

Farmacochemie van geneesmiddelen

voor cardiovasculaire aandoeningen

FA-BA302: Cardiovasculaire aandoeningen

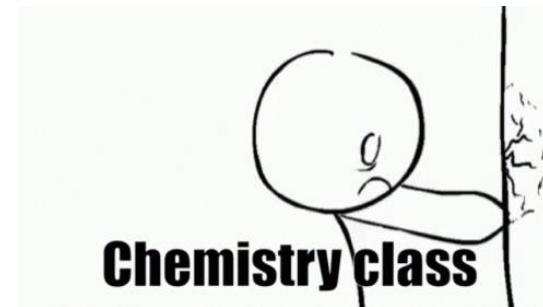
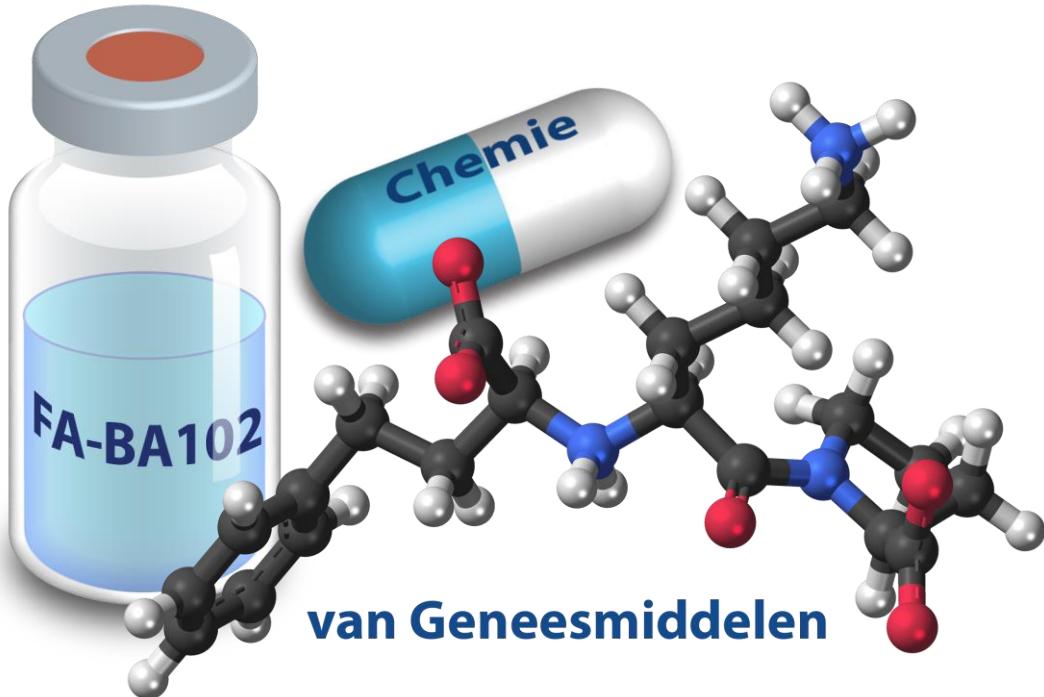
15 November 2024

Dr. Irene van den Broek

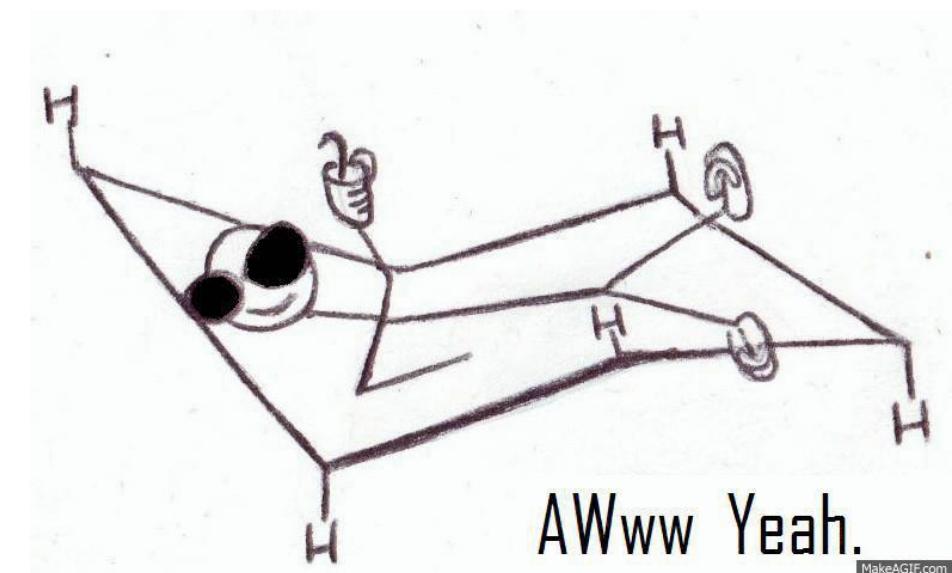
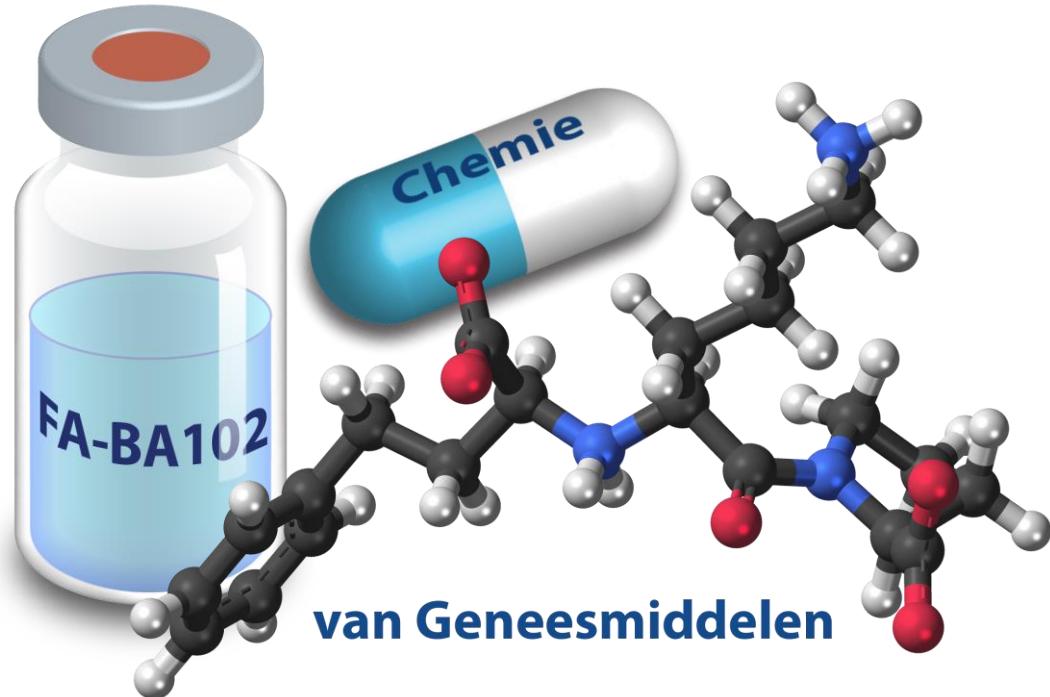
i.vandenbroek@uu.nl



Chemie van geneesmiddelen... lang geleden!



Chemie van geneesmiddelen... lang geleden!



Hoorcollege Farmacochemie



Wat?



Waarom?



Hoe?



Wat?

relatie pH en logP

resonantie

prodrugs

functionele groepen

pKa

metabole (afbraak)processen

nucleofiel - elektrofiel

lipofiel - hydrofiel

stereochemie

ladingstoestand

oplosbaarheid

elektronegativiteit

absorptie

orale beschikbaarheid

geneesmiddelinteracties

logP

(bio)isosteren

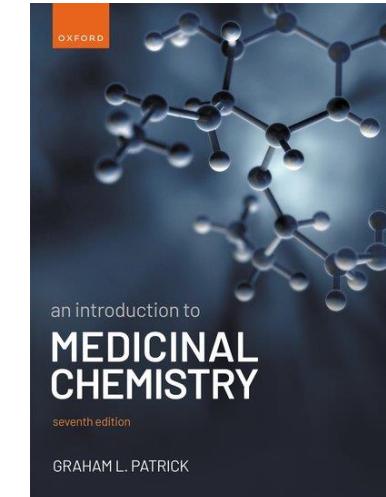
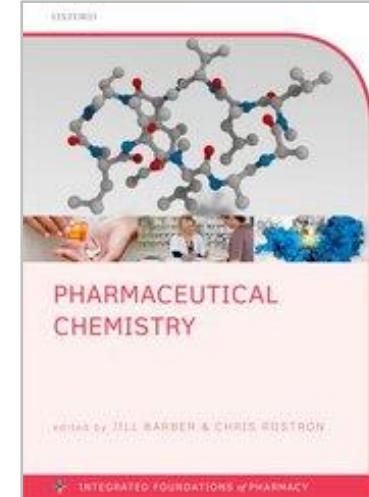
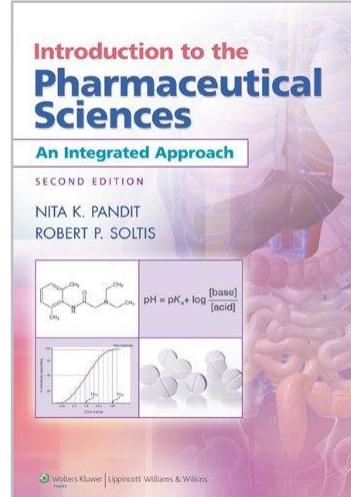
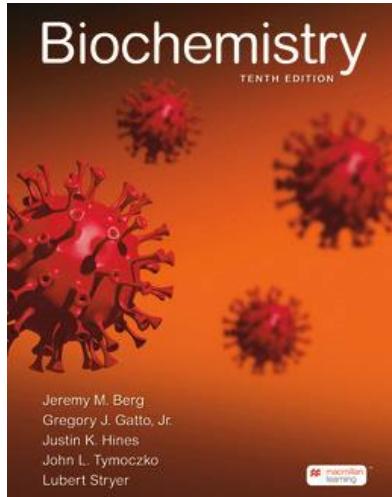
farmacofoor

bindingsinteracties

Boeken

O.a.:

- **Stryer**, Biochemistry
- **Pandit**, Pharmaceutical Sciences
- **Barber**, Pharmaceutical Chemistry
- **Nieuw**: Patrick, An introduction to Medicinal Chemistry



Blackboard

Course content > cursusmateriaal week 1 > Studiematerialen Farmacochemie (BA102)

FA-BA102
Chemie van Geneesmiddelen

TW270820 versie 3

Cursuswijzer FA-BA102
Bacheloropleiding Farmacie
Undergraduate School Bètawetenschappen
Faculteit Bètawetenschappen
Universiteit Utrecht
Studiejaar 2020/2021, periode 1

Te kennen functionele groepen	
R = C	
R-OH	alcohol
	aldehyde
	keton
	carbonzuur
	ester
R-O-R'	ether
R-SH	thiol
R-S-R'	thioether of sulfide
	sulfoxide
	sulfonzuur
	sulfon
	hemi-acetaal (koolhydraten)
R = H of C	
	amide
	sulfonamide
	alkeen
	alkyn

Te kennen triviale namen	
CH ₃ OH	methanol
CH ₃ CH ₂ OH	ethanol
	1-propanol
	2-propanol
	glycerol
	fenol
	benzeen
	tolueen
	azijnzuur
	benzoëzuur
	acetamide
	ureum
	β-lactam
	pyridine
	piperidine
	imidazool
	pyrrol
	aniline
	diethylether
	aceton
	aceetaldehyde
	triethylamine

Blackboard

Course content > cursusmateriaal week 1 > Studiematerialen Farmacochemie (BA102)

Te kennen pK_a 's

zure vorm (HA of BH^+)	pKa	geconjugeerde base (A^- of B)
	16	
	10	
	4	
	10	
	< 0	
	17	
	> 30	
	5	
	5	
	7	

pKa van alle **alcoholen ROH** is ongeveer 16, niet erg zuur dus, sterk basisch milieu nodig om ze te deprotoneren

aromatiche alcoholen, **fenolen** zijn aanzienlijk zuurder dan alifatische alcoholen ROH

pKa van alle **carbonzuren RCO_2H** is ongeveer 4, ze zijn dus zuur

amines zijn basen en de pKa van alle geprotoneerde **amines HN^+R_3** (dus primaire, secundaire en tertiare amines) is ongeveer 10

amides zijn geen basen

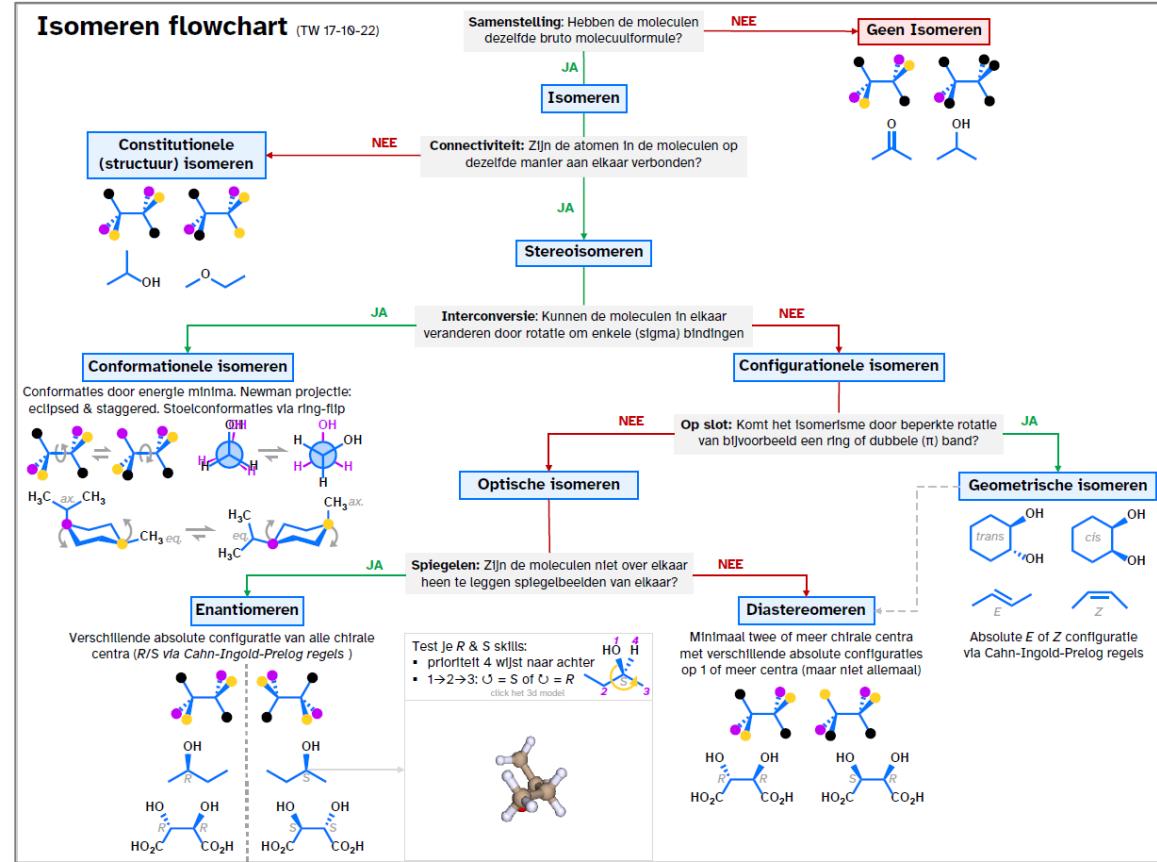
een **amide** proton kan wel verwijderd worden, in sterk basisch milieu, vergelijk met ROH

een neutrale **amine** met een proton (HNR_2) is geen zuur

een **aromatiche amine** is veel minder basisch dan een amine zonder aromaat eraan

pyridine is een base

imidazool is een base



Kennisclips chemie



[https://video.uu.nl/channels/#chemie-kennisclips-voor-bachelor-farmacie 66504](https://video.uu.nl/channels/#chemie-kennisclips-voor-bachelor-farmacie_66504)

o.a.:

- Zuren en basen
- Hydrofiel en hydrofoob
- Log P en Log D
- Resonantie
- Stereoisomeren
- Reactiemechanismen

Main channels > Personal channels > Tom Wennekes > Kennisclips over Chemie voor de...

Kennisclips over Chemie voor de Bachelor Farmacie

Used size: 10.33 GB

Filters Select

Medias

Atoomopbouw: hoe kwamen we er achter?
De elektronen zitten verdeeld over de massa van het atoom

18 m 22 s

Een Sucrose molecuul is erg klein! hoe klein?
Hoeveel keer kleiner dan een appel?

30 m 38 s

Covalente bindingen in moleculen door hybridisatie van atoom orbitalen
 $S + p_x + p_y + p_z = 4 \times sp^3$

28 m 20 s

Kennisclip 1: Atomen...
385 views - 1 year ago

Kennisclip 2: Molecu...
285 views - 1 year ago

Kennisclip 3: Hybridi...
410 views - 1 year ago

Wat? is farmacochemie

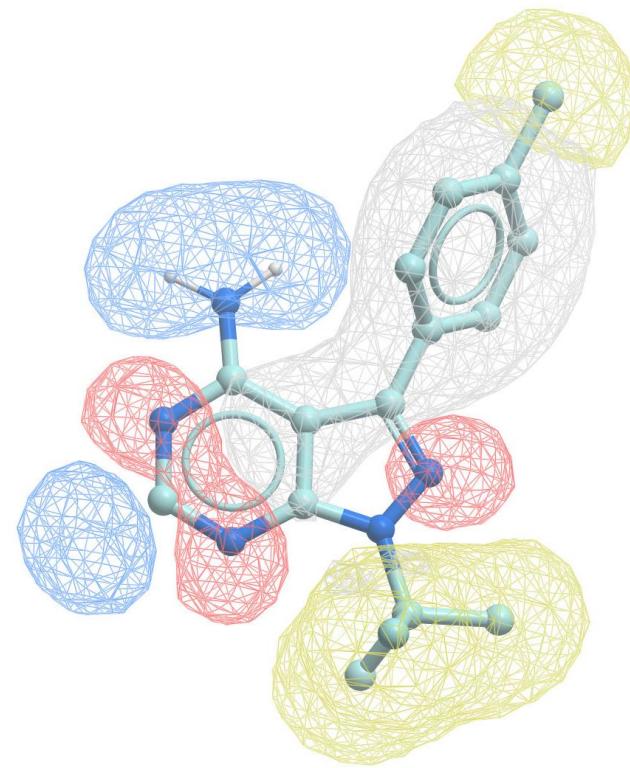
Begrippen binnen de ontwikkeling
van geneesmiddelen.



Wat is Farmacochemie?

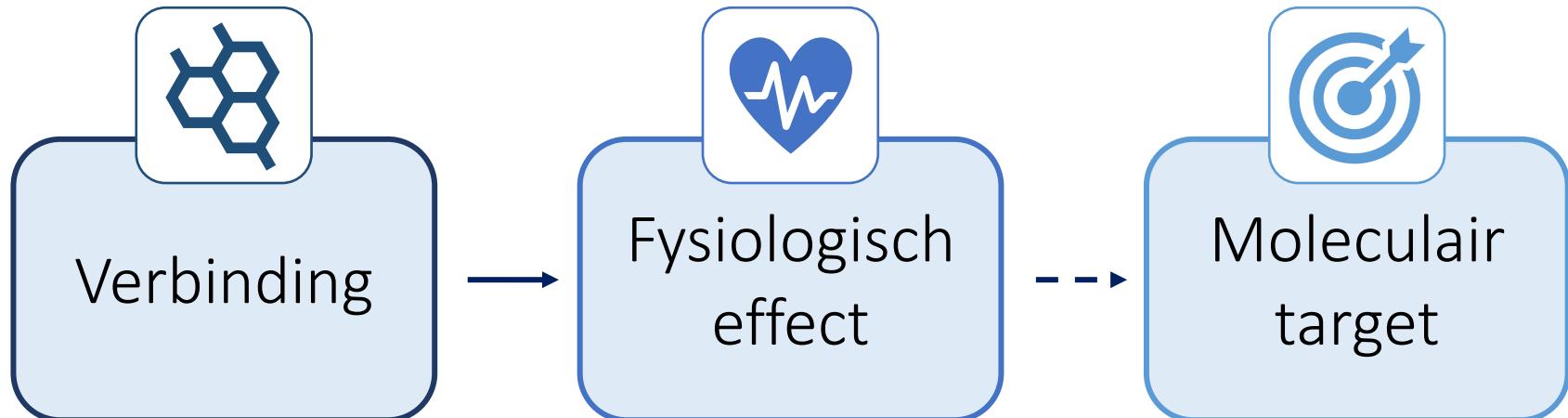
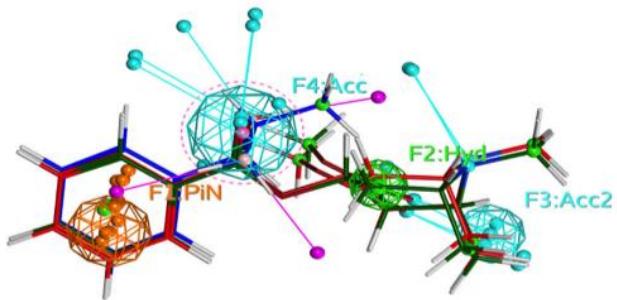
- *Het ontwerpen en synthetiseren van verbindingen met een geselecteerde **biologische activiteit**;*
- *De bestudering van de relatie tussen de **structuur** en de biologische activiteit en op basis daarvan het ontwerpen van nieuwe, voor de bedoelde activiteit **geoptimaliseerde** verbindingen.*

– H. Timmerman, Teaching medical chemistry: an introduction.



Geneesmiddelontwikkeling: 2 manieren

1) Farmacofoor

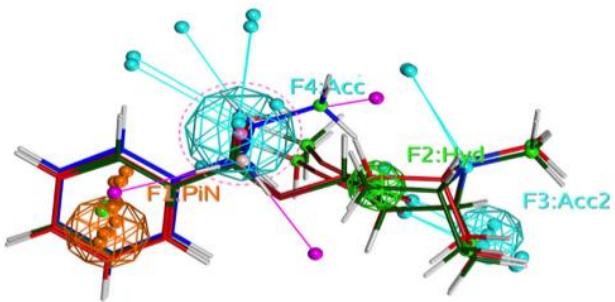


2) Receptor / Target

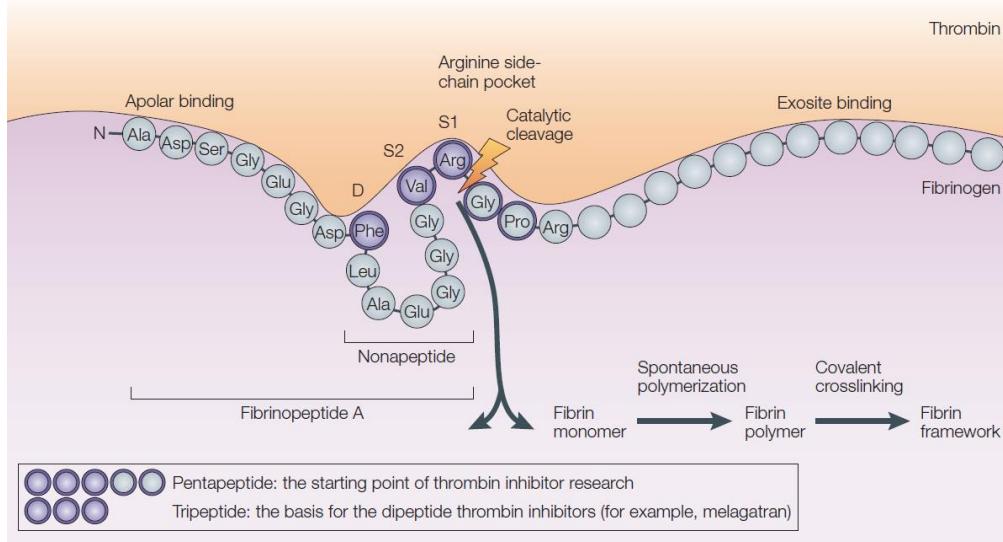
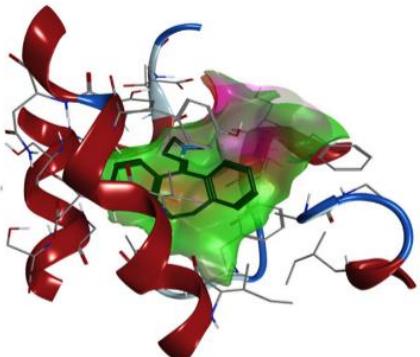


Geneesmiddelontwikkeling: 2 manieren

1) Farmacofoor



2) Receptor / Target



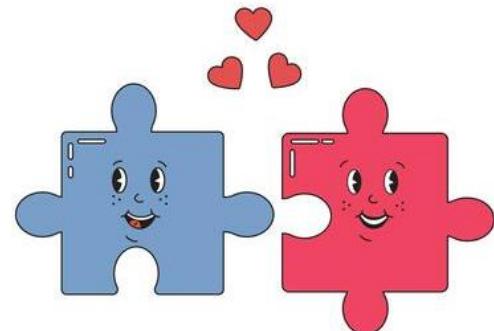
(Nieuwe) begrippen



Biologische activiteit



Bindings-interacties



Farmacofoor



(Bio-) isosteren



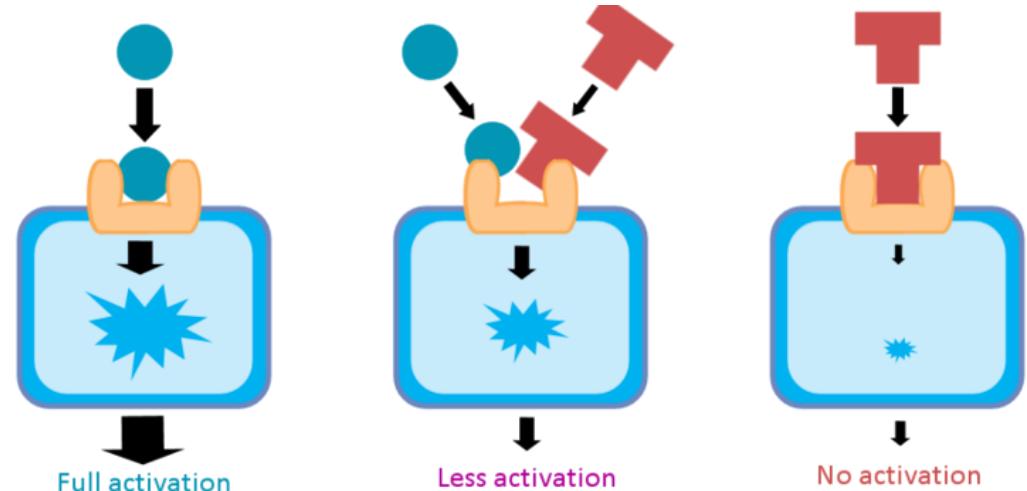
Biologische activiteit

- De mate van de (on)gewenste fysiologische respons van een geneesmiddel
 - **Werkzaamheid (Efficacy):** Het maximale biologische effect dat door het geneesmiddel kan worden bereikt.
 - **Potentie:** De hoeveelheid geneesmiddel die nodig is om het gewenste biologische effect te bereiken.
 - **EC₅₀:** De concentratie die nodig is om 50% van het maximale biologische effect te bereiken.
 - **ED₅₀:** De dosis waarbij 50% van de populatie het gewenste biologische effect ondervindt.
 - **IC₅₀:** De concentratie die nodig is om een biologisch process met 50% te remmen.
-
- The graph illustrates the relationship between the biological effect and the logarithm of the drug concentration for four different substances (A, B, C, D). The y-axis represents the 'Effect (%)' from 0 to 100, and the x-axis represents the 'log Concentration'. The curves are sigmoidal, indicating a threshold effect. The distance between the EC₅₀ values of two curves is used to measure their relative potency. The height of the curves at their midpoint is used to measure their relative efficacy. Substance A is the most potent and efficacious, while substance D is the least potent and efficacious.

