

Lovastatin
IC_{50} 24 nM

Simvastatin
IC_{50} 11 nM

Pravastatin



Rosuvastatin
IC_{50} 5 nM

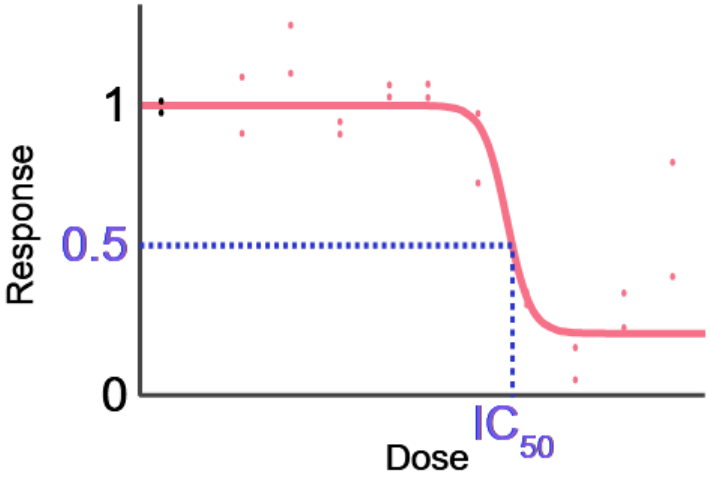
Atorvastatin
IC_{50} 8 nM

Pitavastatin
IC_{50} 6.8 nM

Q: Why are type I statins difficult to synthesize?

IC_{50}

- Half maximal inhibitory concentration
- Metric for potency of an inhibitor



- Not the same as the affinity/dissociation constant K_d / K_i , but related!

- For enzymatic reactions and competitive inhibition: $$K_i = \frac{IC_{50}}{1 + \frac{[S]}{K_m}}$$

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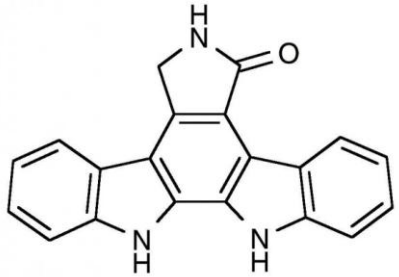
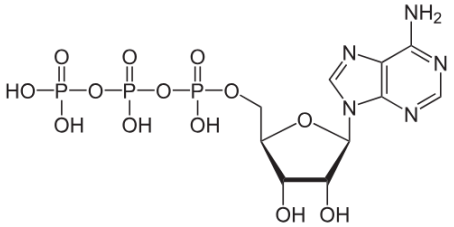
Staurosporine Aglycone

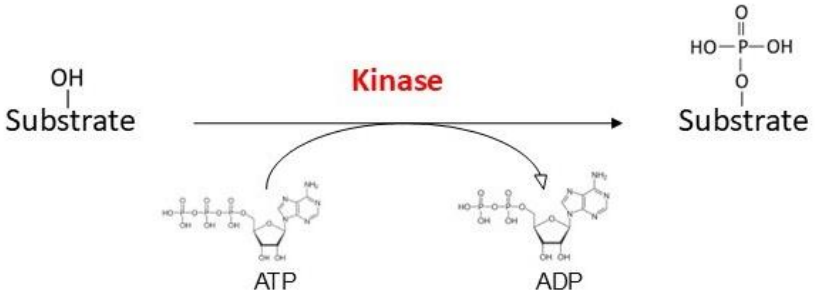
- Inhibitor of protein kinases
- Competitive binding of ATP site
- Broad-spectrum of targets
- Anti-microbial, anti-cancer etc.