Affiniteit: hoe sterk bindt het geneesmiddel?

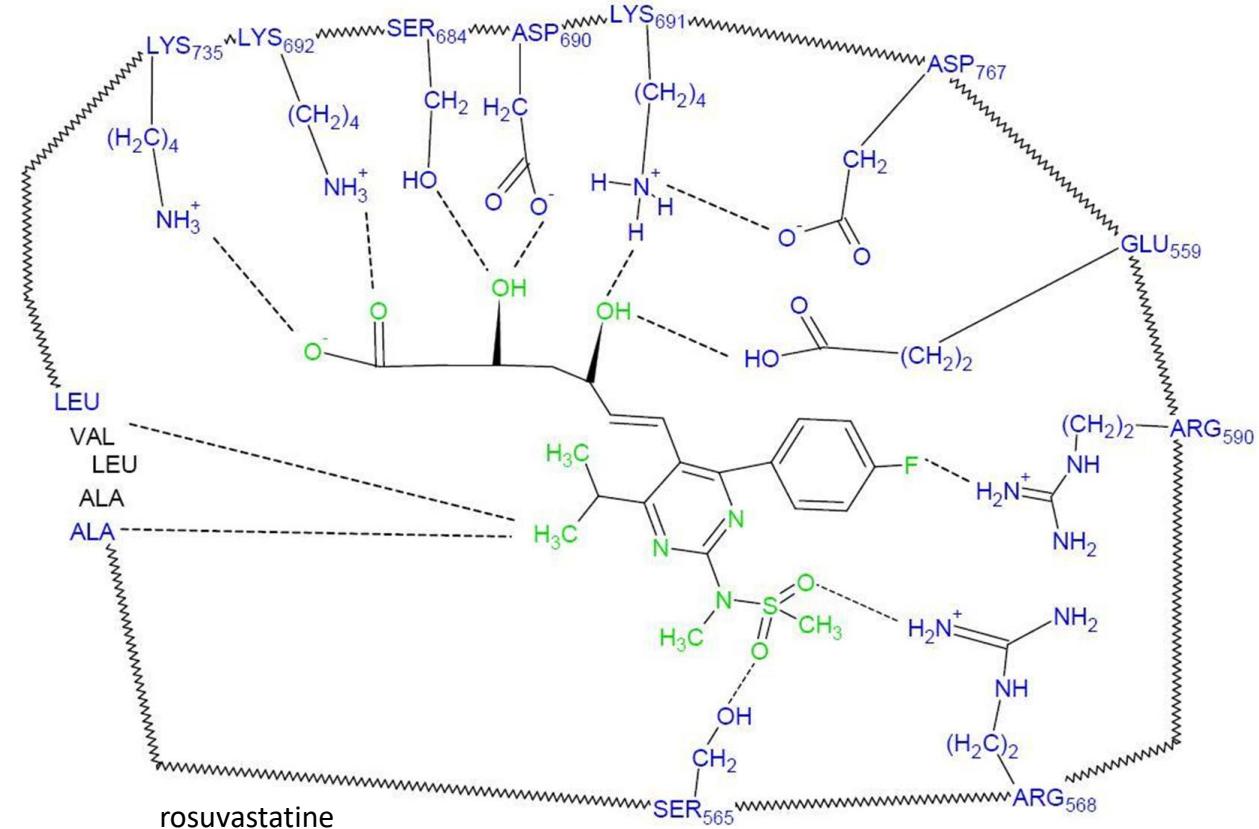
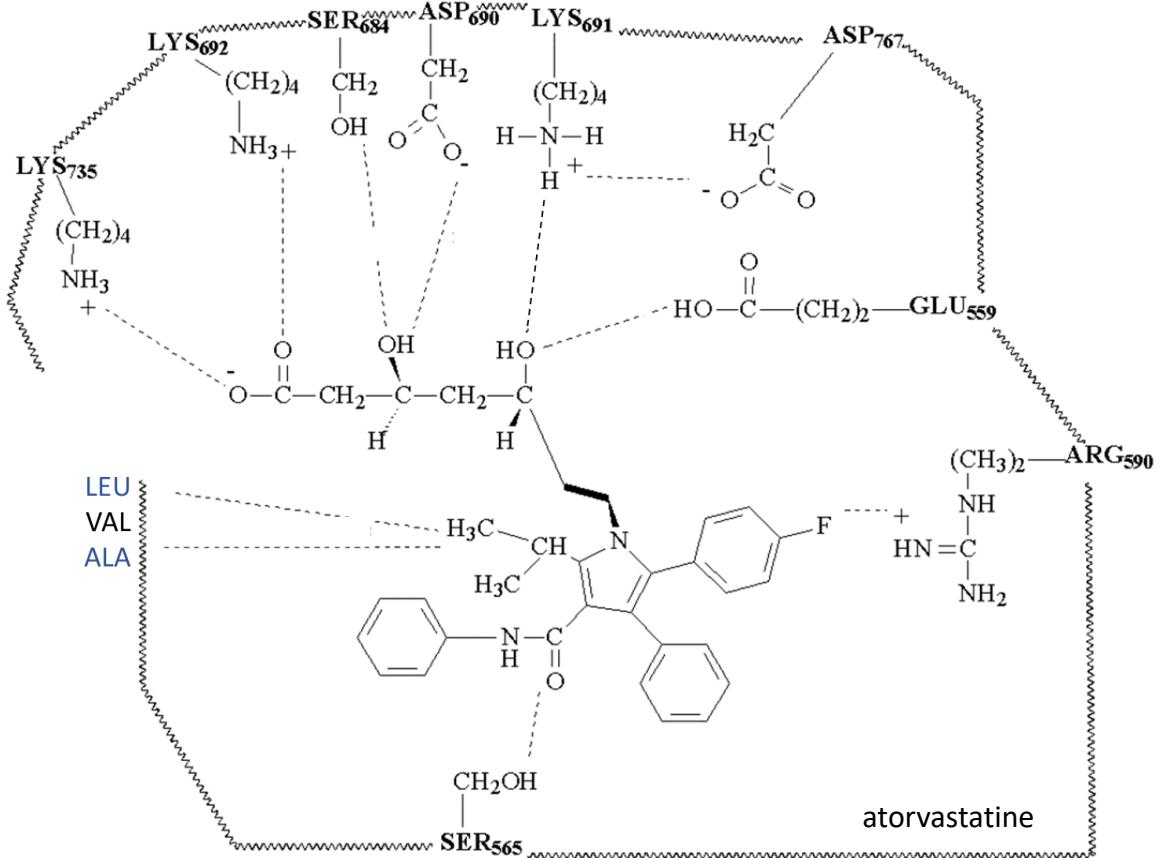
Potentie is afhankelijk van:

- 1) De **affiniteit** van het geneesmiddel voor de bindingssite.
- 2) De **efficiëntie** waarmee de geneesmiddel-receptor interactie is gekoppeld aan de respons.

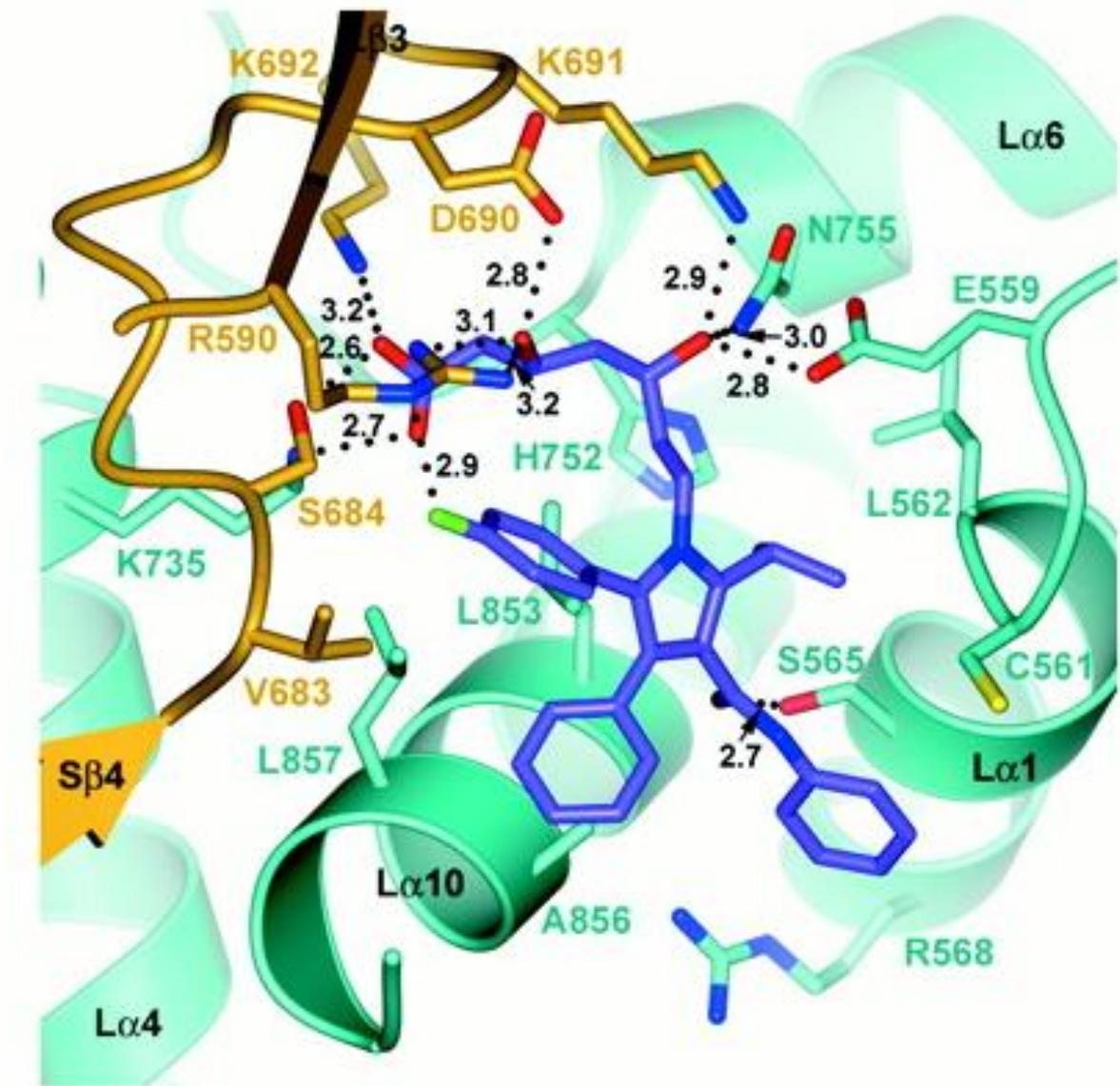
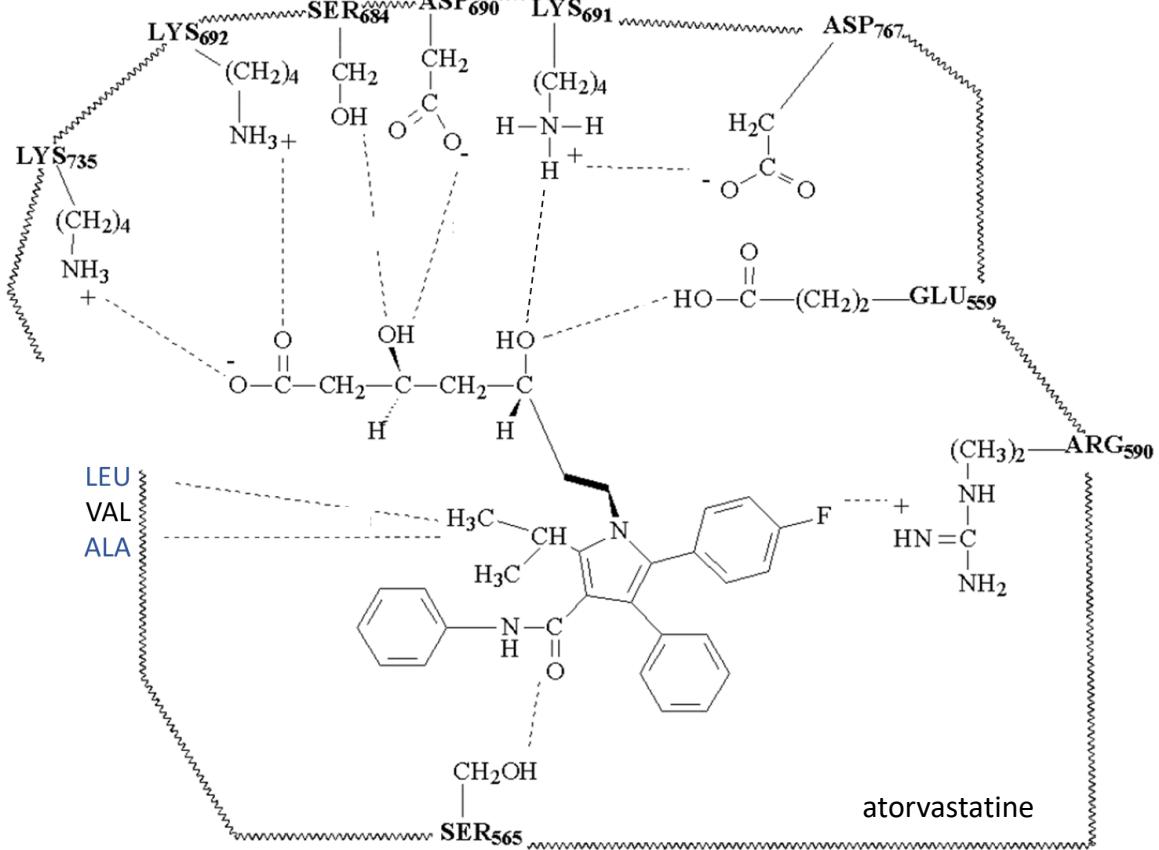


- Het is mogelijk dat een geneesmiddel een hoge affiniteit heeft voor een receptor (i.e., sterke **bindingsinteracties**), maar lage werkzaamheid (efficacy).

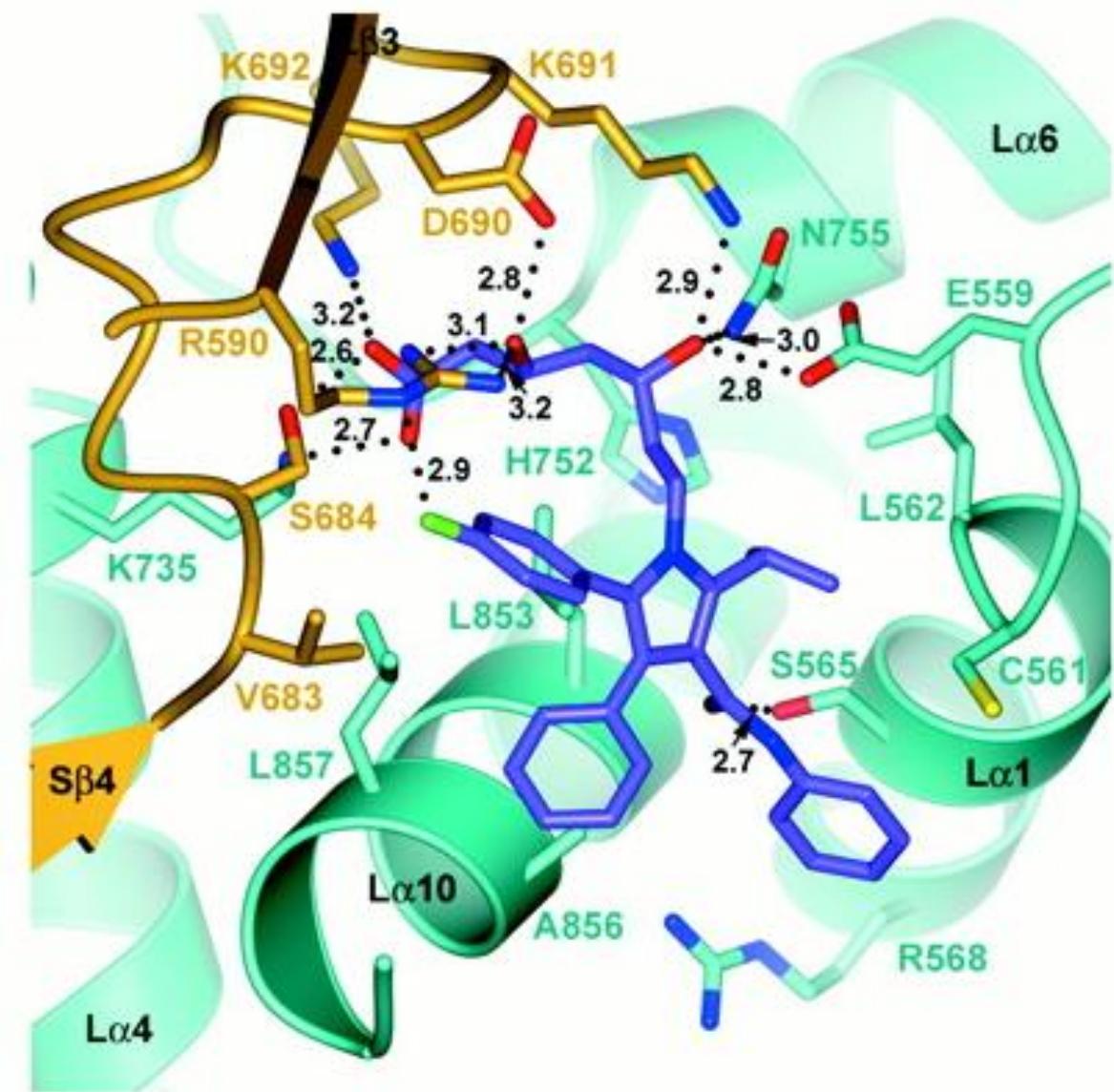
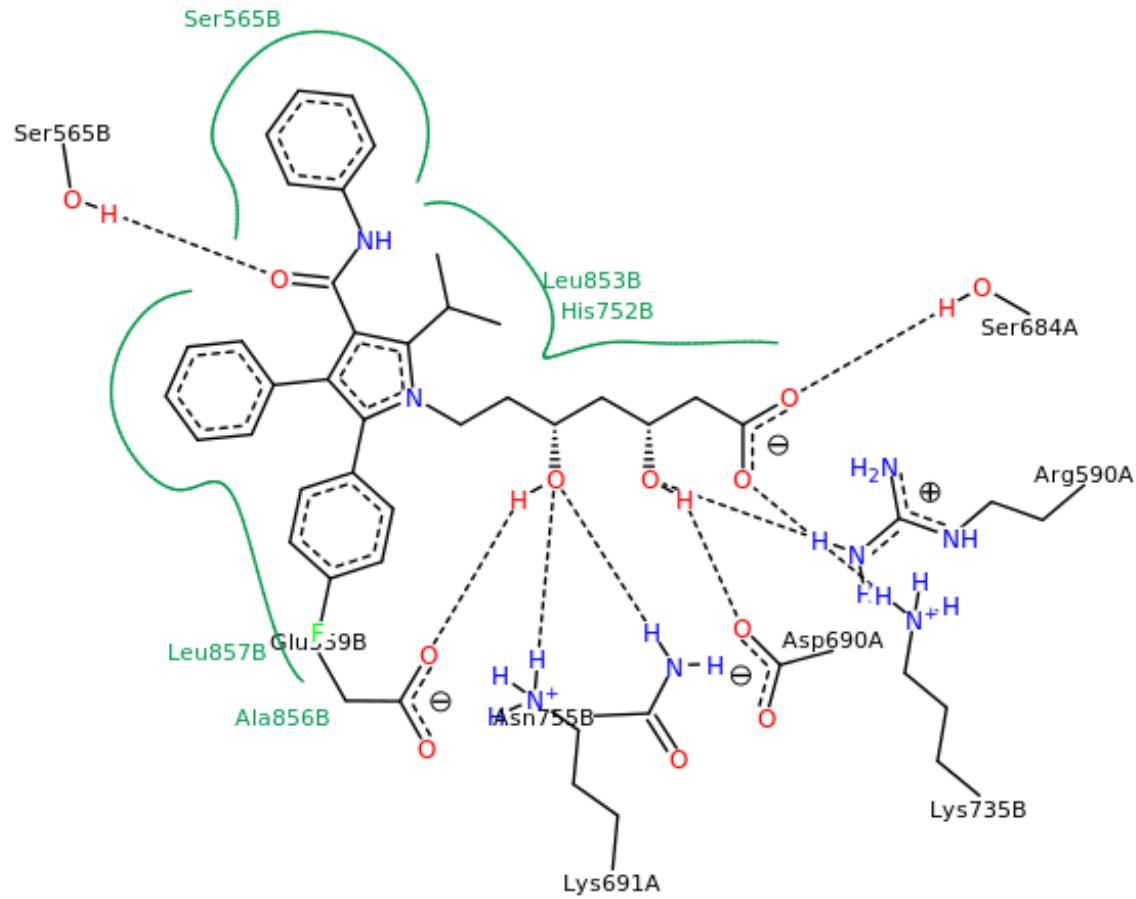
Bindingsinteracties bepalen *affiniteit*



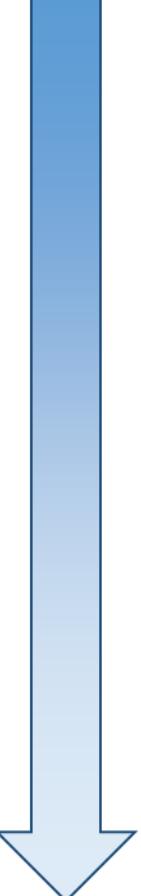
Bindingsinteracties



Bindingsinteracties



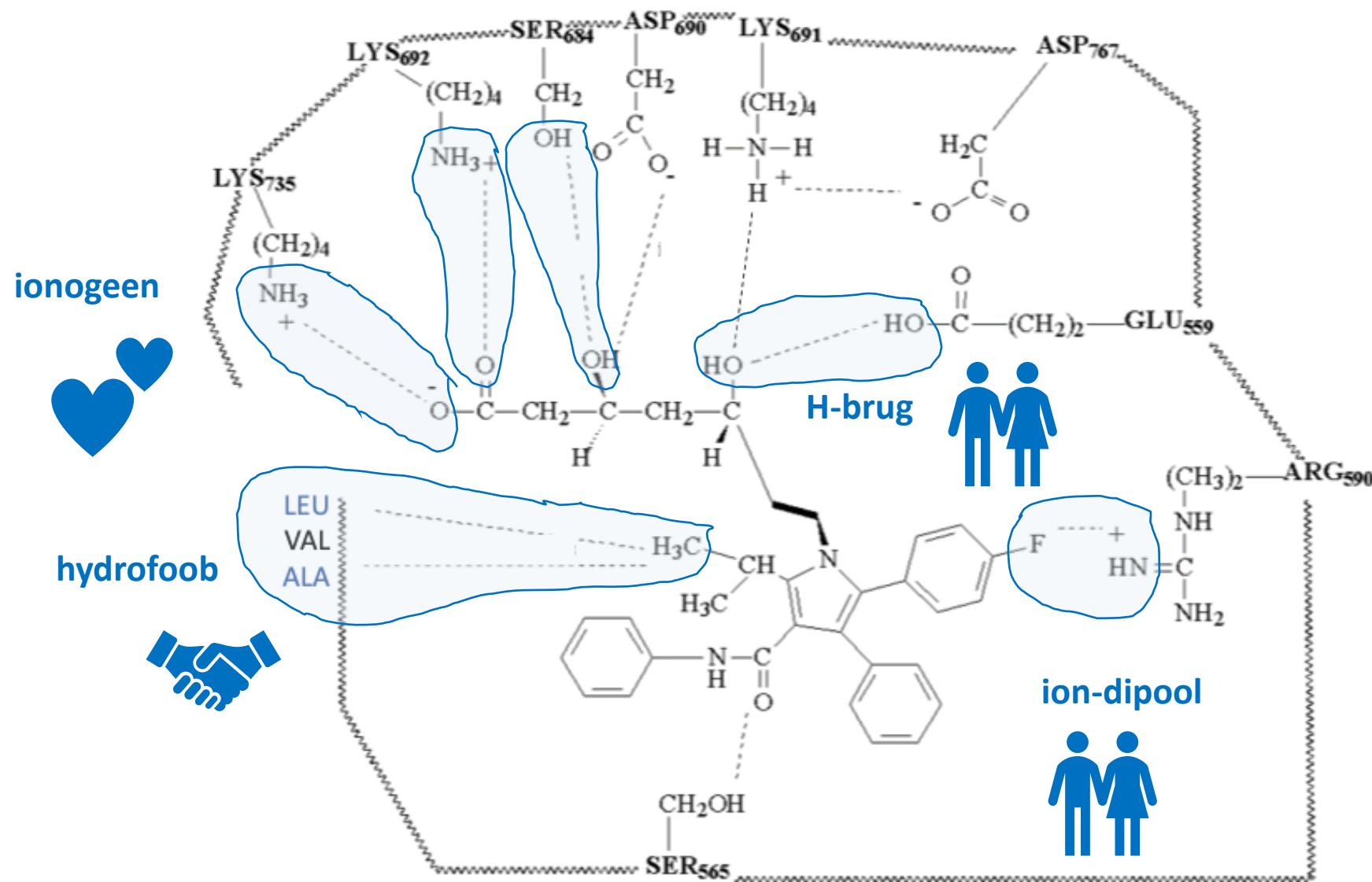
Bindingsinteracties



	Covalent	$\text{---C}(\text{H})\text{---N---Receptor}$
	Ionogeen	$\text{---H}_2\text{N}^{\oplus}\text{---O}^{\ominus}\text{---C}=\text{O---Receptor}$
	Waterstofbrug	$\text{---O---H}^{\delta\oplus}\text{---O}^{\delta\ominus}\text{---C}=\text{O---Receptor}$
	Ion-dipool	$\text{---H}_3\text{N}^{\oplus}\text{---O}^{\delta\ominus}\text{---C}=\text{O---Receptor}$
	Dipool-dipool	$\text{---C=O---O}^{\delta\ominus}\text{---C=O---Receptor}$
	Hydrofoob	$\text{---C}(\text{H})\text{---C}(\text{H})\text{---Receptor}$

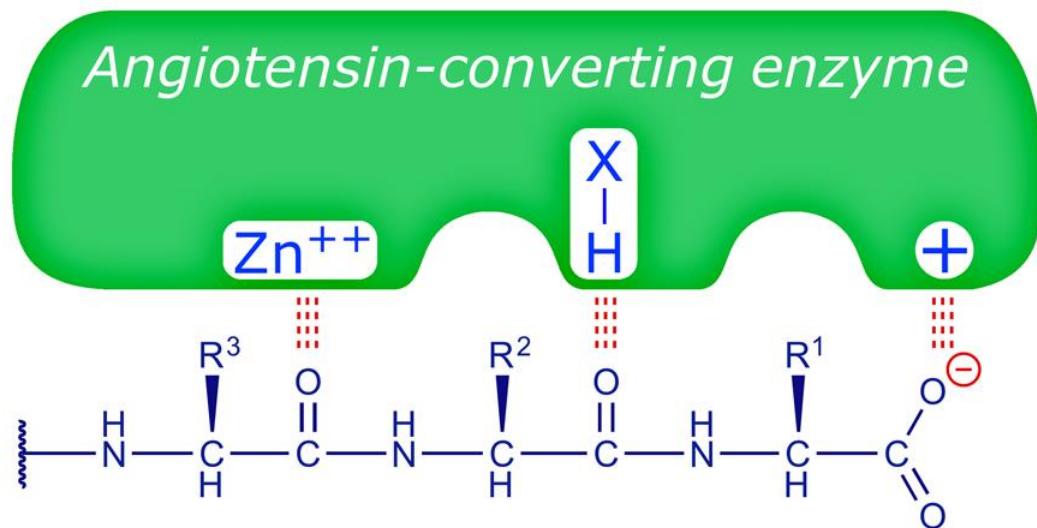
Afnemende
bindingssterkte

Bindingsinteracties

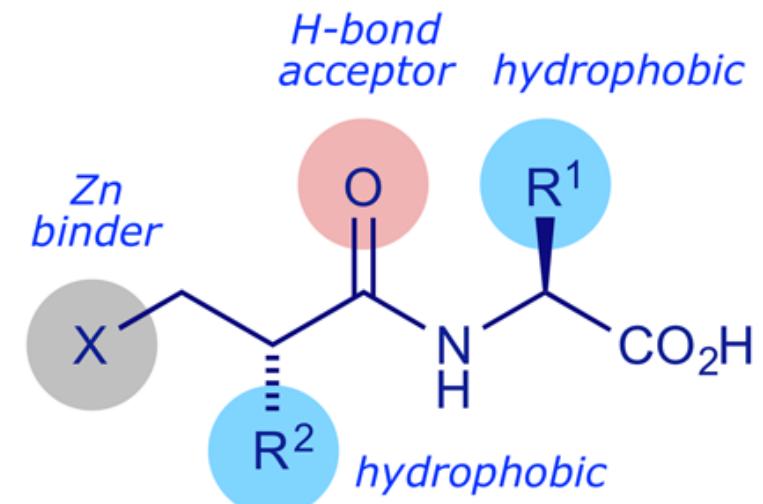


De Farmacofoor

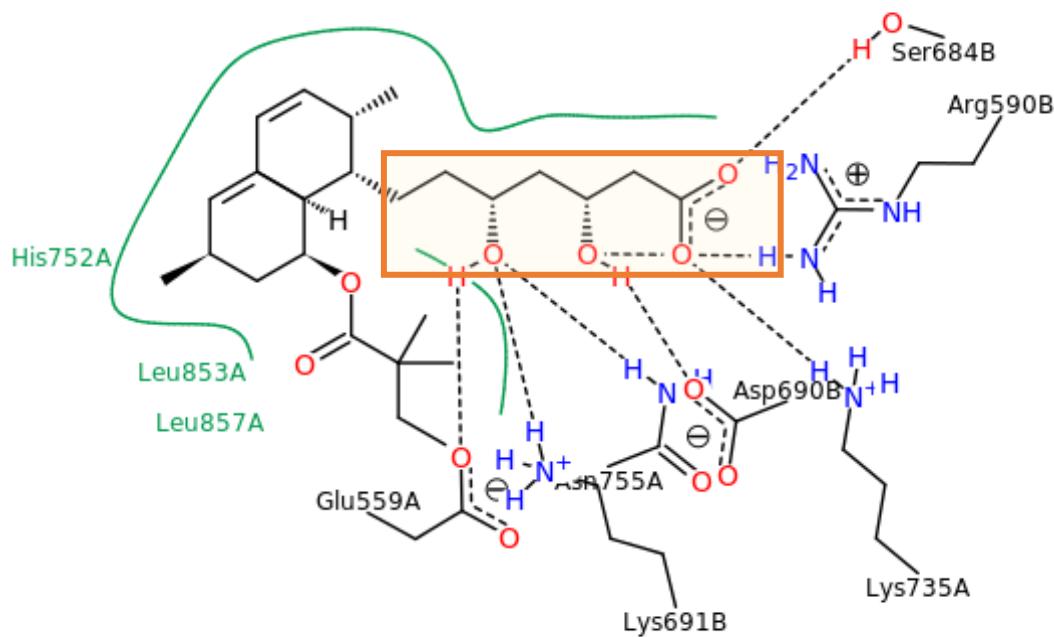
- De atomen en functionele groepen (en hun onderlinge ruimtelijke positionering) die nodig zijn voor een specifieke farmacologische activiteit.



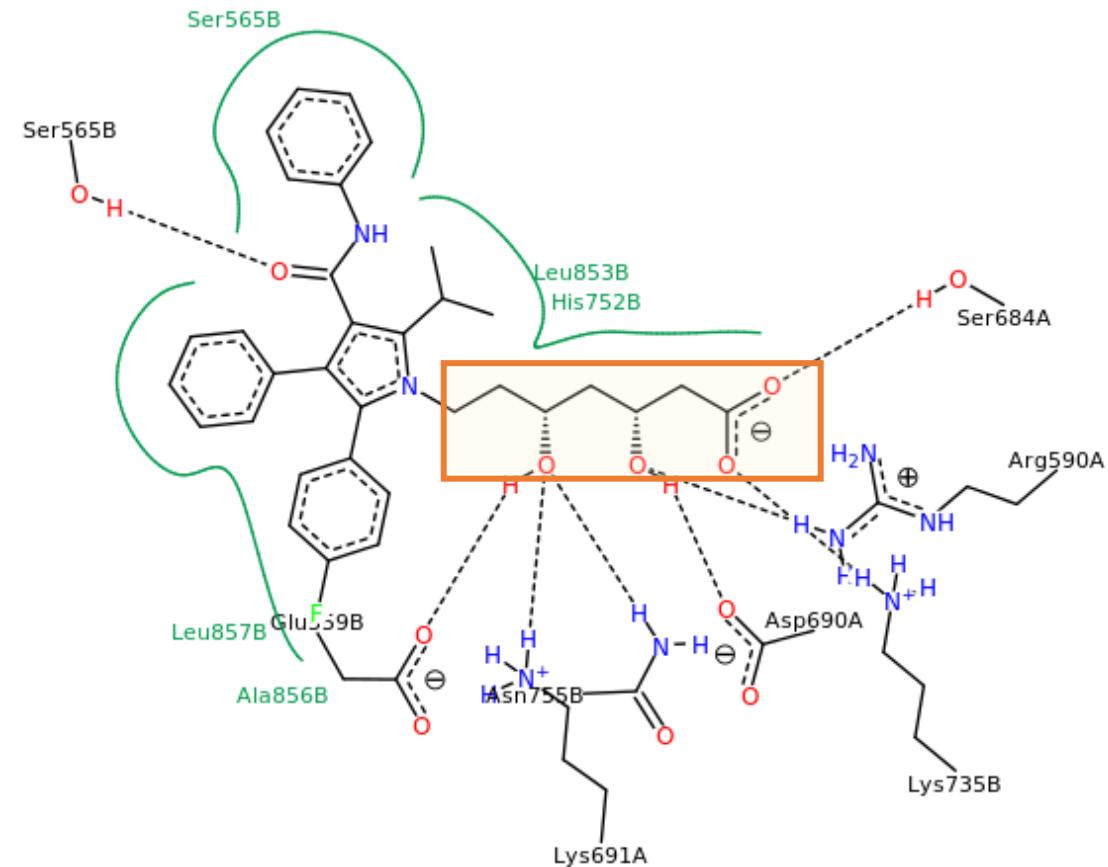
Proposed inhibitors



De Farmacofoor - statines

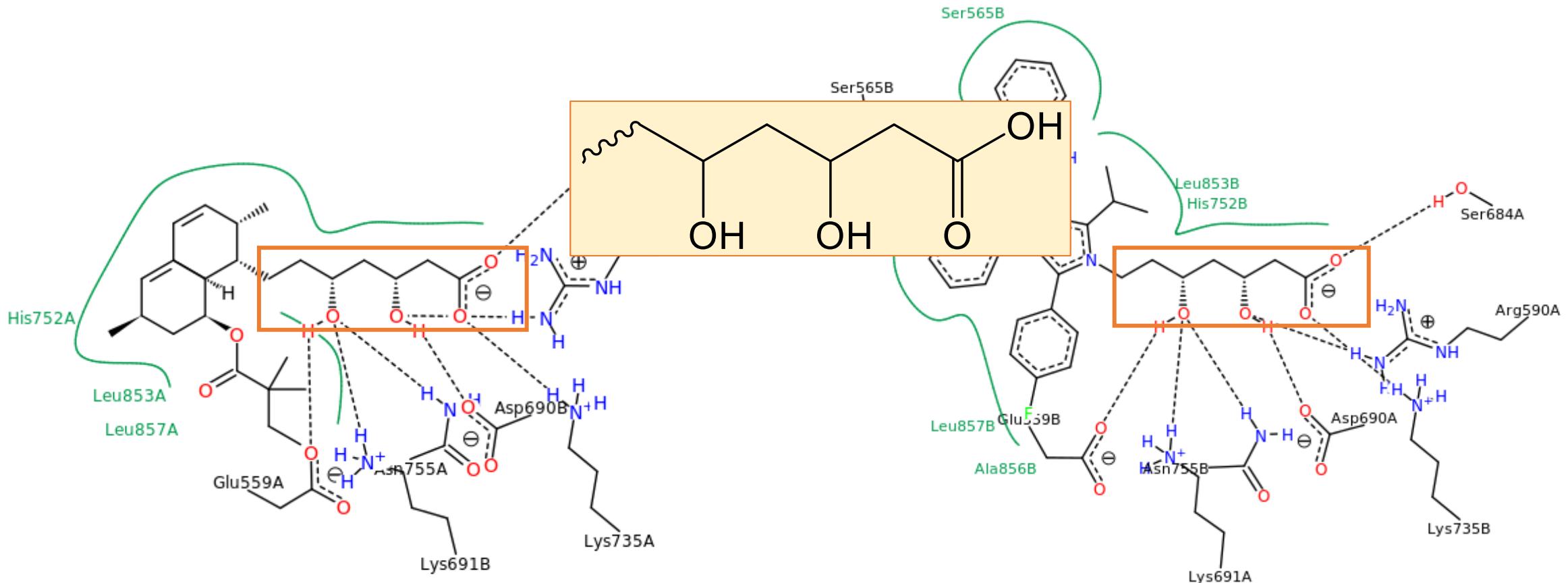


simvastatine



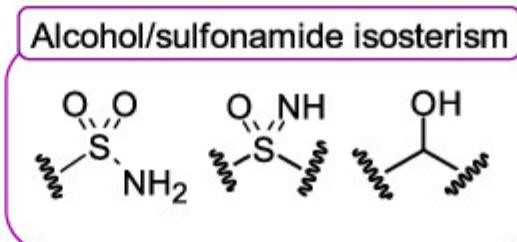
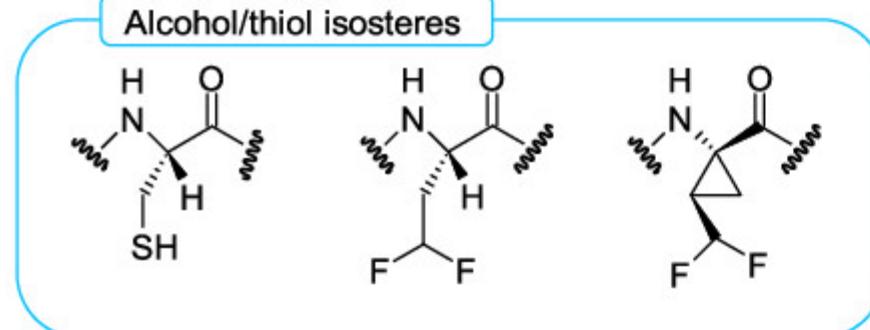
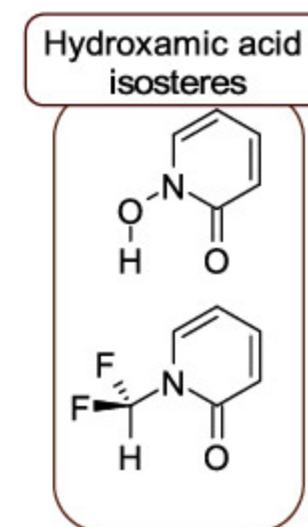
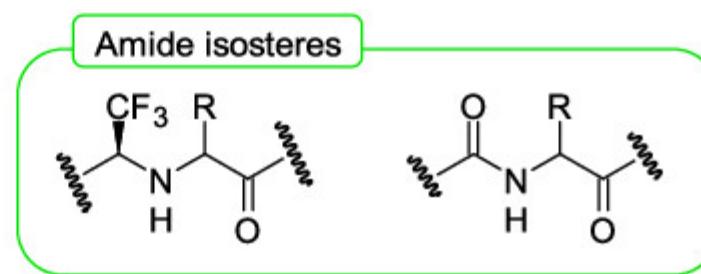
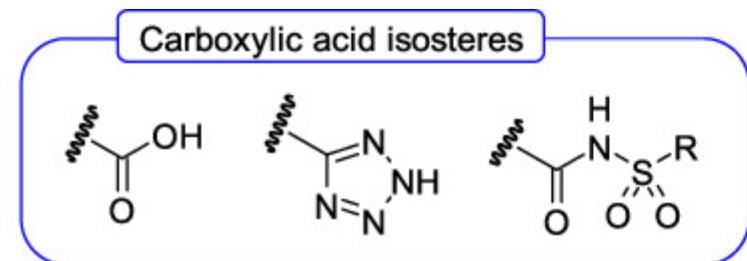
atorvastatine

De Farmacofoor - statines



Bioisosteren

➤ **Bioisosteer:** Een moleculaire eenheid die qua **vorm**, **grootte** en **eigenschappen** een andere eenheid **nabootst** waarbij een belangrijk kenmerk substantieel anders is. Een bioisosteer kan een andere chemische groep kan vervangen zonder de gewenste **biologische activiteit** nadelig te beïnvloeden.



Bioisosteren

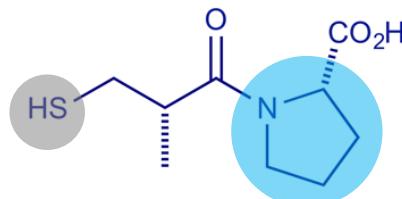
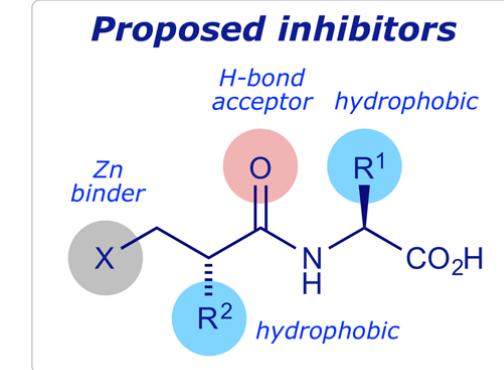
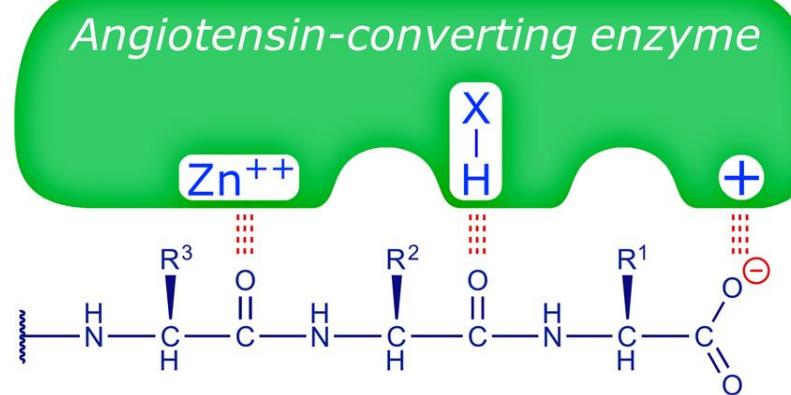
➤ **Bioisosteer:** Een moleculaire eenheid die qua **vorm, grootte en eigenschappen** een andere eenheid **nabootst** waarbij een belangrijk kenmerk substantieel anders is. Een bioisosteer kan een andere chemische groep kan vervangen zonder de gewenste **biologische activiteit** nadelig te beïnvloeden.

Waarom?

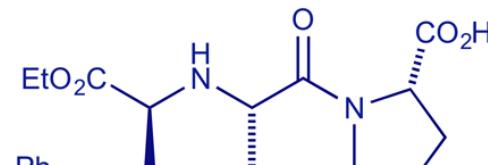
- Verbeteren potentie
- Verminderen bijwerkingen
- Verminderen toxiciteit
- Verbeteren biologische beschikbaarheid
- Verbeteren selectiviteit
- Verbeteren stabiliteit



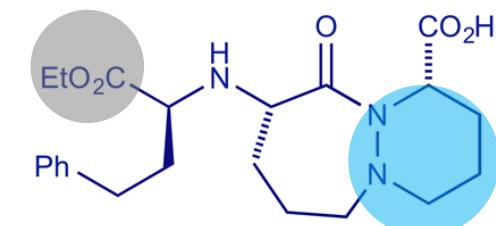
Bioisosteren – ACE remmers



captopril
Capoten; Squibb, 1981



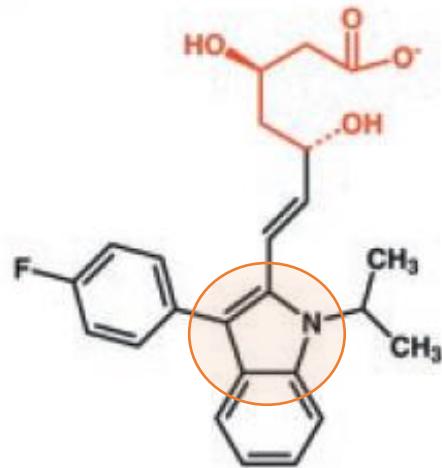
enalapril
Merck & Co., 1985



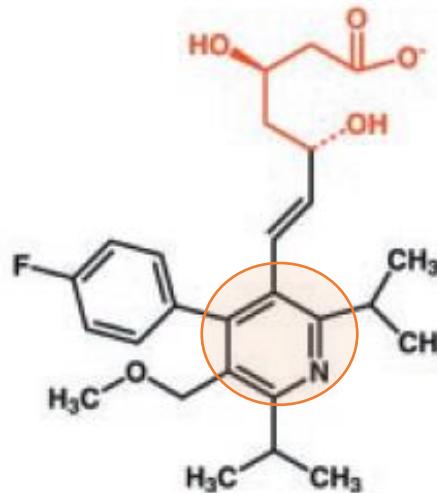
cilazapril
Roche, 1989

Bioisosteren - statines

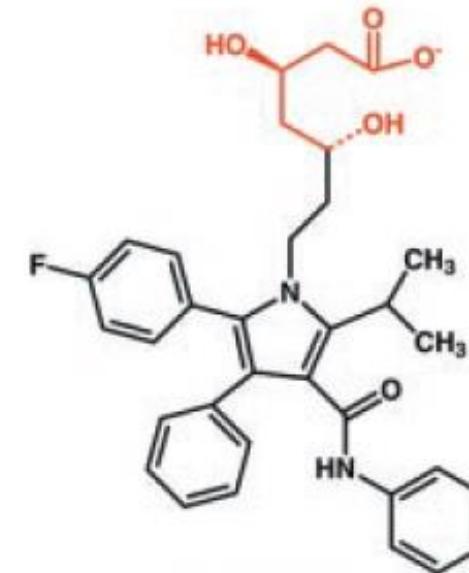
Type 2



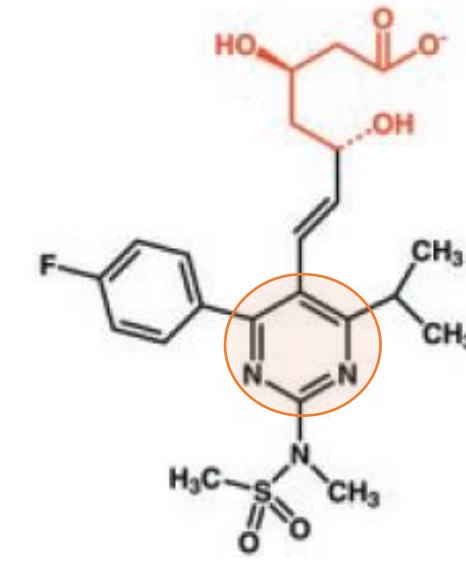
Fluvastatin
 $(IC_{50} = 28\text{nM})$



Cerivastatin
 $(IC_{50} = 10\text{nM})$



Atorvastatin
 $(IC_{50} = 8\text{nM})$



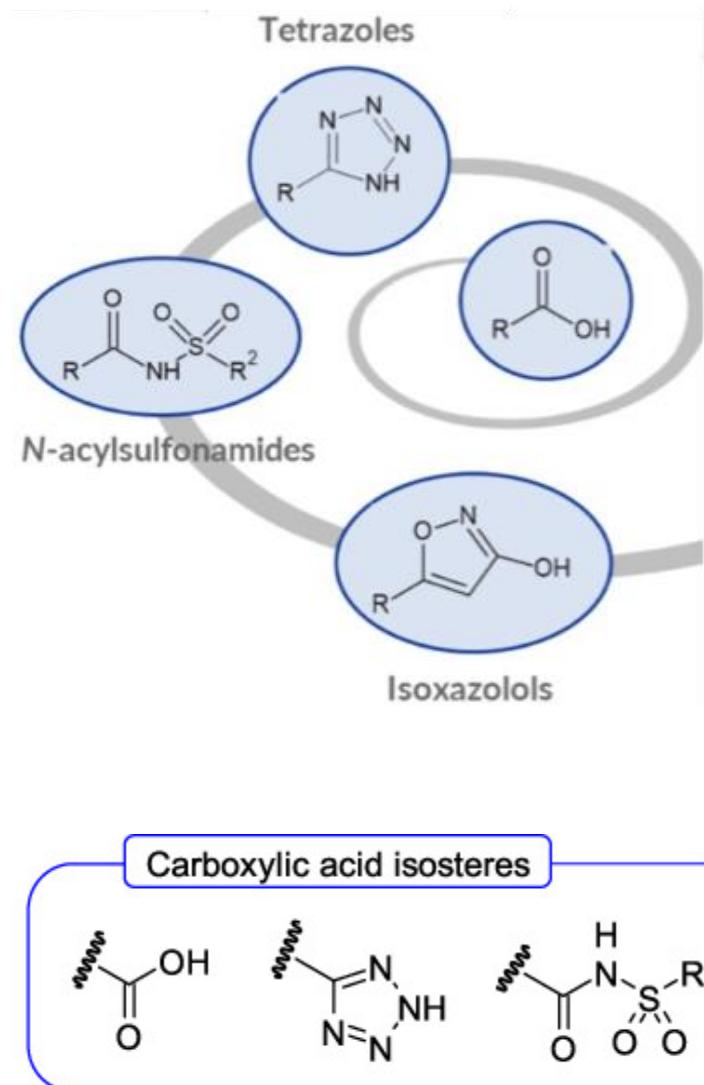
Rosuvastatin
 $(IC_{50} = 5\text{nM})$

pyrrool

pyridine

pyrimidine

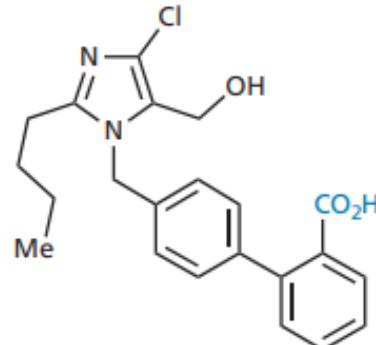
Bioisosteren voor carbozuur: tetrazool



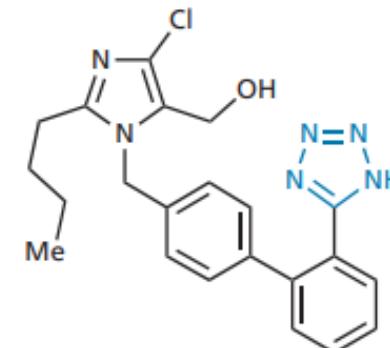
BOX 14.1 The use of bioisosteres to increase absorption

The biphenyl structure (Structure I) was shown by Du Pont to inhibit the receptor for angiotensin II and had potential as an antihypertensive agent. However, the drug had to be injected

as it showed poor absorption through the gut wall. Replacing the carboxylic acid with a tetrazole ring led to **losartan**, which was launched in 1994.



Structure I



Losartan

FIGURE 1 Development of losartan.