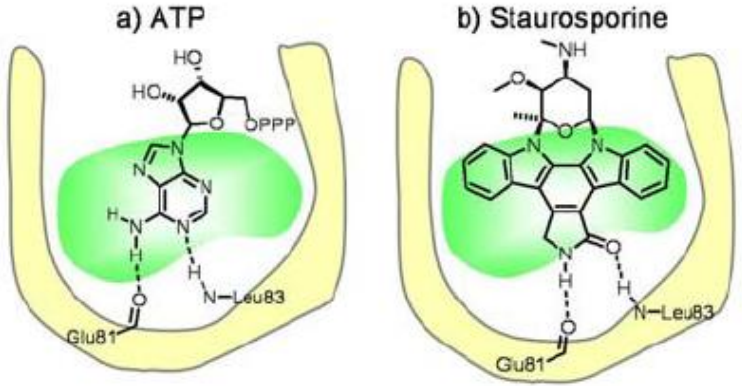


Staurosporine aglycone



ATP





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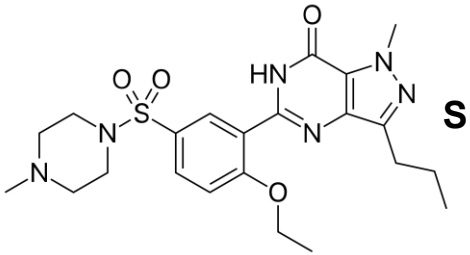
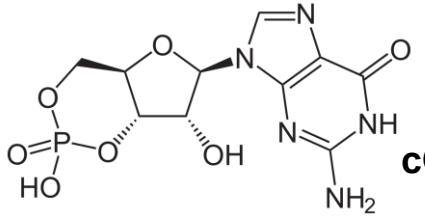
Sildenafil (“Viagra”)

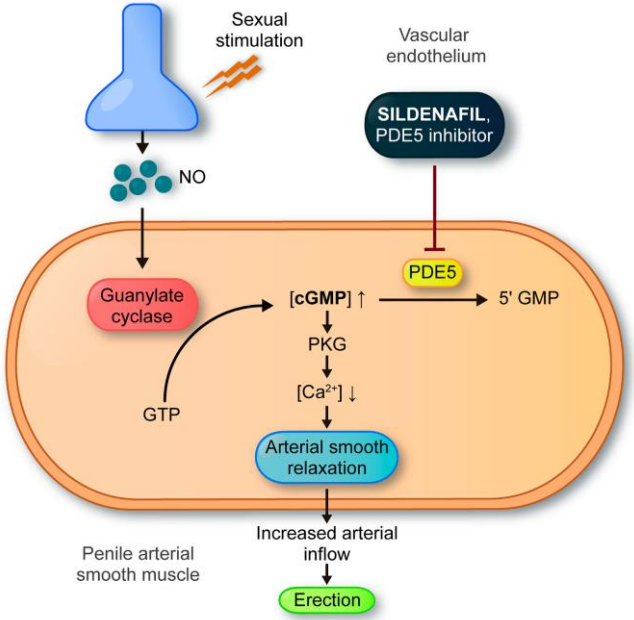
- Inhibitor of phosphodiesterase 5 (PDE5)
- PDE5 promotes breakdown of cGMP
- cGMP regulates blood flow through smooth muscle relaxation
- Erectile dysfunction, pulmonary hypertension etc.



Sildenafil



cGMP



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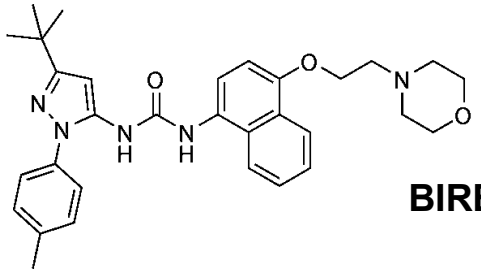
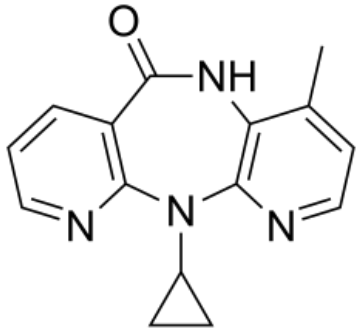
Non-competitive Inhibitor Drugs