Negatieve lading blijft behouden
Minder polair → beter absorptie

Waarom?

is deze kennis van
belang

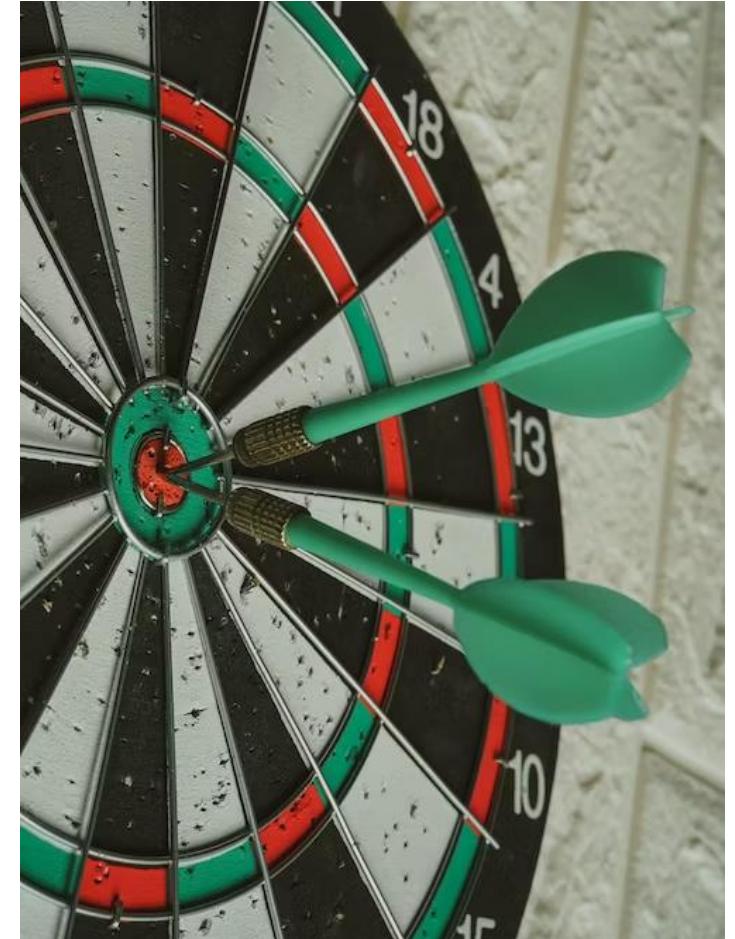
Casussen:

- De ontwikkeling van nieuwe orale anticoagulantia
- Leverselectiviteit van statines

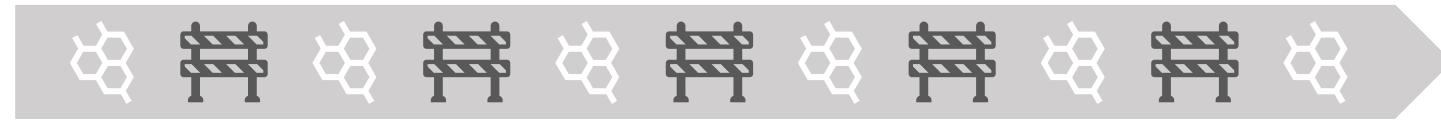


Leerdoelen Farmacochemie

- Het ANALYSEREN van chemische structuren en op grond daarvan uitspraken doen over de werking en toepasbaarheid als geneesmiddel.



Waarom farmacochemie?



De chemicus

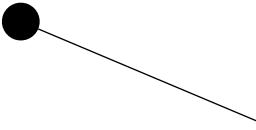


De **farmaceut**

- Het [ANALYSEREN](#) van chemische structuren en op grond daarvan uitspraken doen over de werking en toepasbaarheid als geneesmiddel.

De zoektocht naar nieuwe anticoagulantia

Tolerantie bij hoge doses



A NEW ORAL ANTICOAGULANT: THE 50-YEAR CHALLENGE

David Gustafson, Ruth Bylund, Thomas Antonsson, Ingemar Nilsson, Jan-Erik Nyström, Ulf Eriksson, Ulf Bredberg and Ann-Catrine Tegen-Nilsson
Nature Reviews Drug Discovery, Volume 3, August 2004, pp. 640–641

It is rare for a new drug to be developed from scratch. Most drugs are either modifications of existing ones or are derived from natural sources. In the case of oral anticoagulants, the search for a safe and effective oral alternative to the older injectable forms of thrombosis treatment has been a long and difficult one.

THROMBOSIS
A temporary or permanent blockage of a blood vessel, either by a clot (thrombus) or by a foreign body (embolus). In a vein, the thrombus frequently originates in the leg, thereby leading to blood flow obstruction.

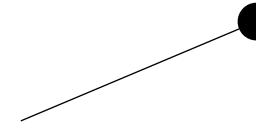
MYOCARDIAL INFARCTION
Commonly known as a heart attack, this is due to a sudden loss of blood supply to part of the heart muscle due to occlusion of the coronary arteries. The loss of oxygen is caused by complete blocking of a coronary artery by a blood clot.

CASE HISTORY During the twentieth century, it was gradually recognized that thrombosis is a major cause of morbidity and mortality in the Western world. A thrombus can partially or fully occlude blood vessels, potentially depriving the tissue of oxygen and nutrients. An embolus is a detached thrombus from a large vessel or the heart that travels with the bloodstream to occlude another vessel, often in a distant part of the body, in various ways, including deep vein thrombosis (DVT) and pulmonary embolism (PE), known collectively as venous thromboembolism (VTE), thromboembolic stroke, and myocardial infarction. Estimates place the annual incidence of VTE in Caucasians in excess of 1 case per 1,000 persons¹; 1.3–4.1 persons in 1,000 experience a stroke²; and 1.5–2.5 persons in 1,000 suffer a myocardial infarction annually³. There are three major groups of risk factors: blood hypercoagulability (as seen in factor V Leiden mutation, protein C deficiency, and so on); blood flow stasis (caused by immobilization, atrial fibrillation and so on); and vessel wall damage (caused by smoking, hypertension, diabetes, and so on).

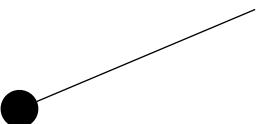
NATURE REVIEWS DRUG DISCOVERY

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Brede therapeutische window: antistolling vs. bloeding



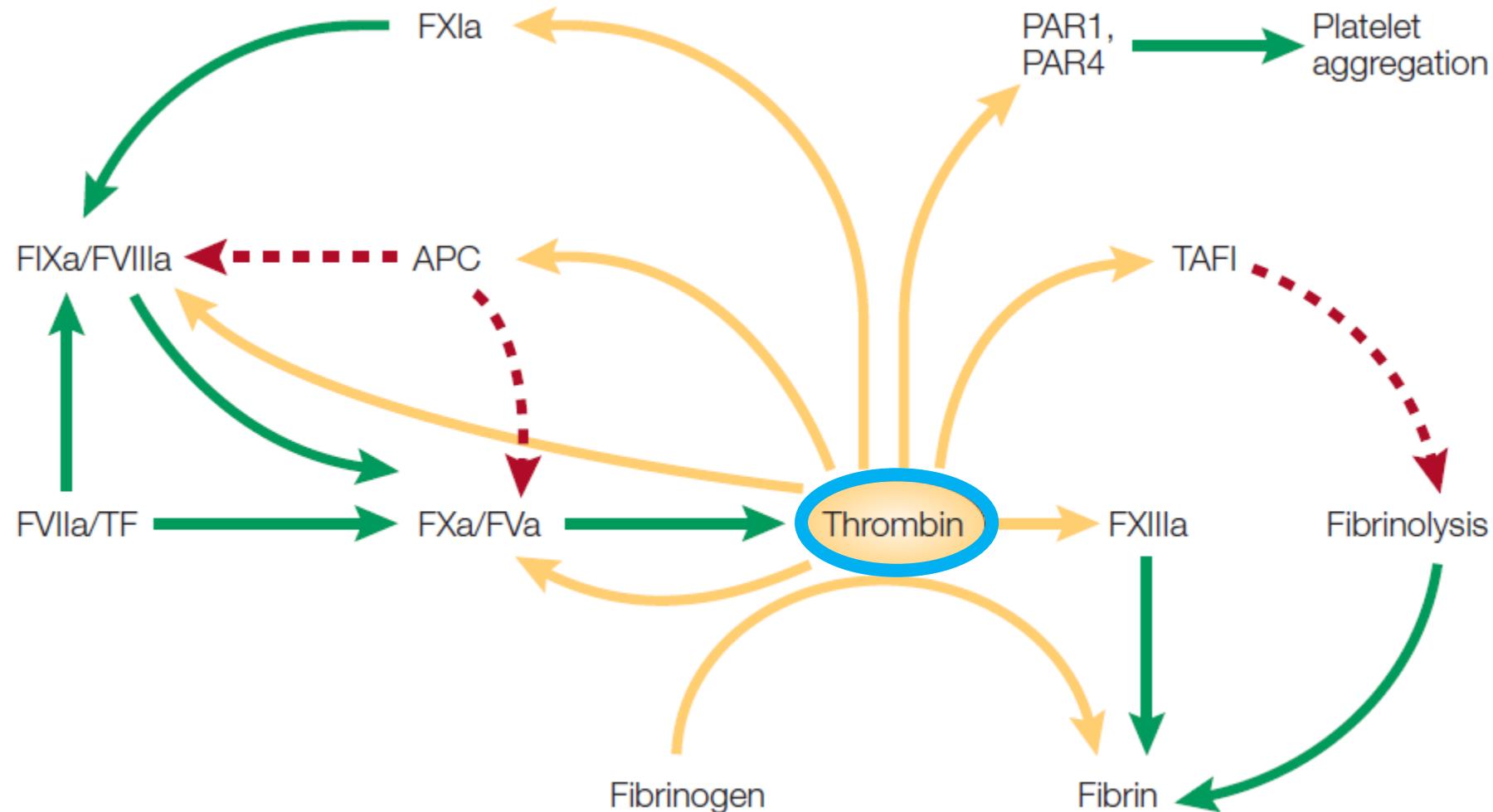
Goede affiniteit én specificiteit



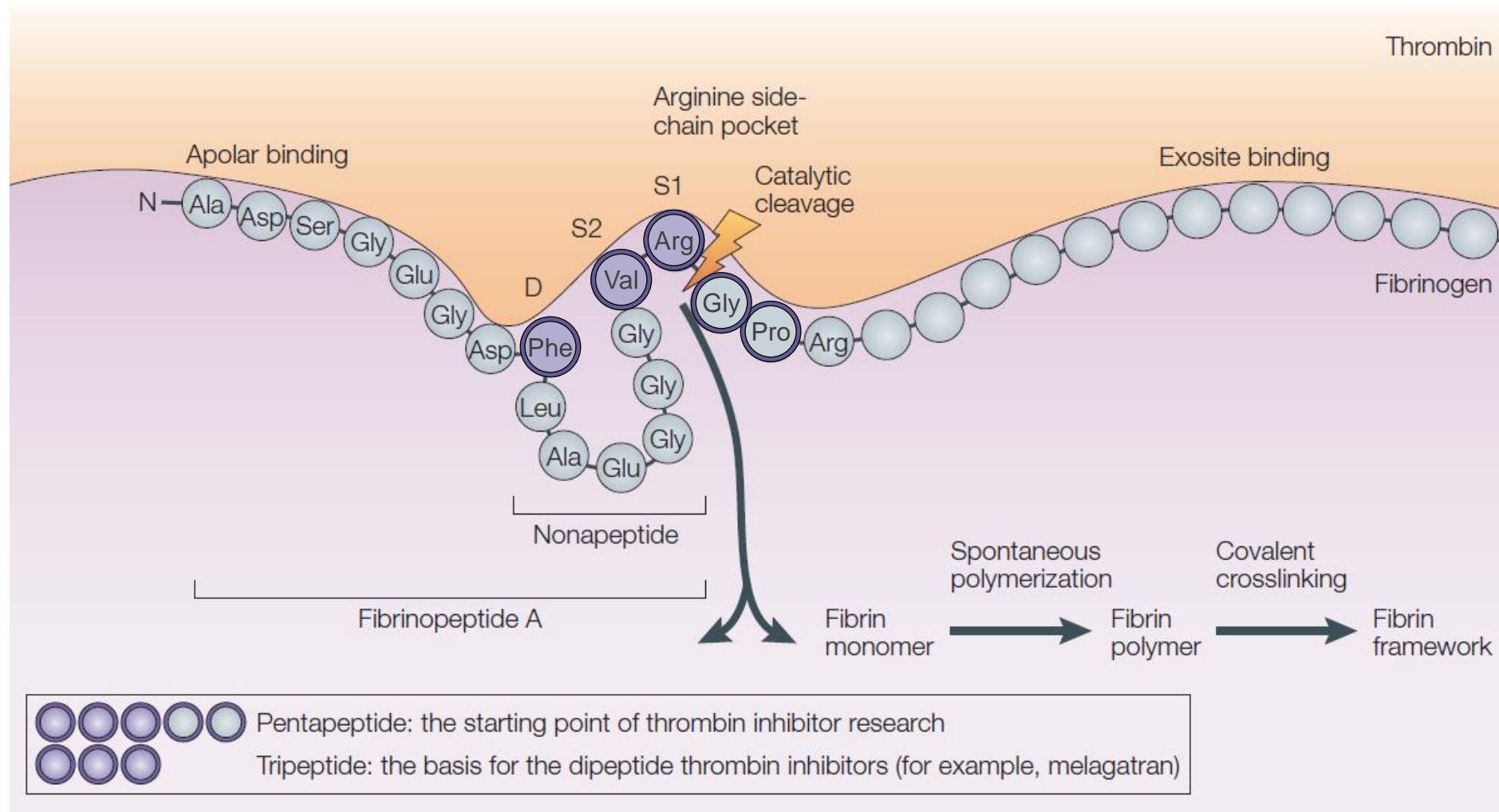
Langdurige werking

Voldoende absorptie en biologische beschikbaarheid na *orale* toediening

Waar beginnen? Alle wegen leiden naar...

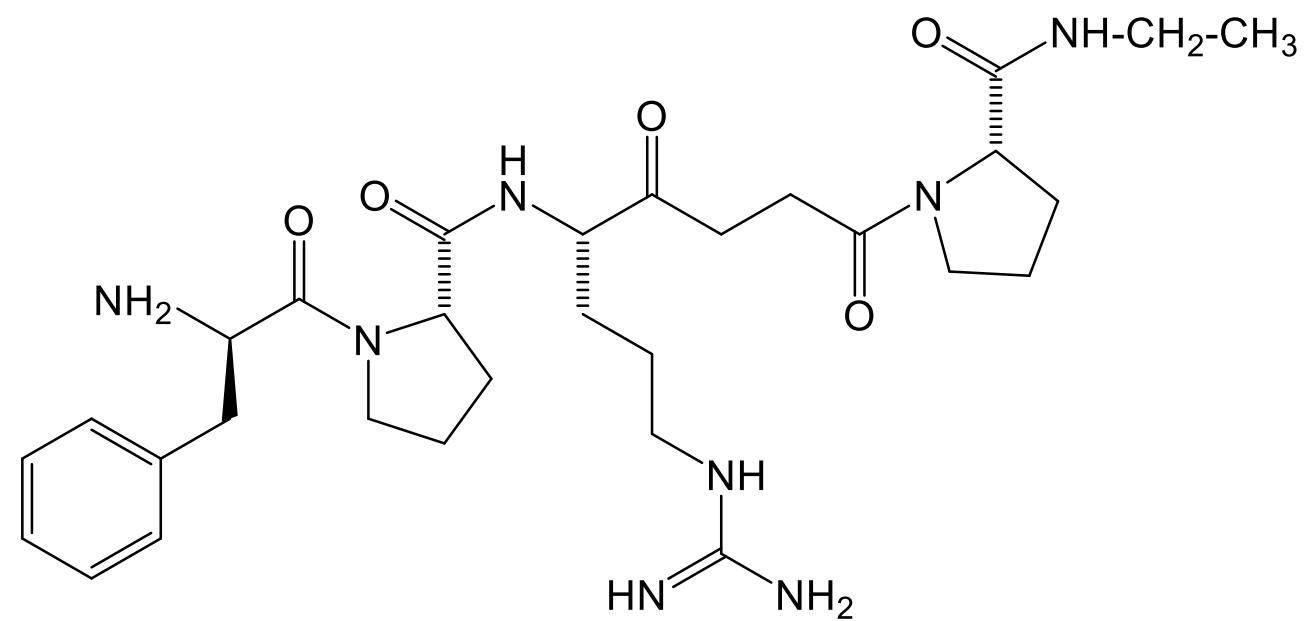


Het startpunt: 5 aminozuren van fibrinogeen



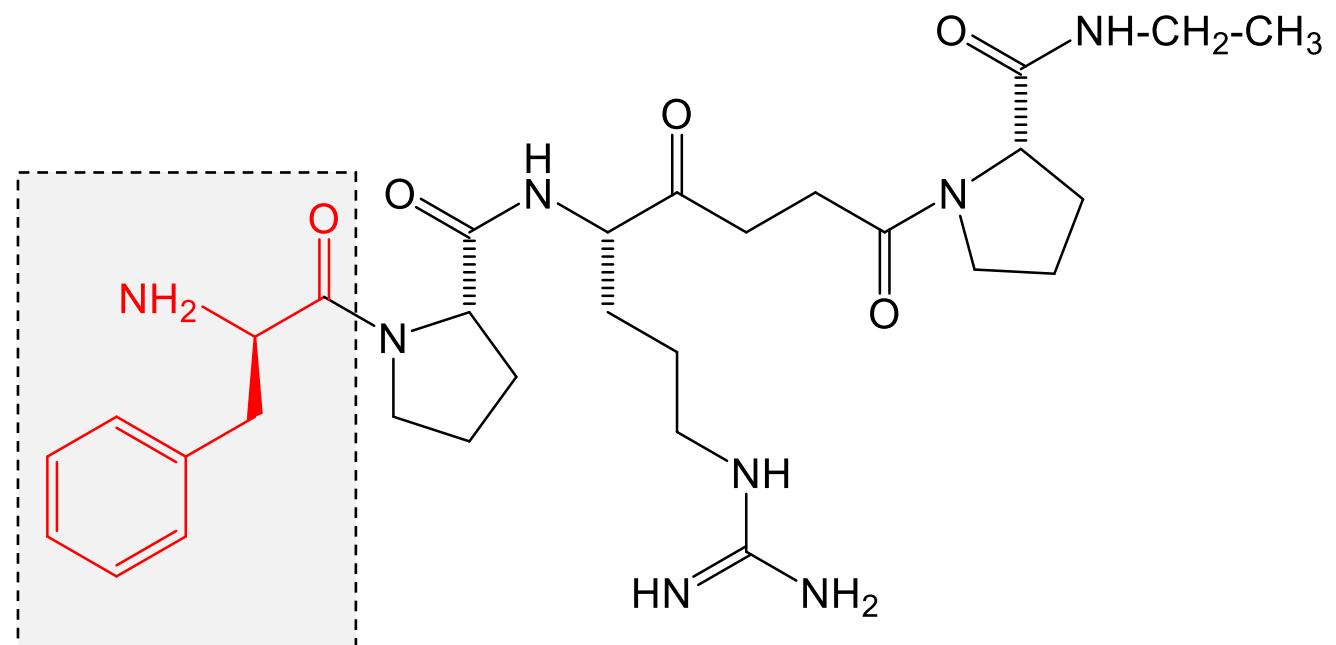
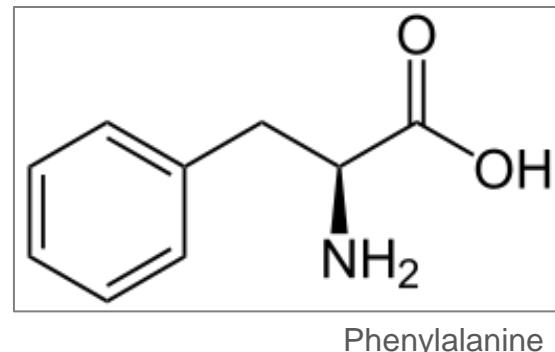
Het startpunt: 5 aminozuren van fibrinogeen

Phe Val Arg Gly Pro



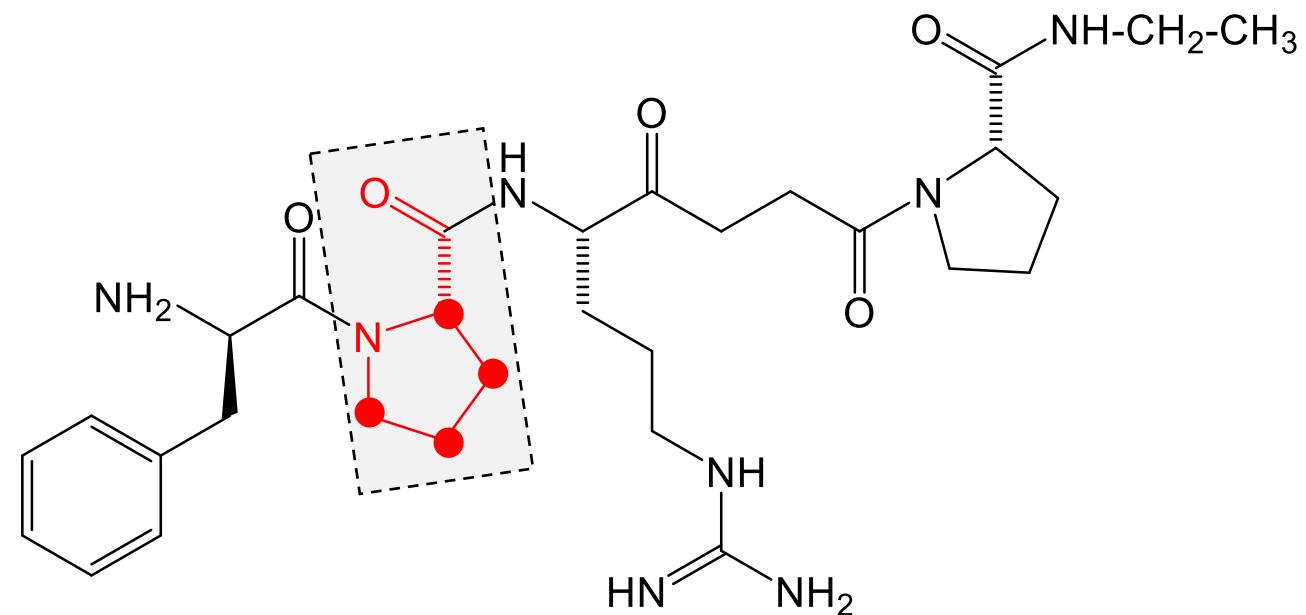
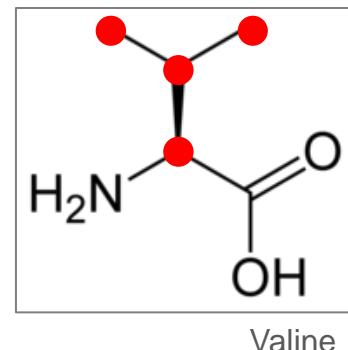
Het startpunt: 5 aminozuren van fibrinogeen

Phe Val Arg Gly Pro

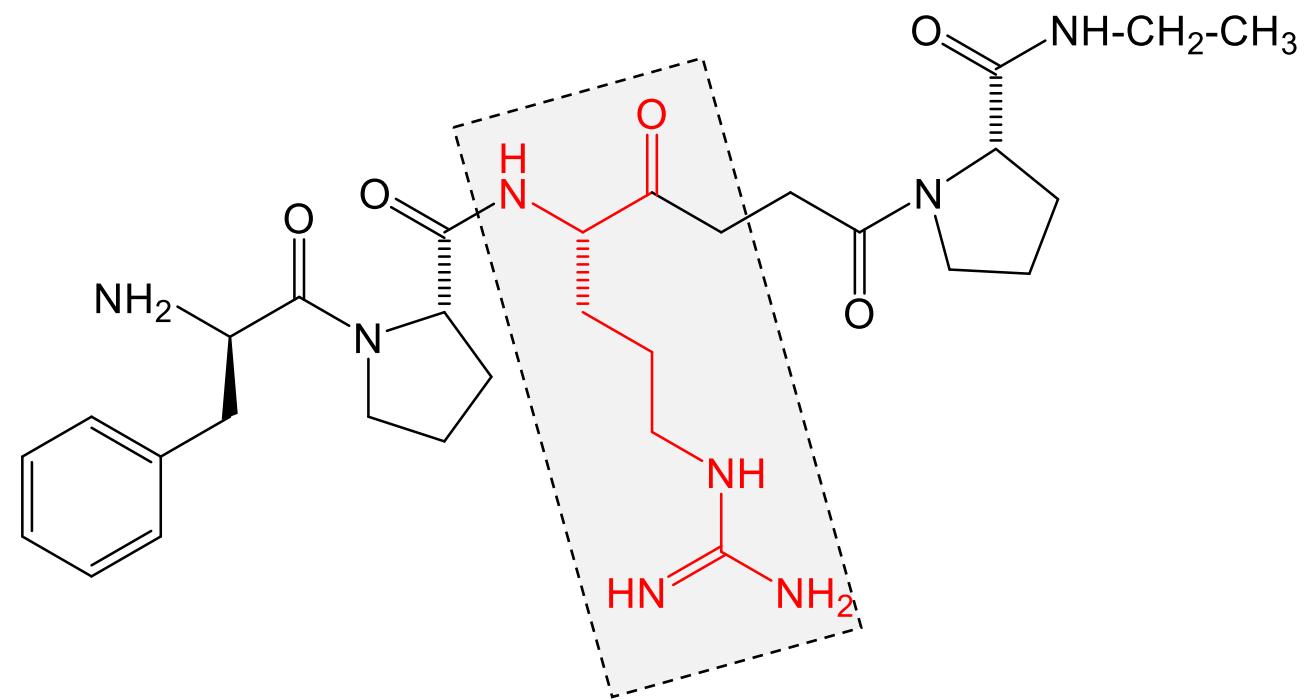
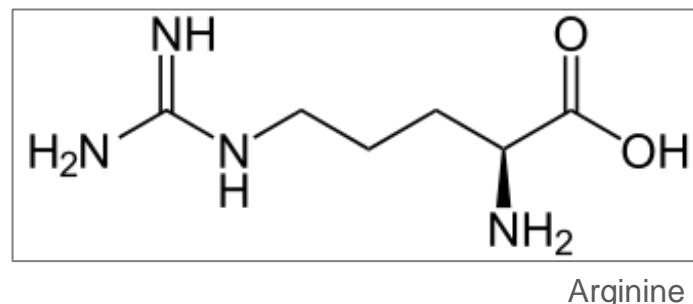
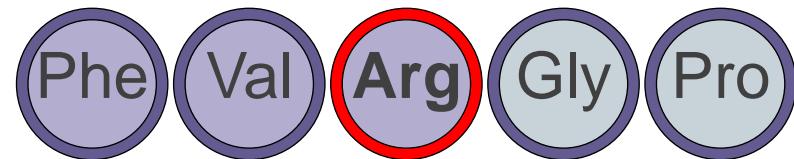


Het startpunt: 5 aminozuren van fibrinogeen

Phe Val Arg Gly Pro

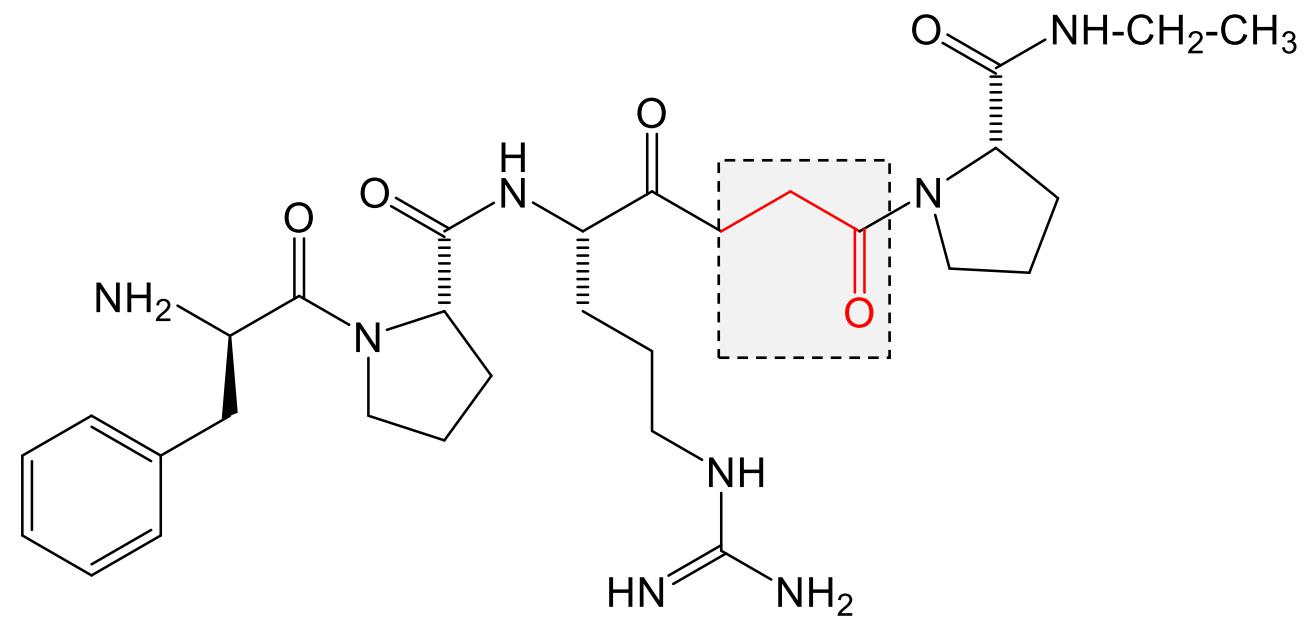
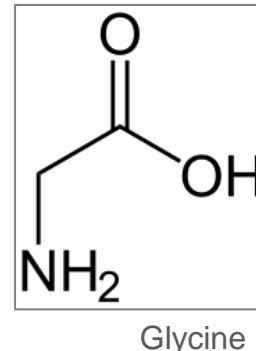


Het startpunt: 5 aminozuren van fibrinogeen



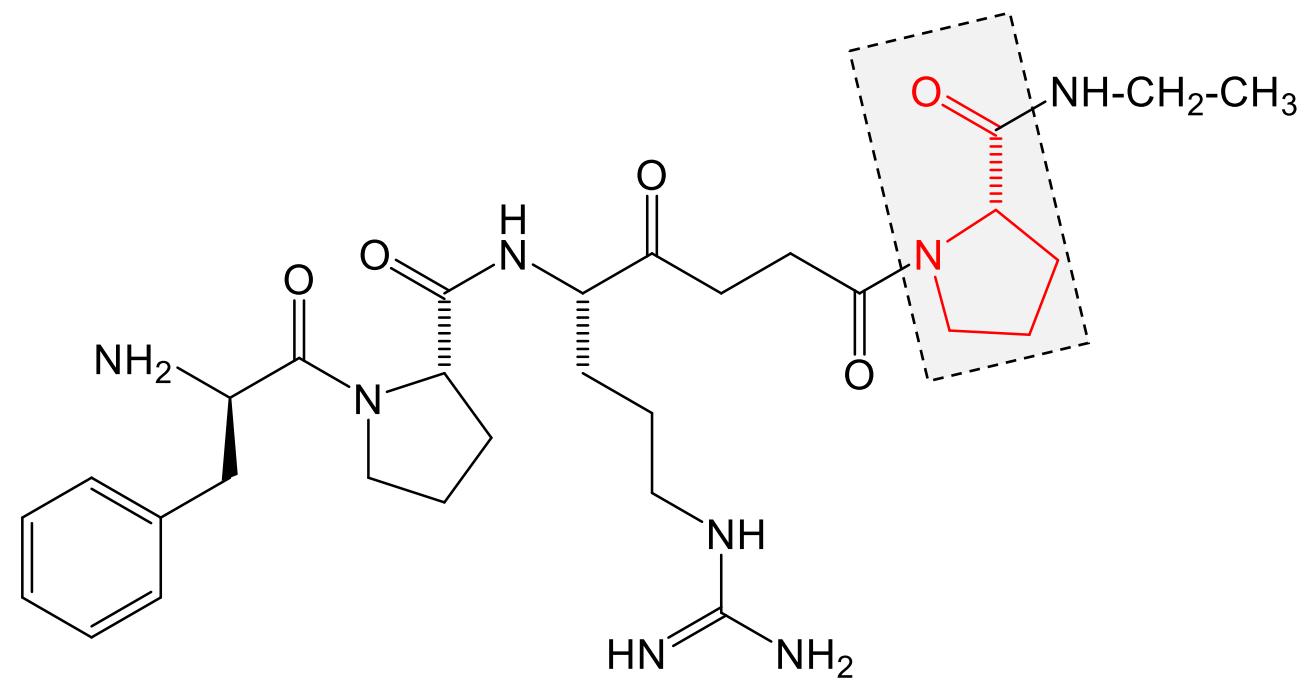
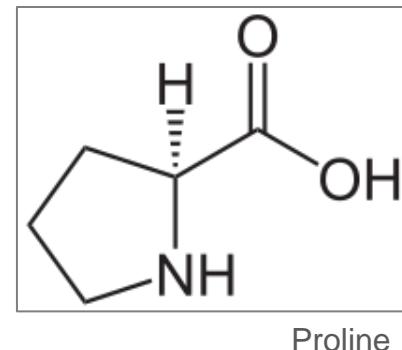
Het startpunt: 5 aminozuren van fibrinogeen

Phe Val Arg Gly Pro

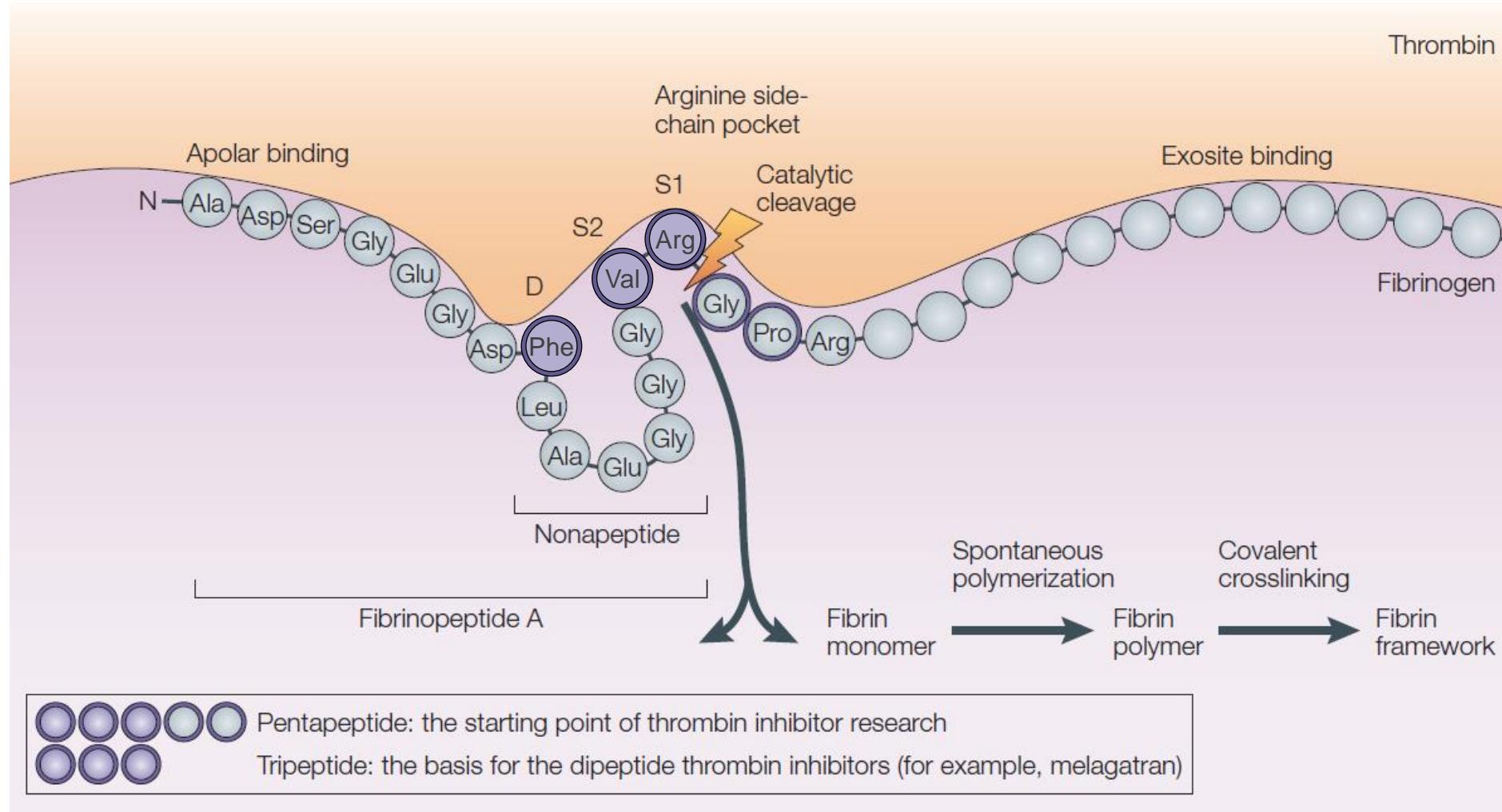


Het startpunt: 5 aminozuren van fibrinogeen

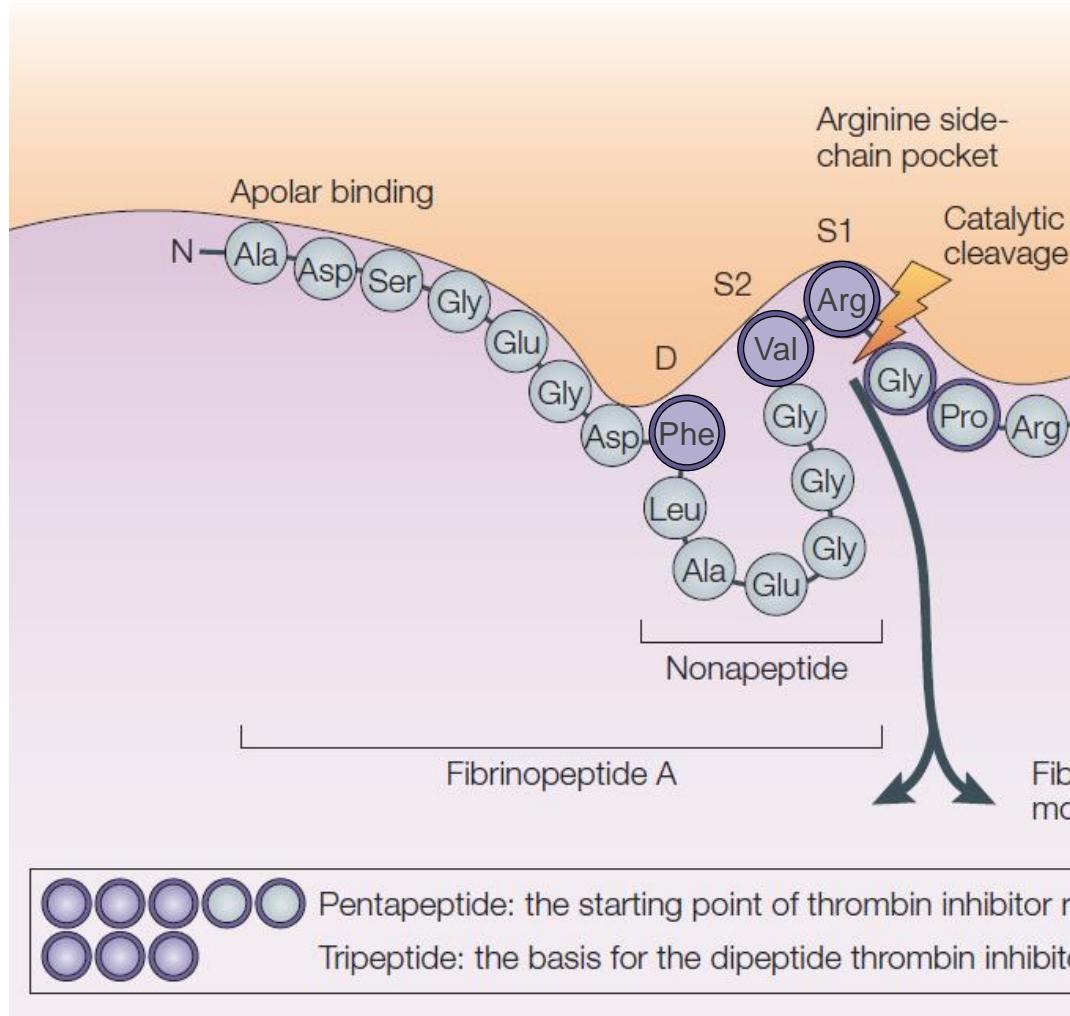
Phe Val Arg Gly Pro



Pentapeptide geeft onvoldoende absorptie bij orale toediening: kan het kleiner?



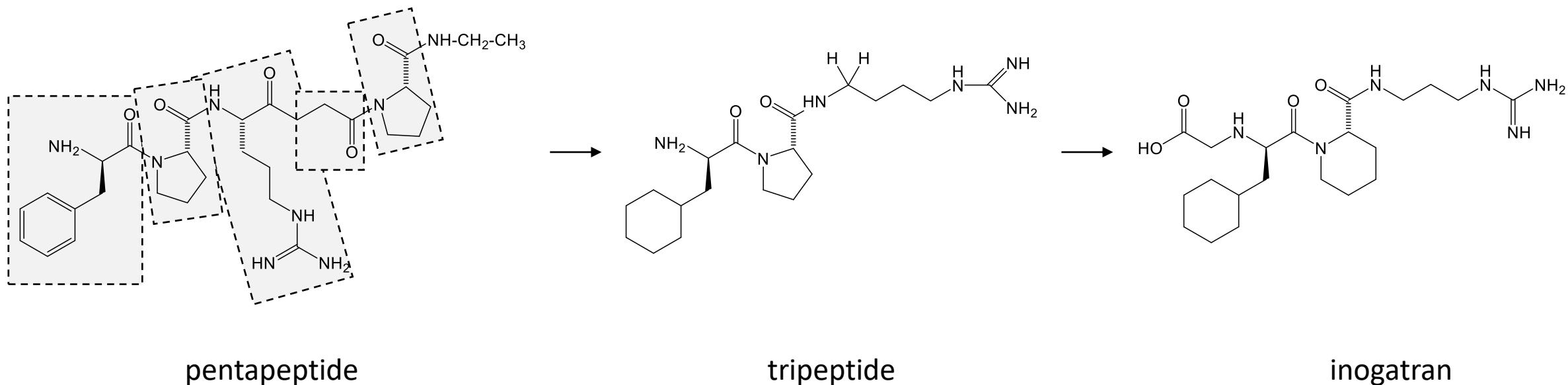
Pentapeptide geeft onvoldoende absorptie bij orale toediening: kan het kleiner?



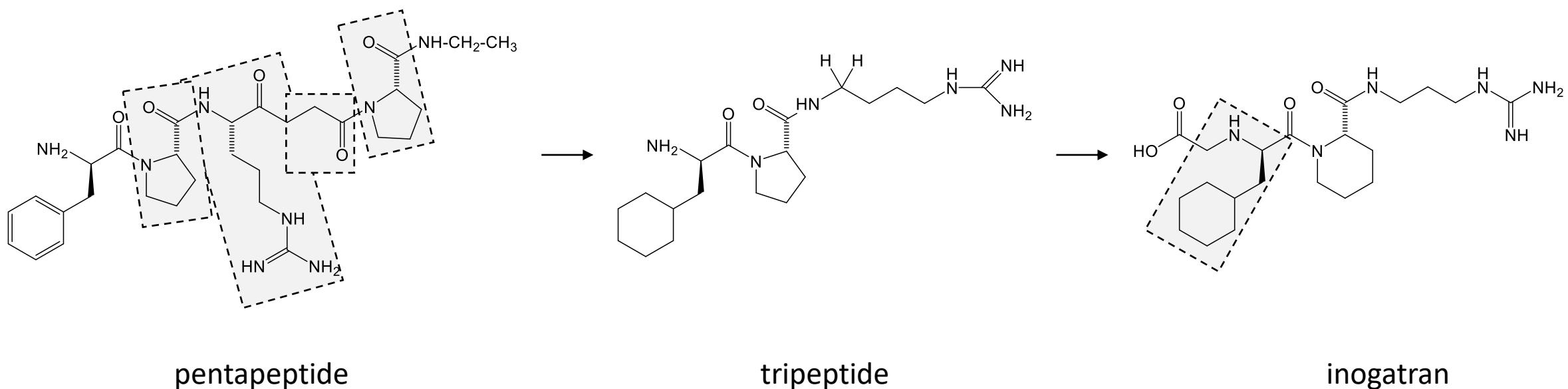
Lipinski's rule of 5:

- < 5 HBD
- < 10 HBA
- MW < 500 Da
- logP < 5

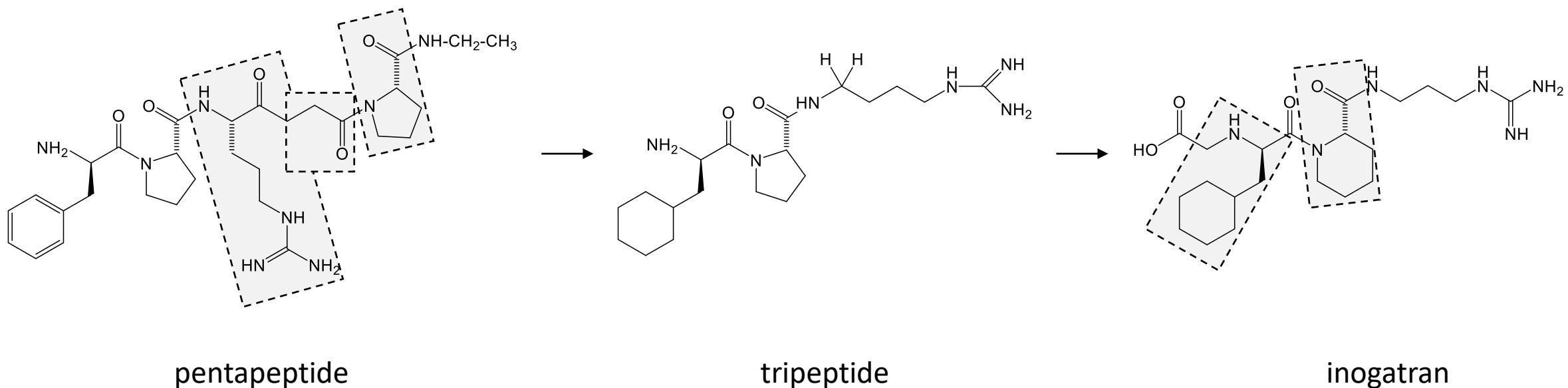
Van penta- naar tripeptide en de 1e kandidaat



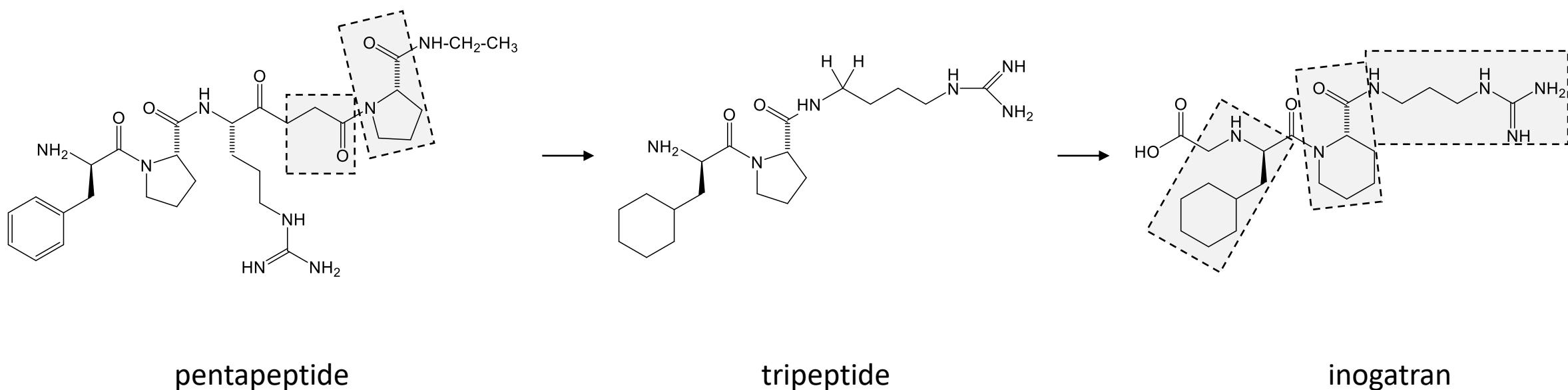
Van penta- naar tripeptide en de 1e kandidaat



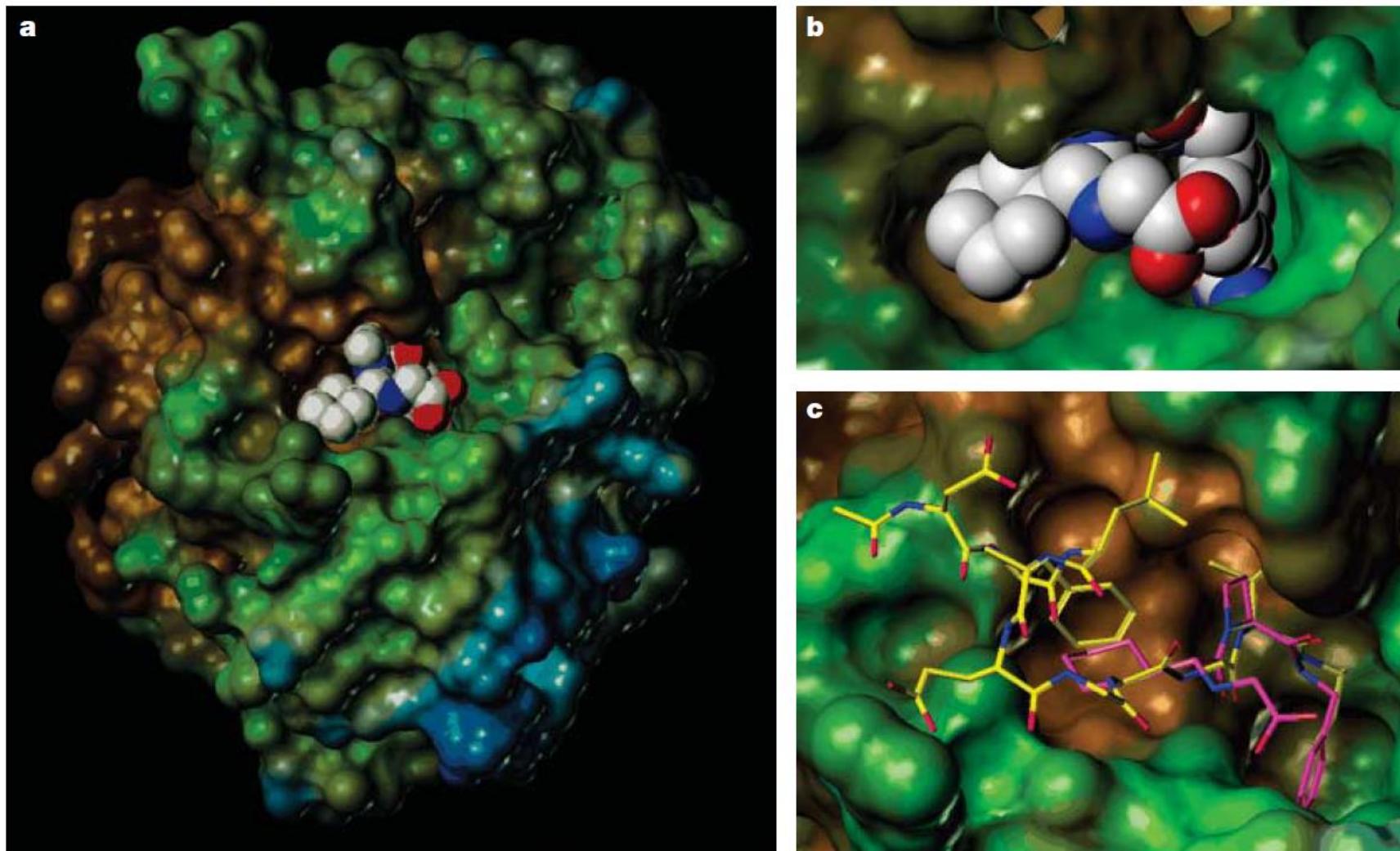
Van penta- naar tripeptide en de 1e kandidaat