- Allosteric binding to target
- No structural resemblance to substrate
- Difficult to design, discovery by screening
- Not outcompeted by natural substrate



BIRB 796

- Examples:
  - BIRB 796
  - Nevirapine



Nevirapine

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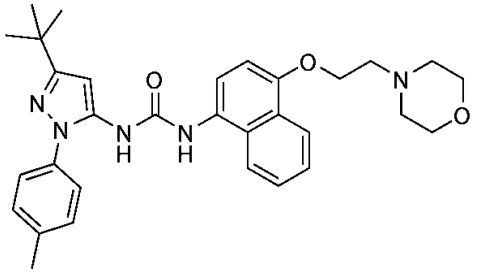
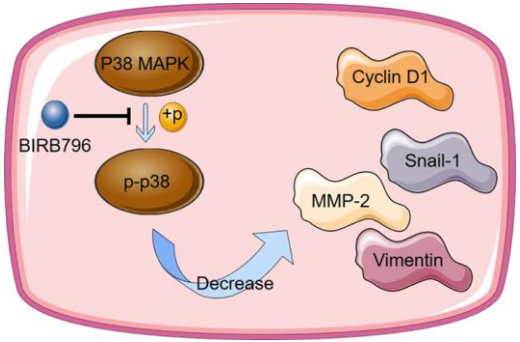
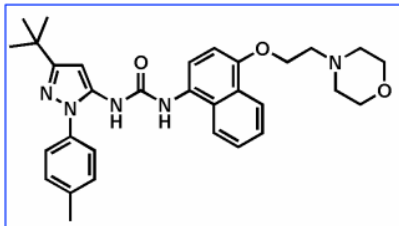
BIRB 796



- Inhibits p38 MAP (mitogen-activated protein) kinase
- P38 MAP kinase:
  - Stress response
  - Regulates cell differentiation, apoptosis, autophagy etc.
- BIRB 796 inhibits uncontrolled proliferation

→ anti-tumor (e.g. glioblastoma), anti-inflammatory etc.





BIRB 796

$k_{on} = 8.5 \times 10^4\ M^{-1}s^{-1}$

$k_{off} = 8.3 \times 10^{-6}\ s^{-1}$

$K_d = 0.1\ nM$

$$K_d = \frac{k_{off}}{k_{on}}$$

Pargellis *et al.*, *Nat Struct Mol Biol* (2002) **9**, 268

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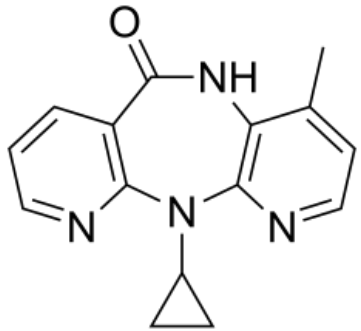
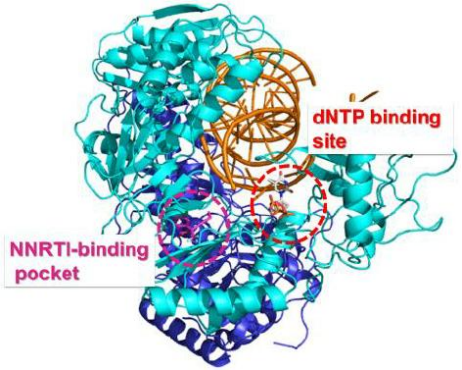
Nevirapine

- Non-nucleoside inhibitor of HIV reverse transcriptase (NNRTI)
- Binds to allosteric site (“NNRTI pocket”)
- HIV therapy
- WHO standard: antiretroviral (ART) regimen

→ combination with other drugs (e.g. AZT)



Nevirapine



Q: What does the reverse transcriptase do?

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