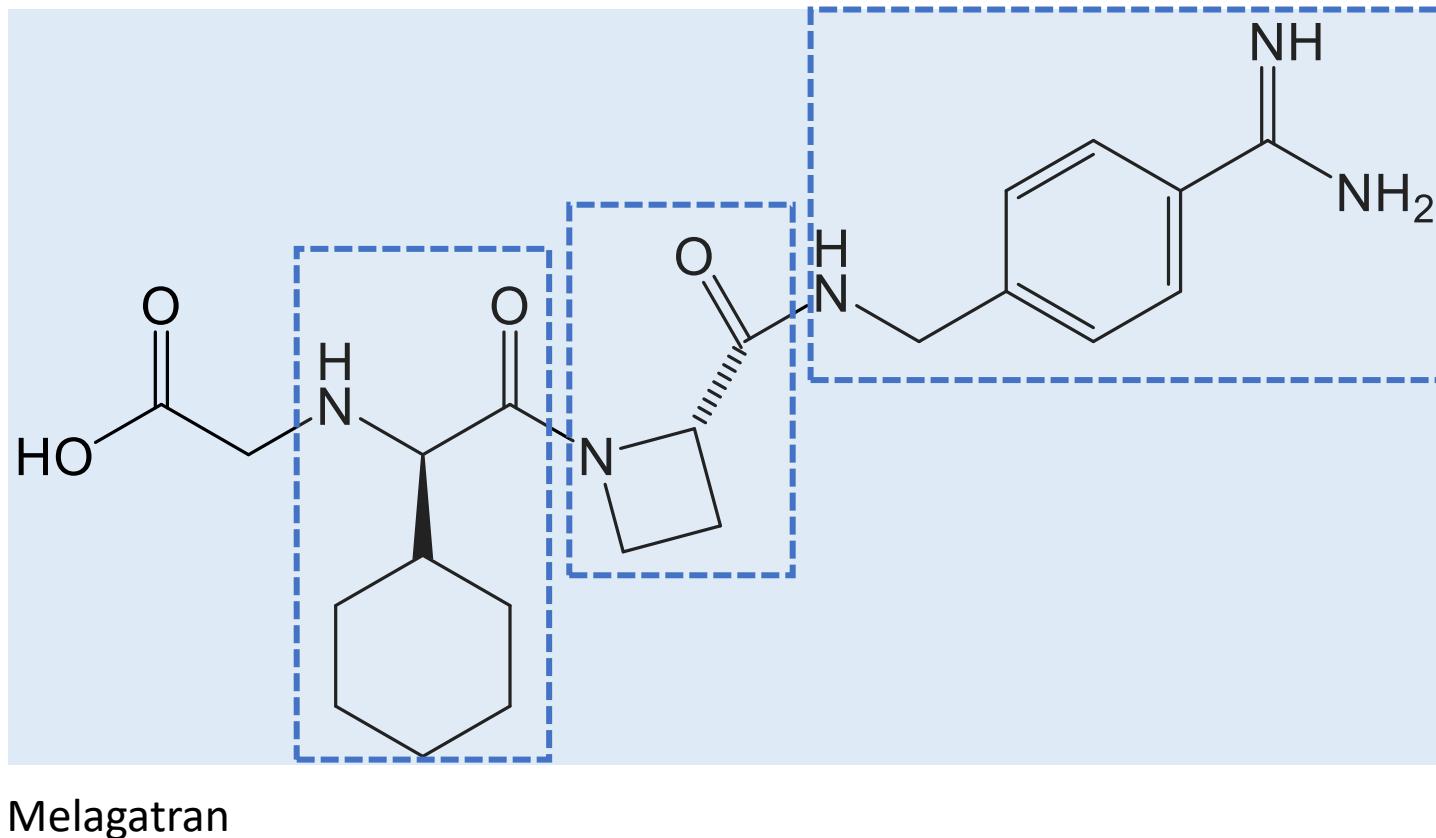
Van penta- naar tripeptide en de 1e kandidaat



Doorbraak: 3D en computer modellen

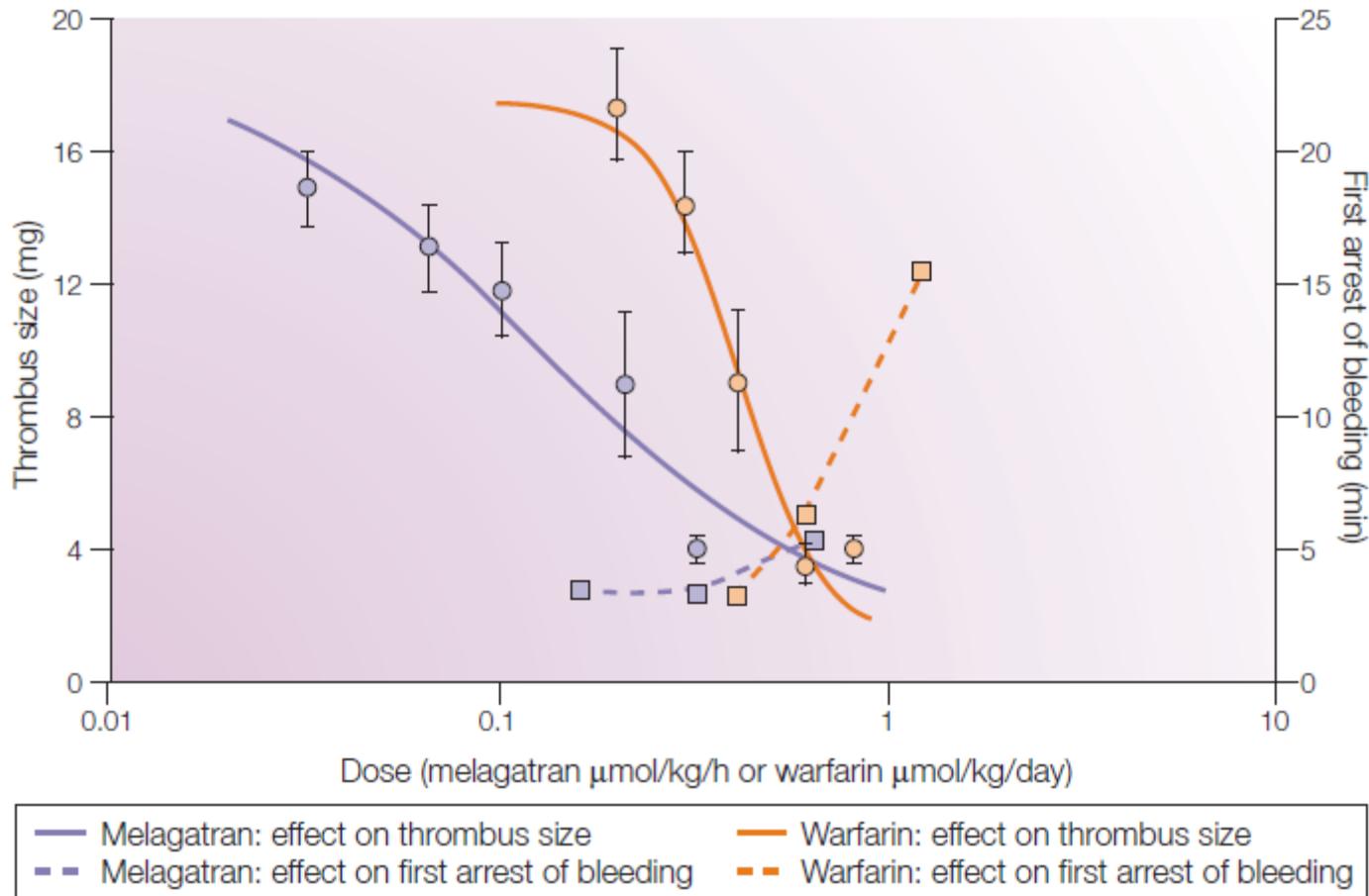


Een van deze verbindingen, Melagatran, lijkt veelbelovend

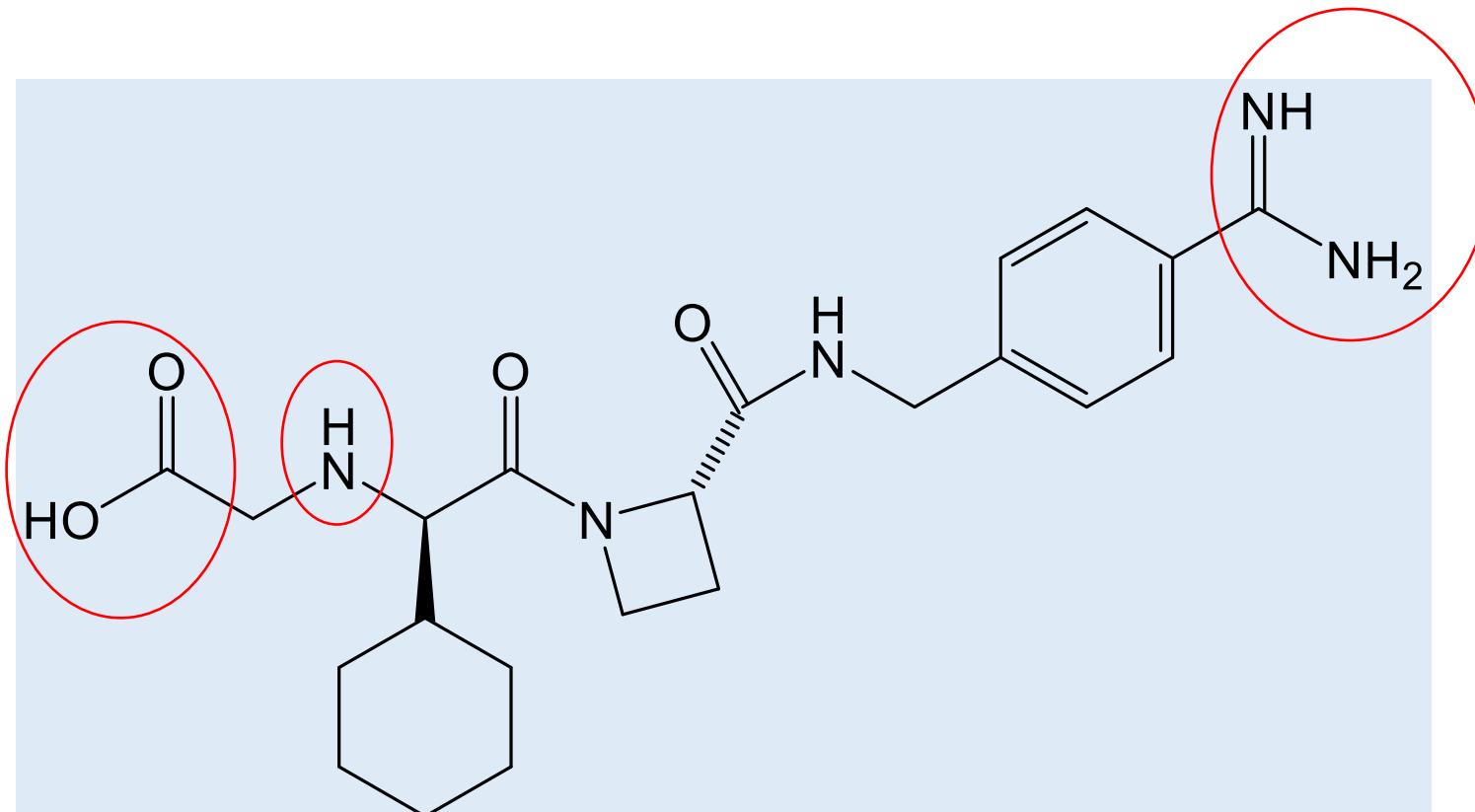


Phe Val Arg

Melagatran heeft een brede therapeutische index

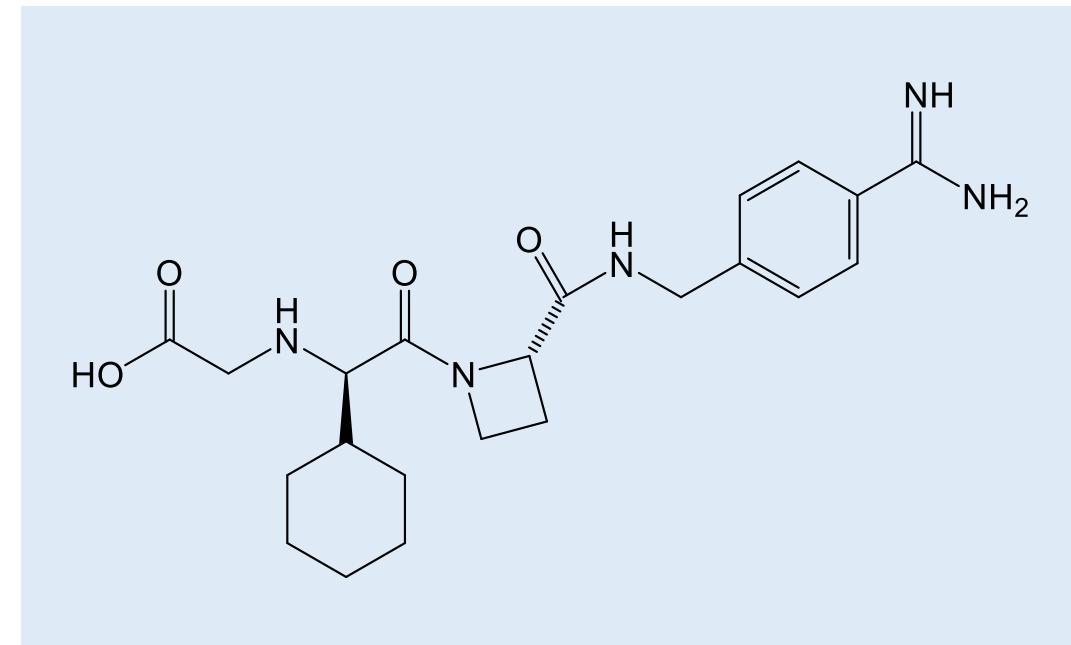
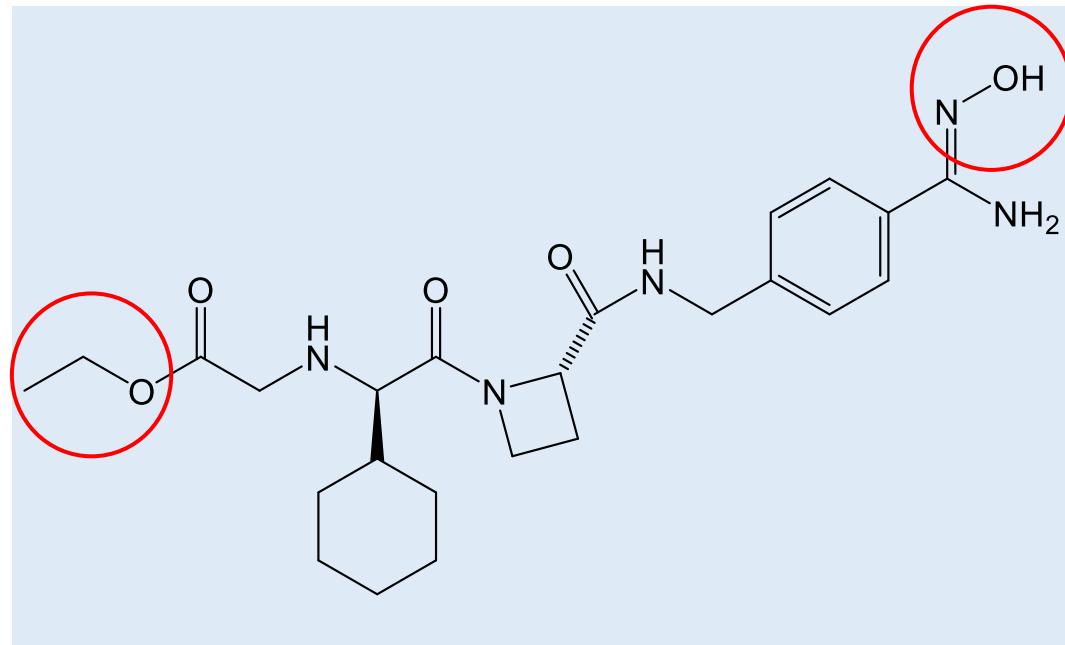


Echter, de biologische beschikbaarheid na orale toediening is slechts 3-7%



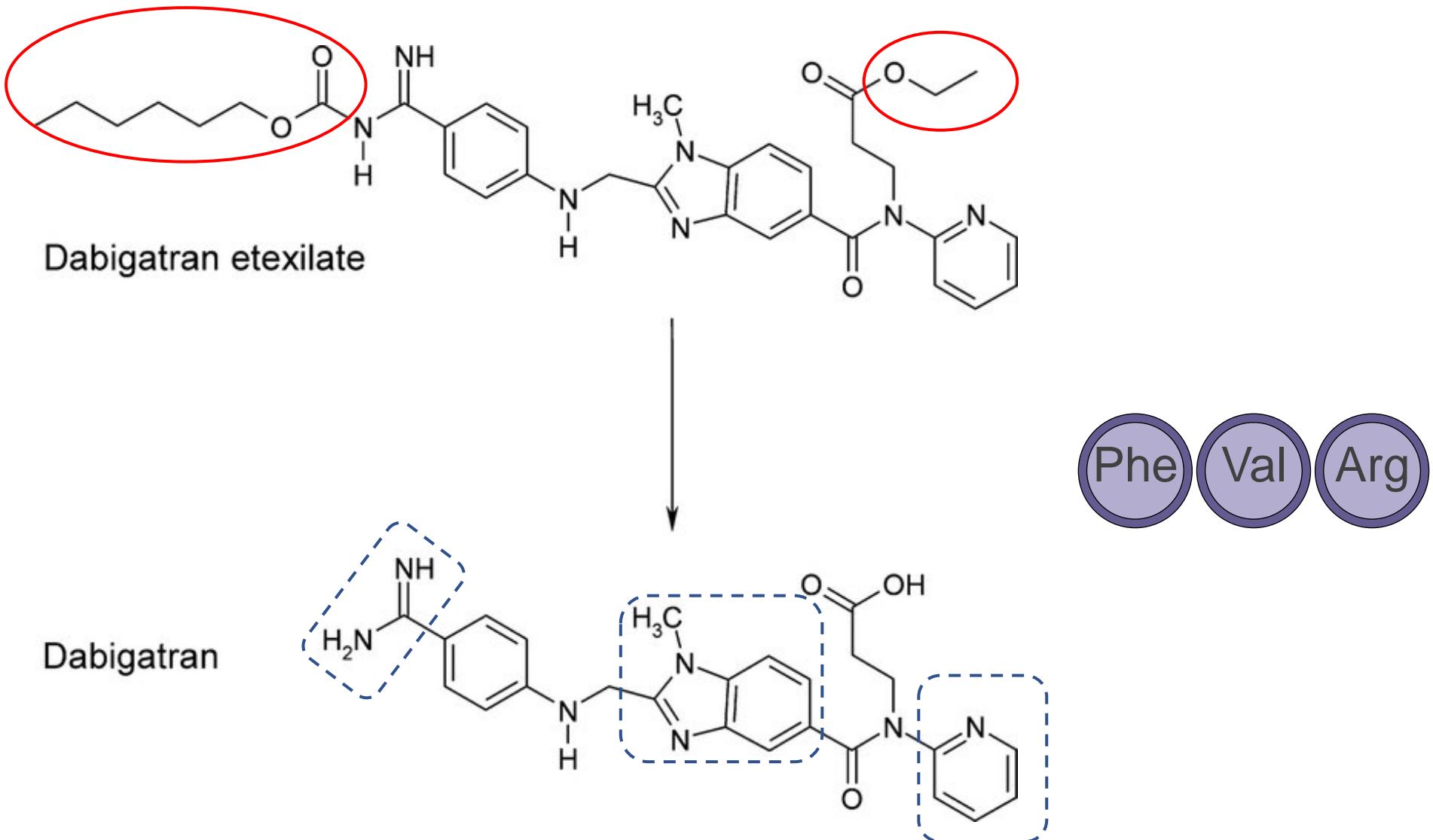
Melagatran

De oplossing: Ximelagatran, een *dubbele* prodrug



Ximelagatran	Melagatran
$\log K_d$ (relatieve lipofiliciteit)	170
AUC (%) (orale biol. beschikbaarheid)	18-24

Eind goed, al goed?



Casus: Atorvastatine en rhabdomyolyse

Een man (58 jaar) wordt 2 weken na aanvang met Atorvastatine (80 mg/dag) opgenomen met klachten van spierpijn, misselijkheid, braken, vermoeidheid en bruinkleurde urine.

Bloedwaarden bij opname:

- serum creatinine: 316 µmol/L
- creatinine kinase (CK): 141.940 U/L

Bloedwaarden 16 dagen na stoppen met Atorvastatine:

- serum creatinine: 241 µmol/L
- creatinine kinase CK: 195 U/L

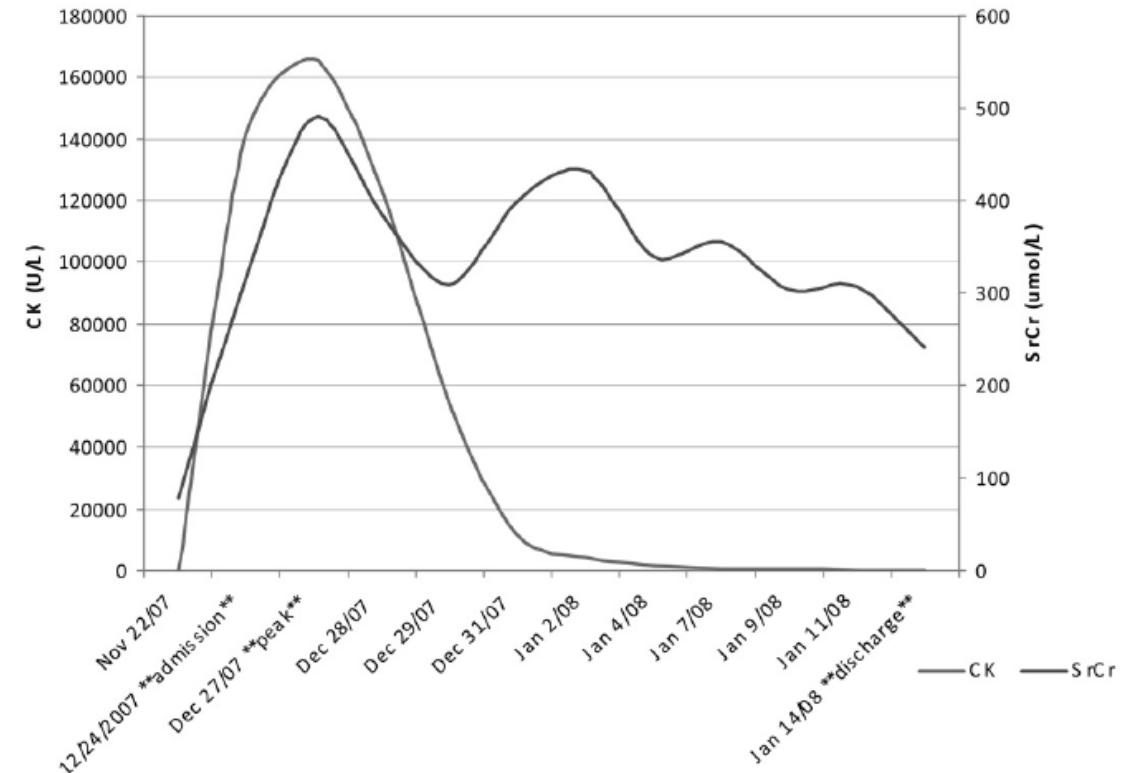
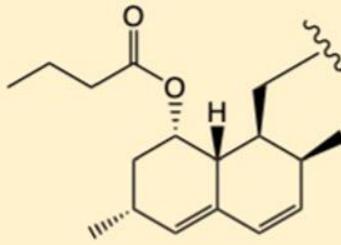
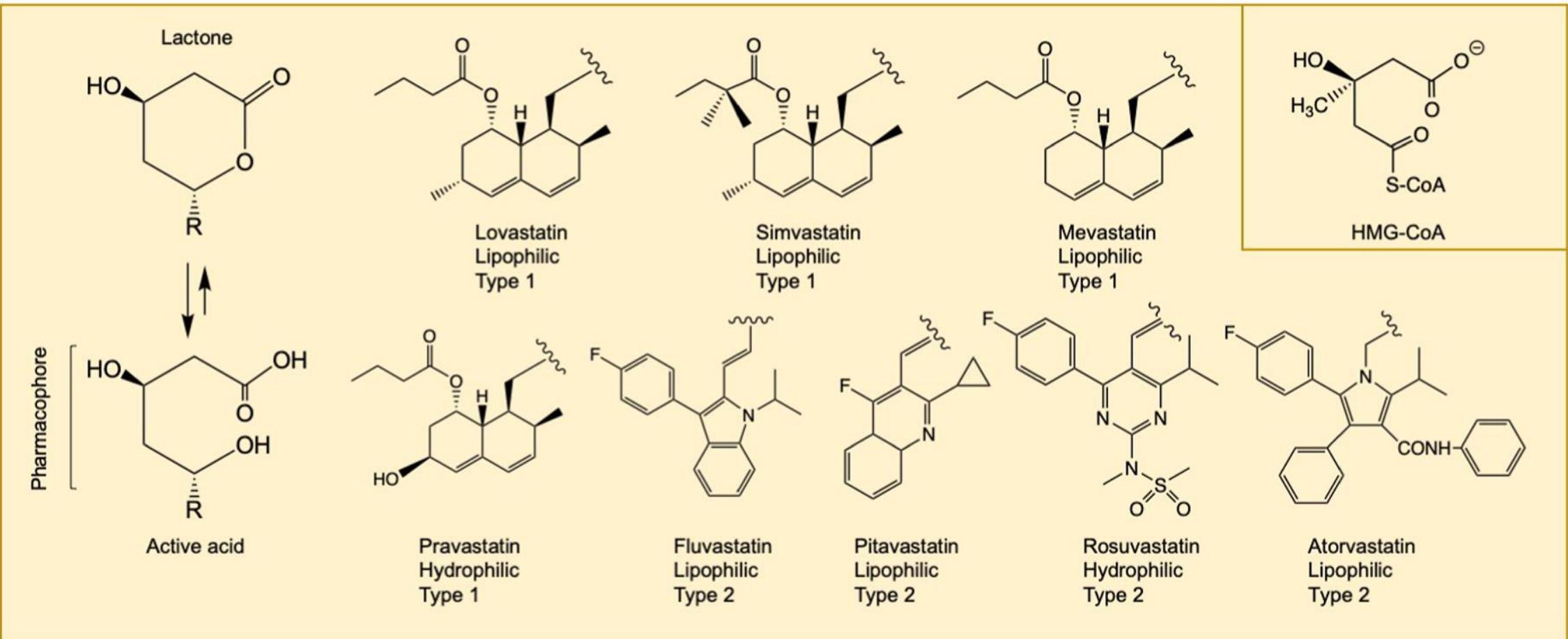
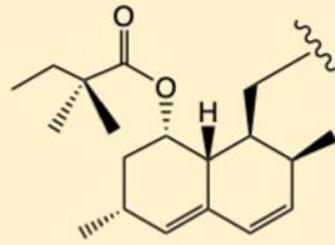


Figure 1. CK and serum creatinine level trends from admission to discharge.

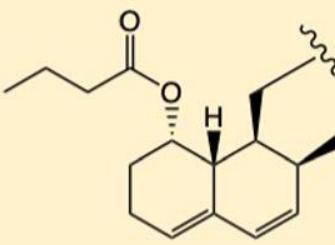
Structuur bepaalt (bij)werking!



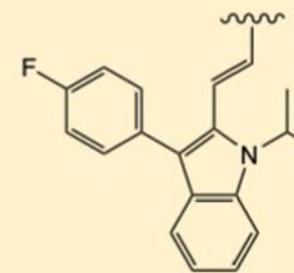
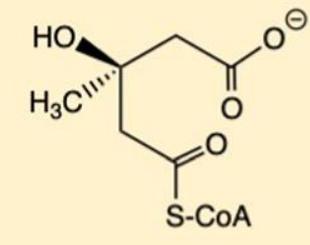
Lovastatin
Lipophilic
Type 1



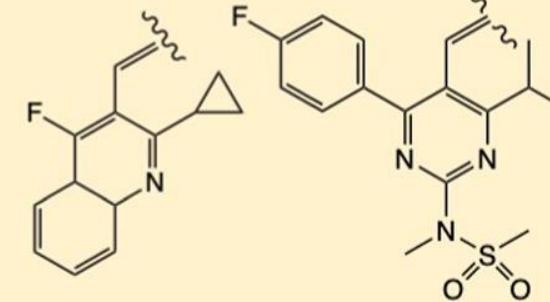
Simvastatin
Lipophilic
Type 1



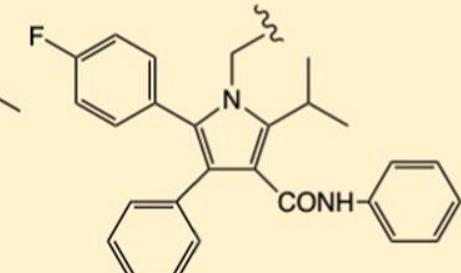
Mevastatin
Lipophilic
Type 1



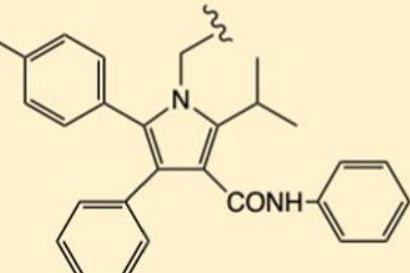
Fluvastatin
Lipophilic
Type 2



Pitavastatin
Lipophilic
Type 2

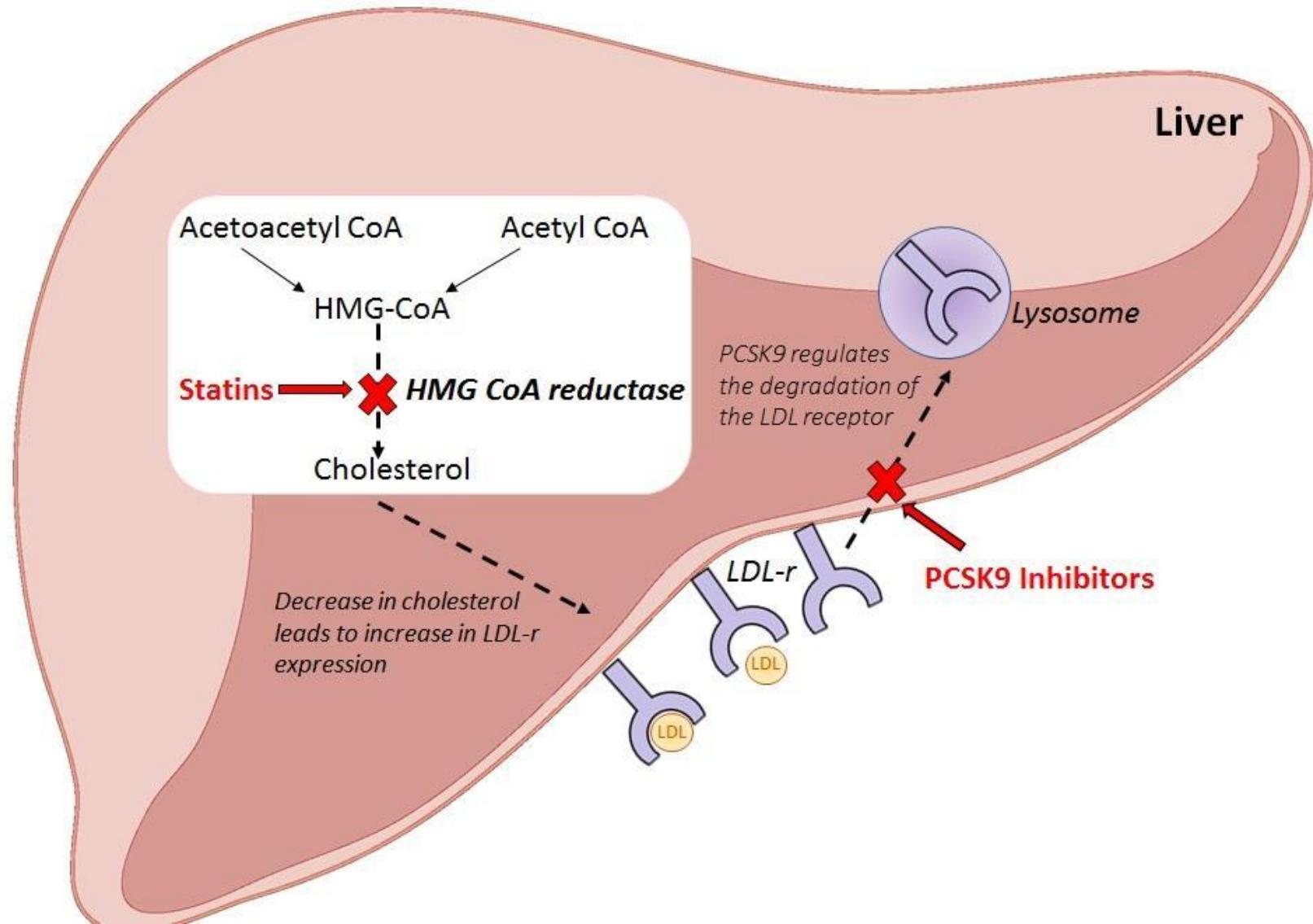


Rosuvastatin
Hydrophilic
Type 2

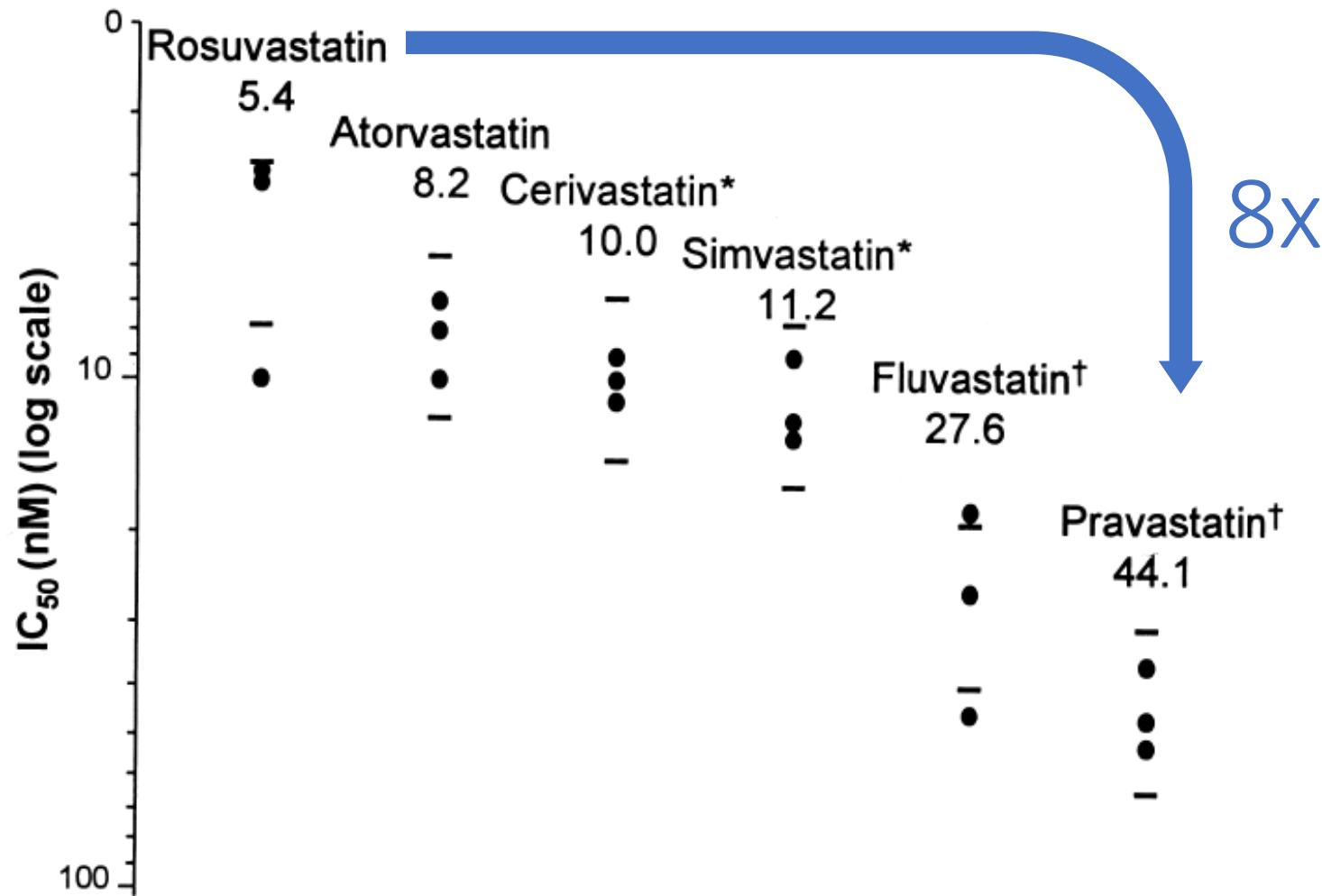


Atorvastatin
Lipophilic
Type 2

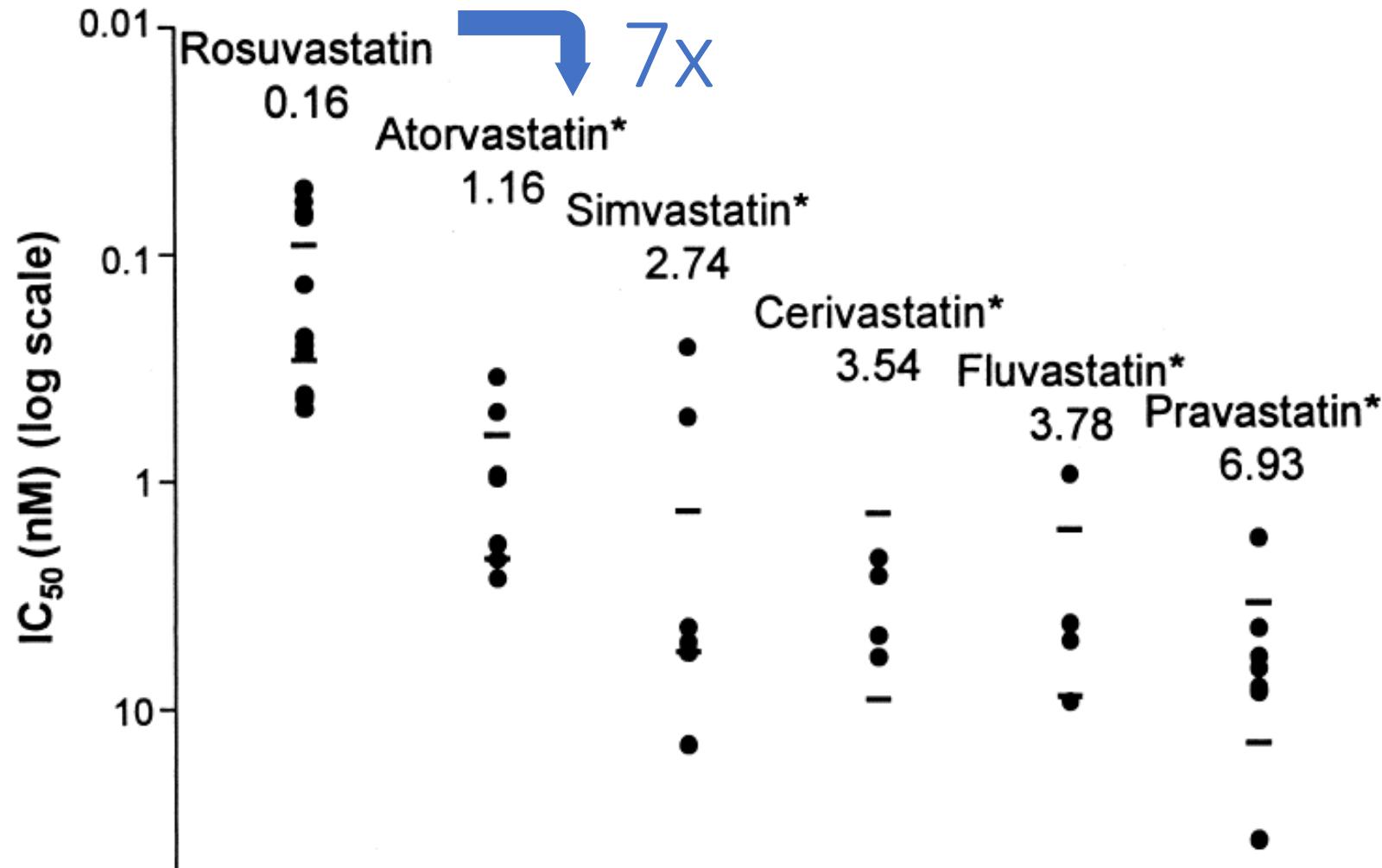
Remming cholesterol synthese in de lever



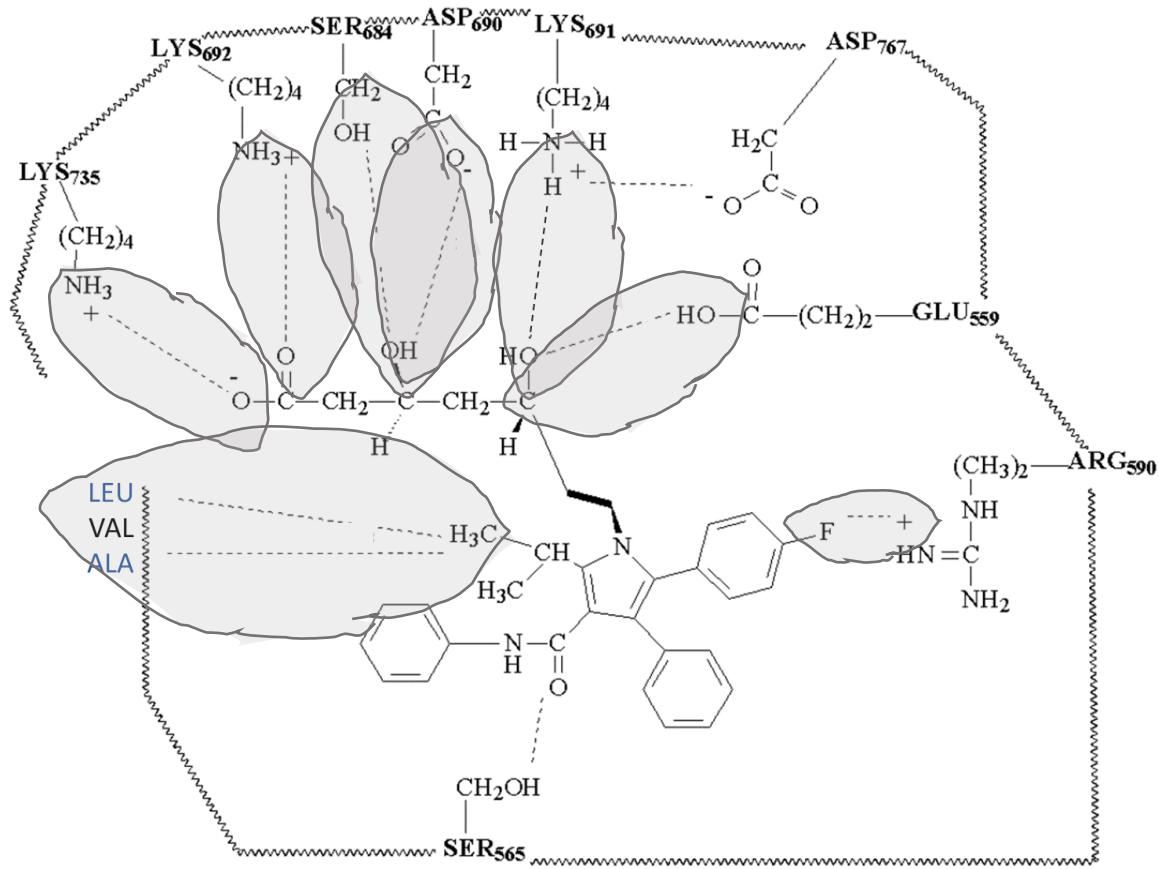
Rosuvastatine remt HMG-CoA reductase het sterkst



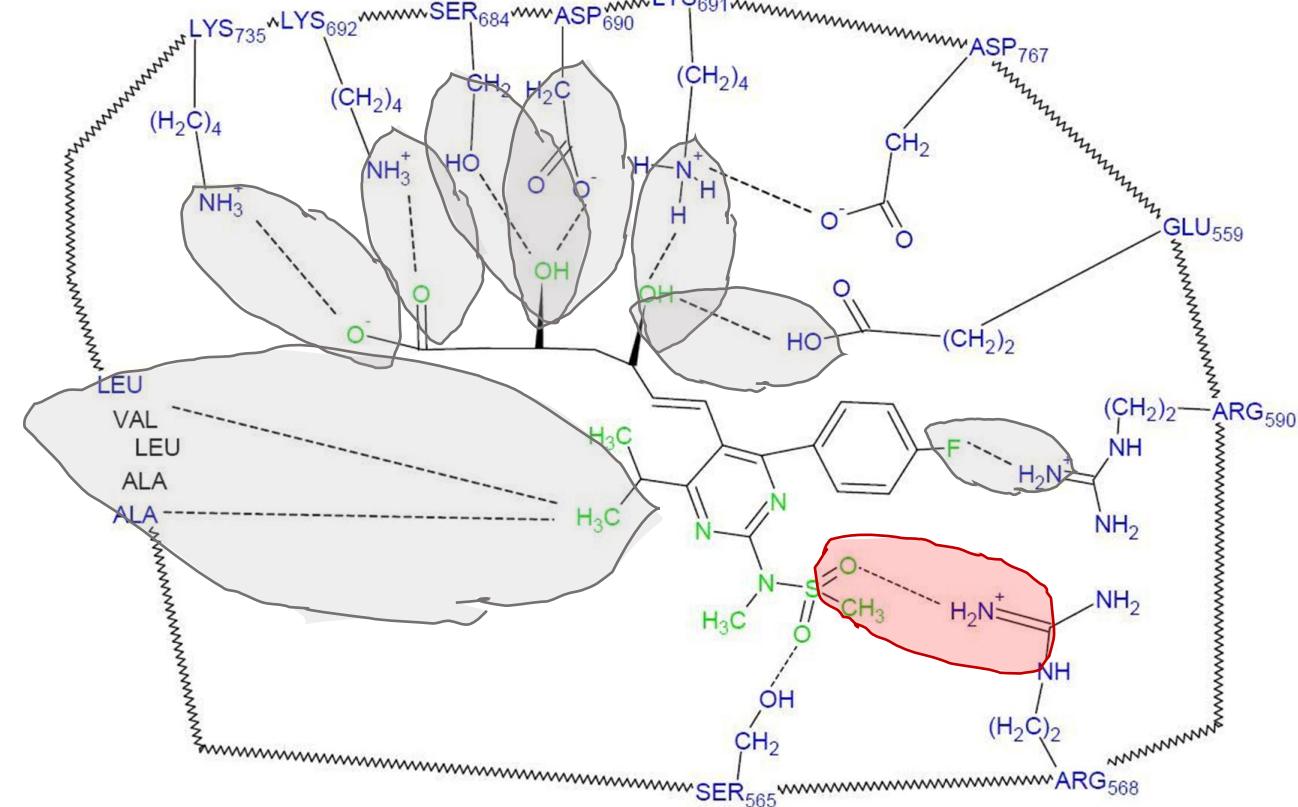
Rosuvastatine remt cholesterololsynthese het sterkst



Rosuvastatine heeft meer affiniteit voor HMG-CoA reductase dan atorvastatine

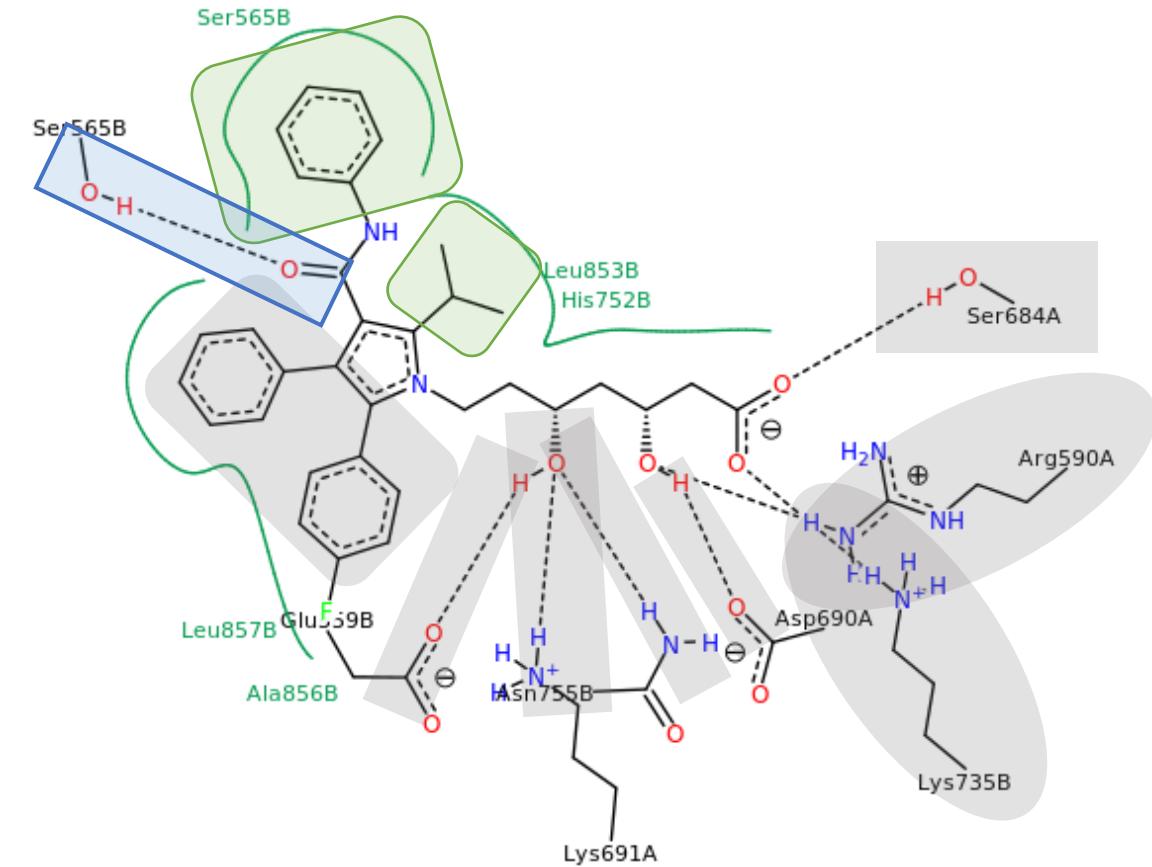
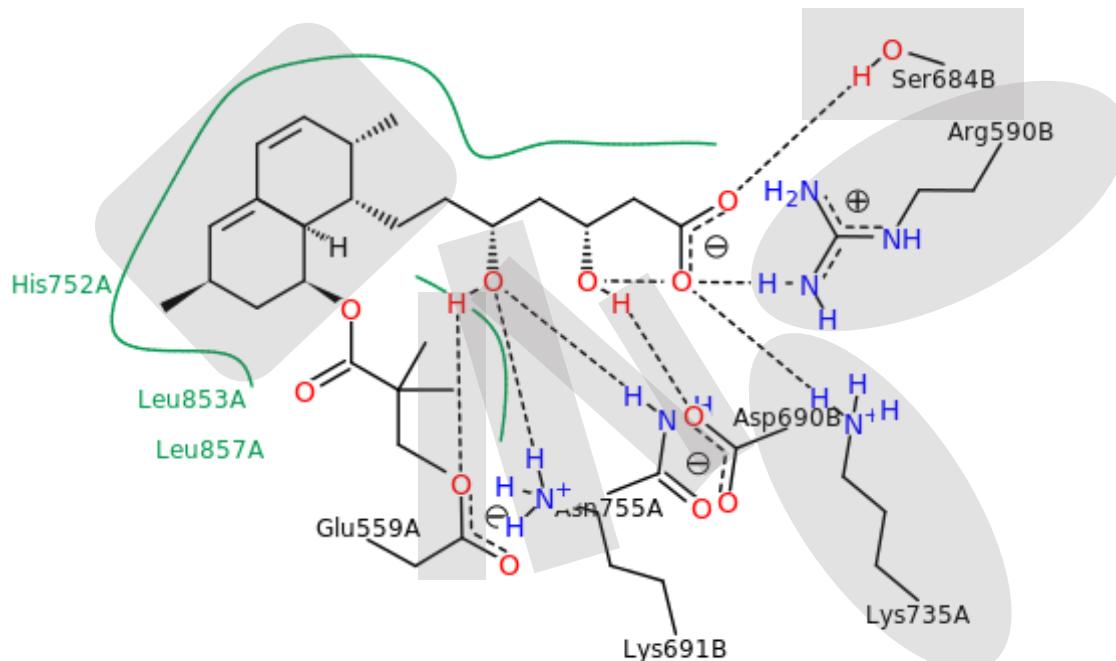


atorvastatine

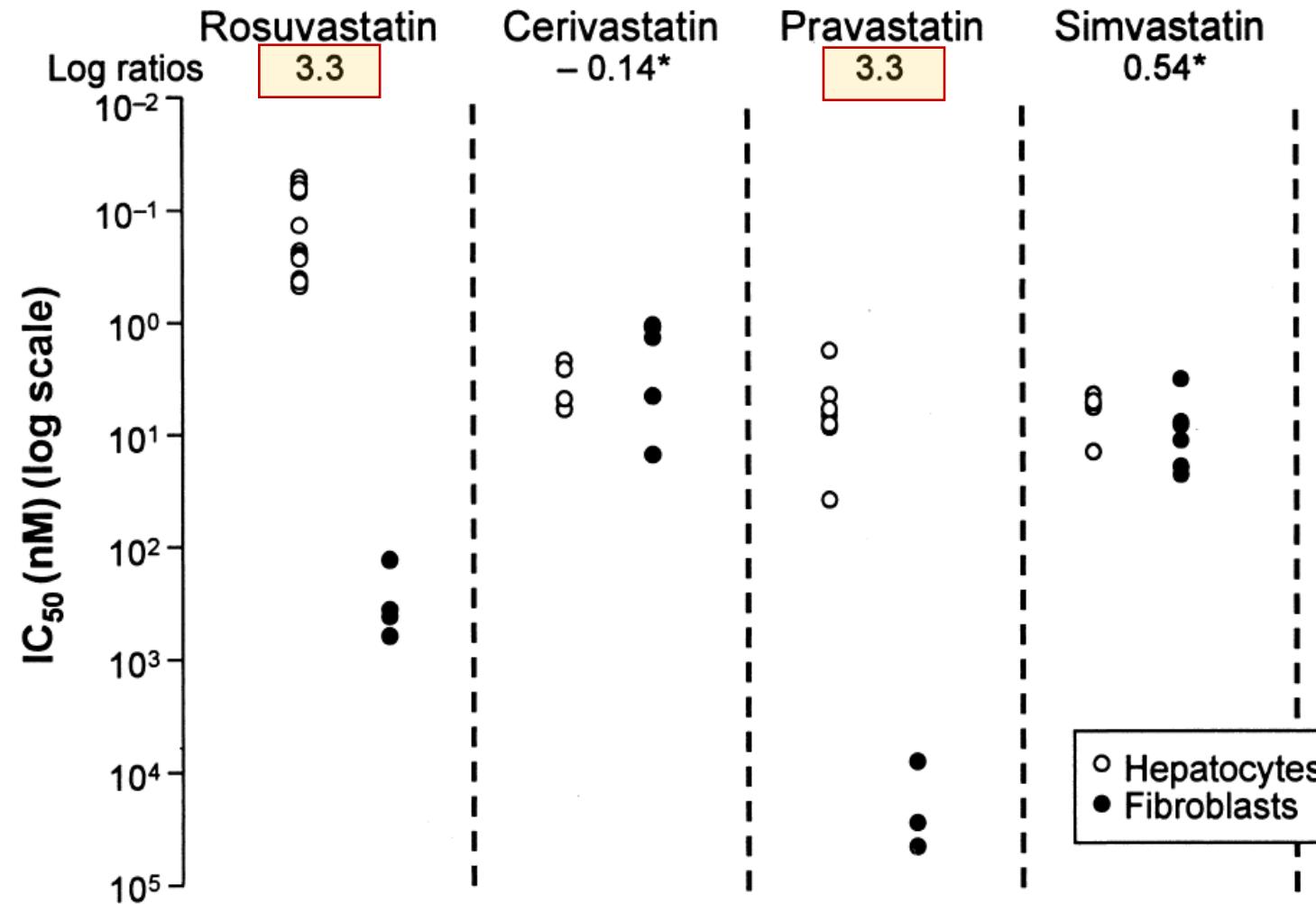


rosuvastatine

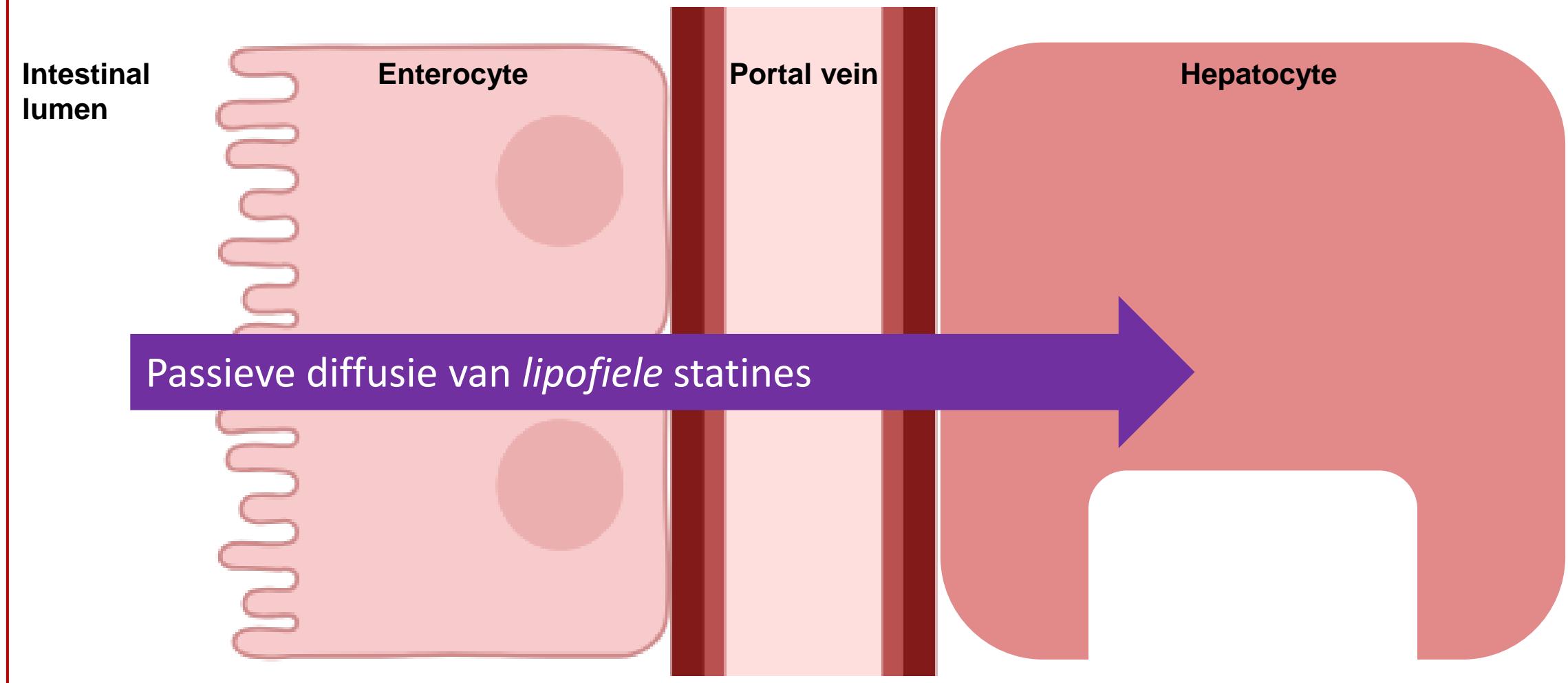
Atorvastatine heeft meer affiniteit voor HMG-CoA reductase dan simvastatine



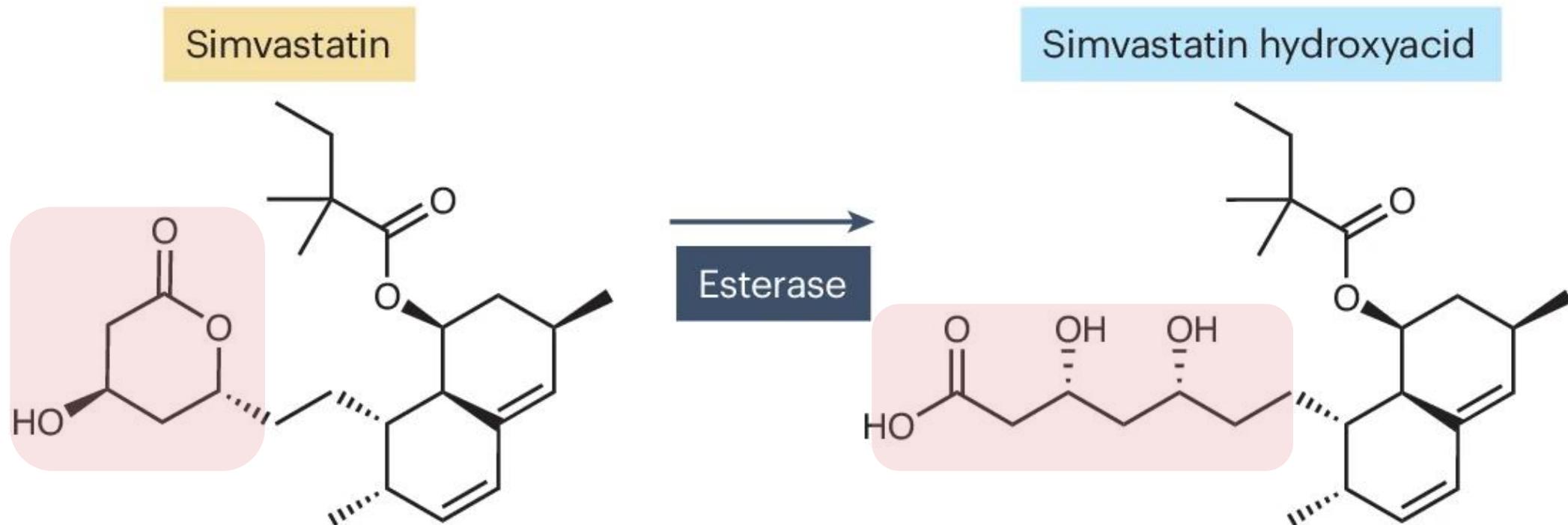
Rosuvastatine en pravastatine hebben hogere selectiviteit voor levercellen



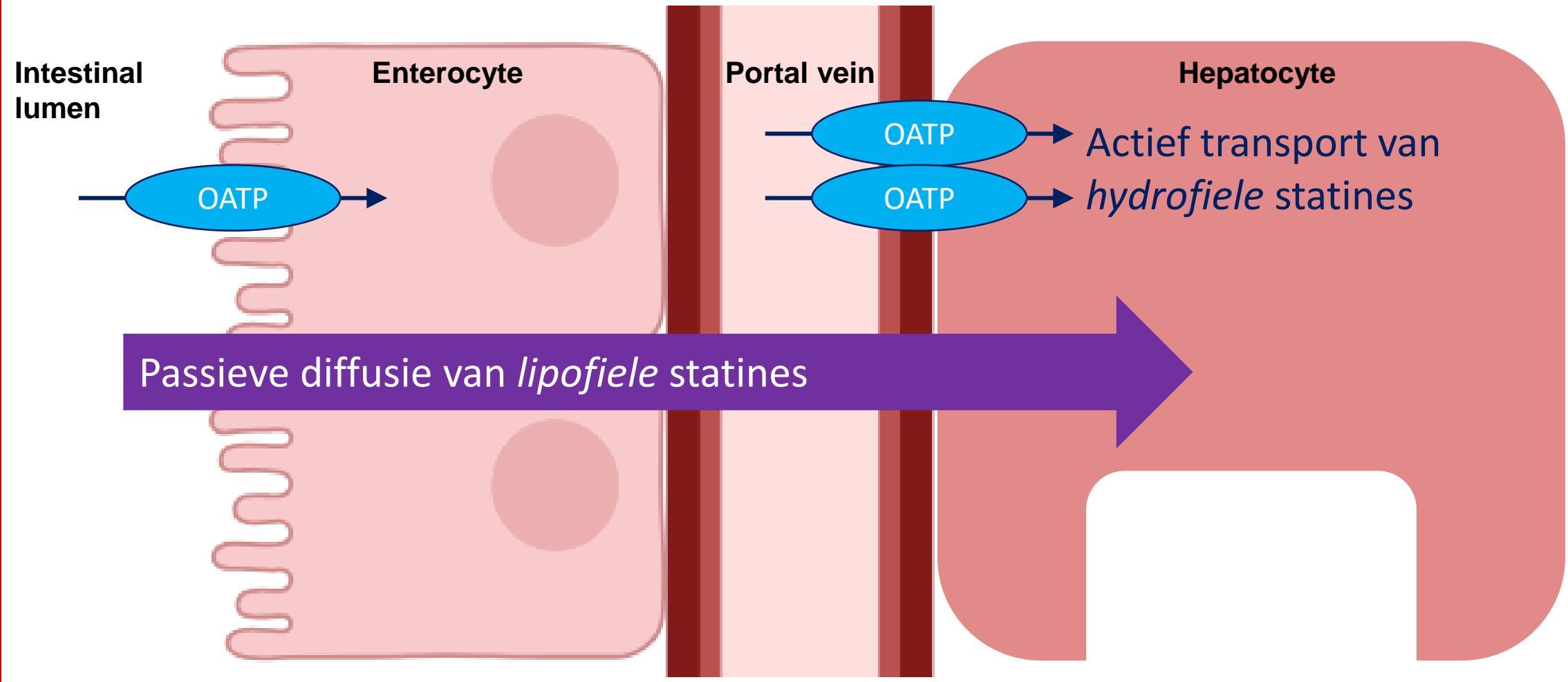
Passieve diffusie van lipofiele statines



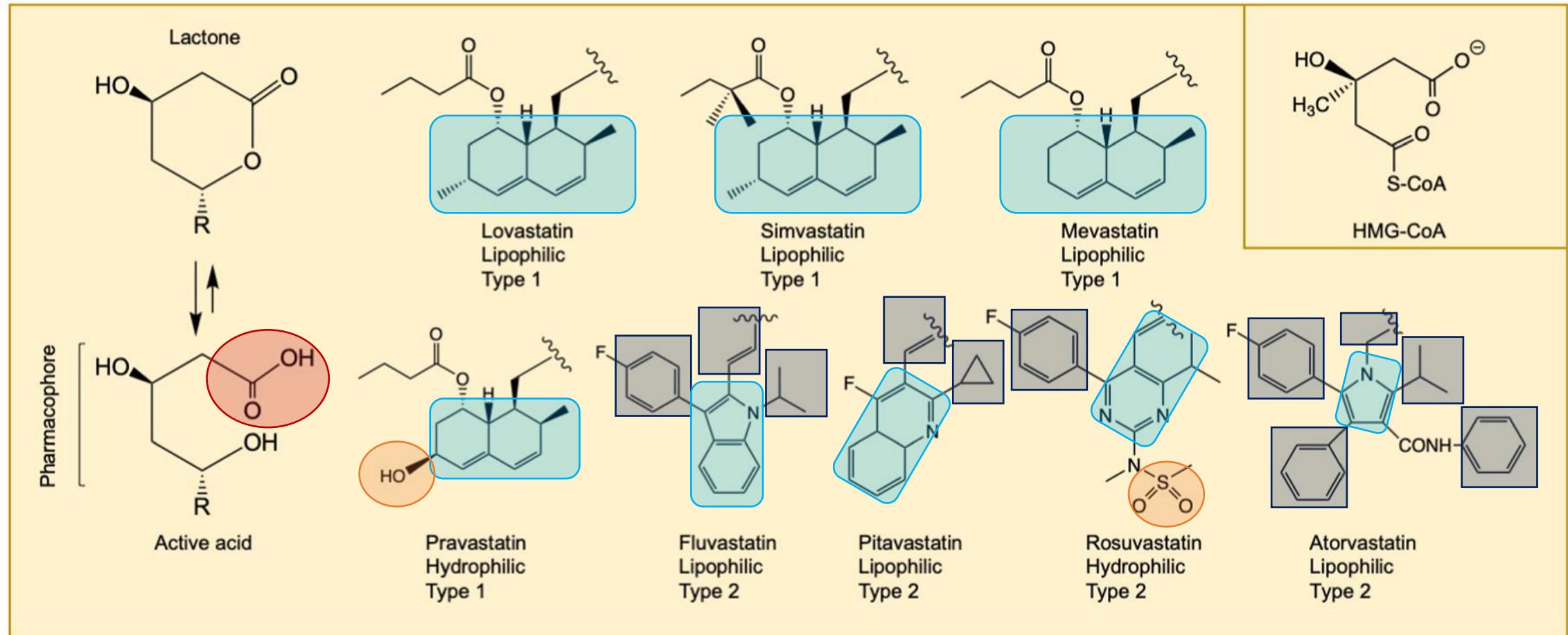
Simvastatin: prodrug vergroot hydrofobiciteit



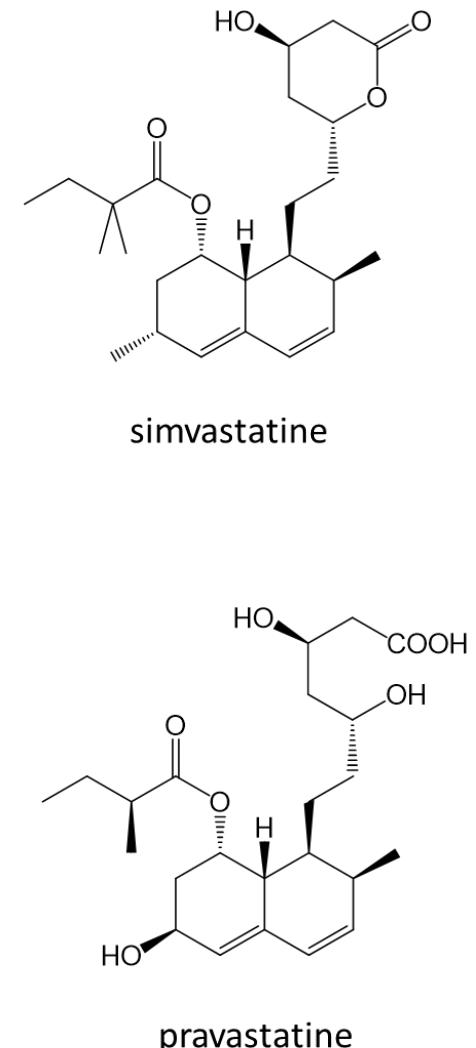
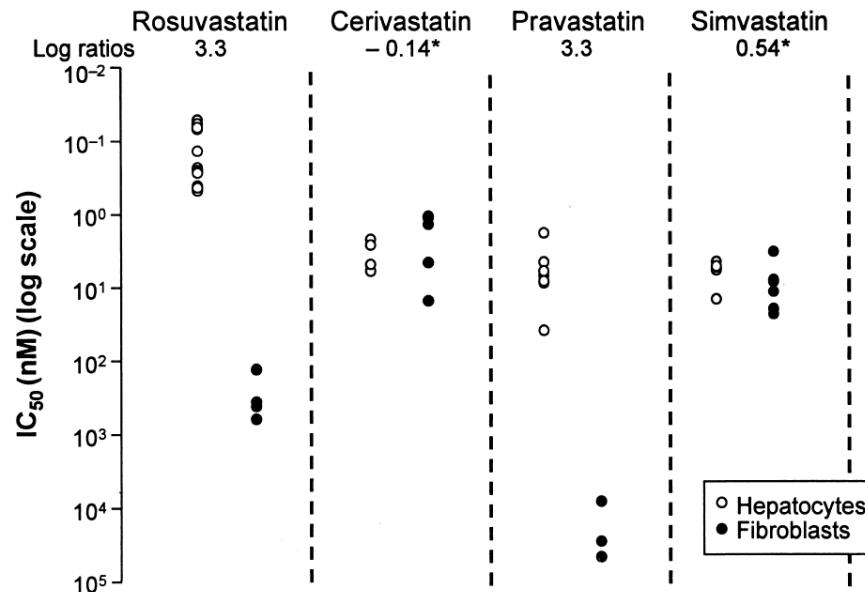
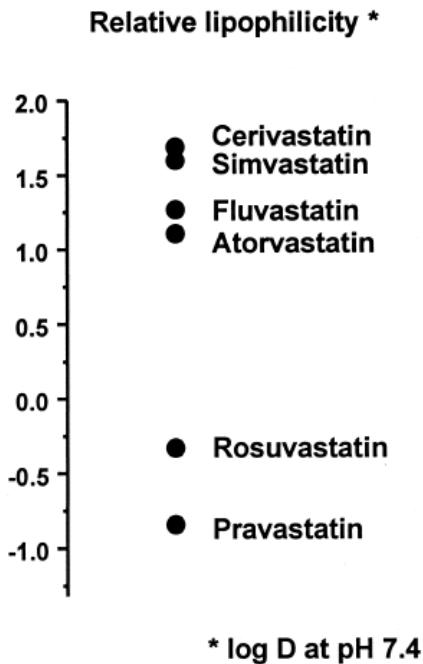
Actief transport van hydrofiele statines



Hydrofiele statines worden selectiever opgenomen door de lever



Hydrofiele statines worden selectiever opgenomen door de lever



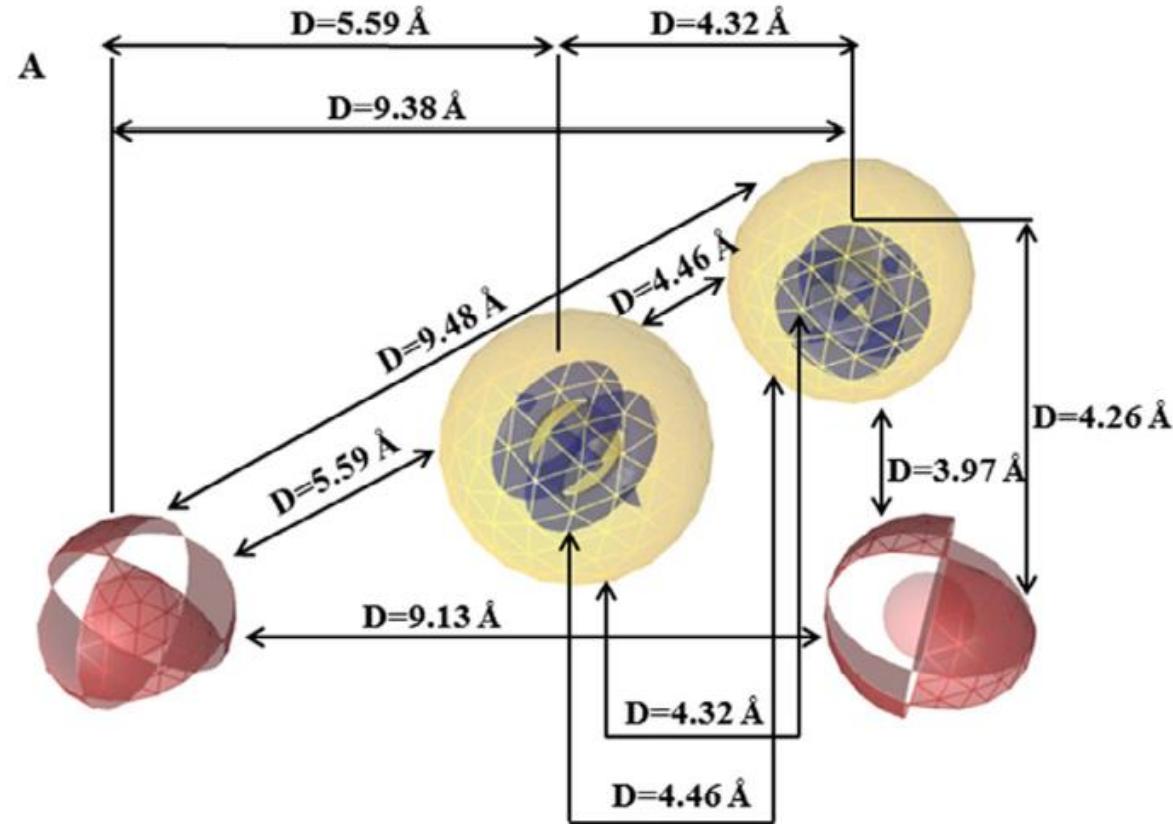
Hoe? pas je deze kennis toe

Angiotensine II antagonisten
Cholesterolverlagers (week 4)



Farmacofoor-model angiotensine-II receptor

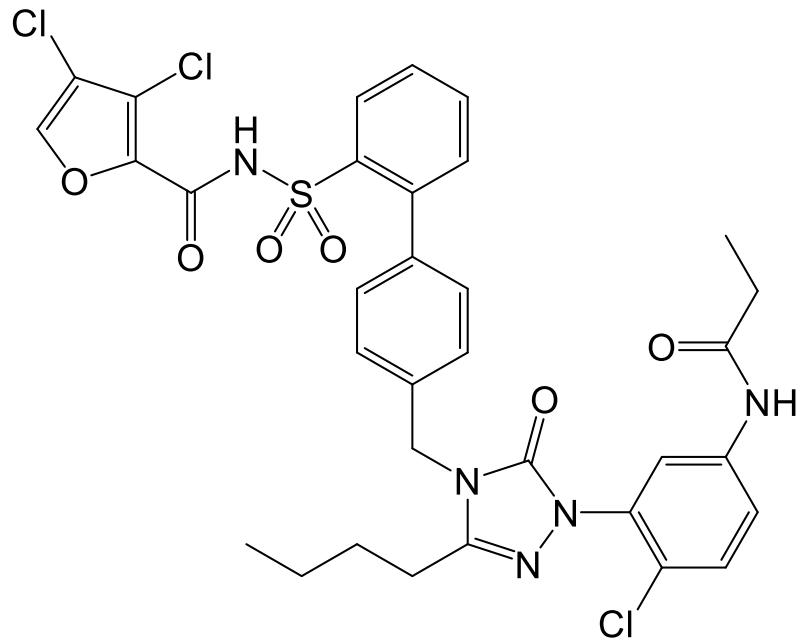
- **Farmacofoor:** De atomen en functionele groepen (en hun onderlinge ruimtelijke positionering) die nodig zijn voor een specifieke farmacologische activiteit.



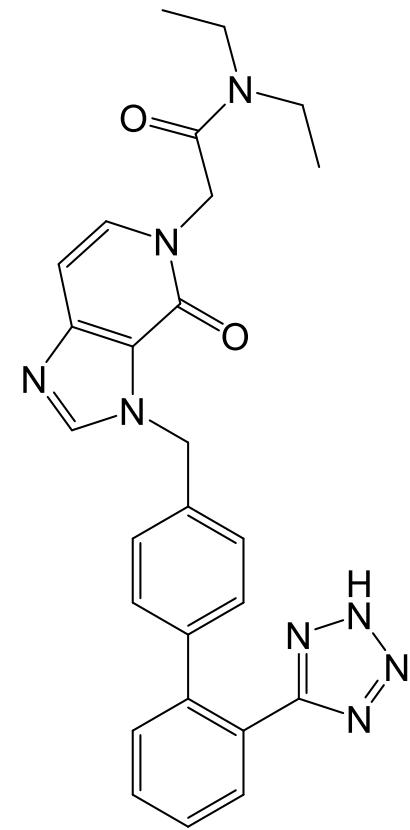
6 structuur-kenmerken vereist:

- 2 Waterstofbrug accepterende eenheden
- 2 Aromatische ringstructuren (bifenylskelet)
- 2 Hydrofobe fragmenten

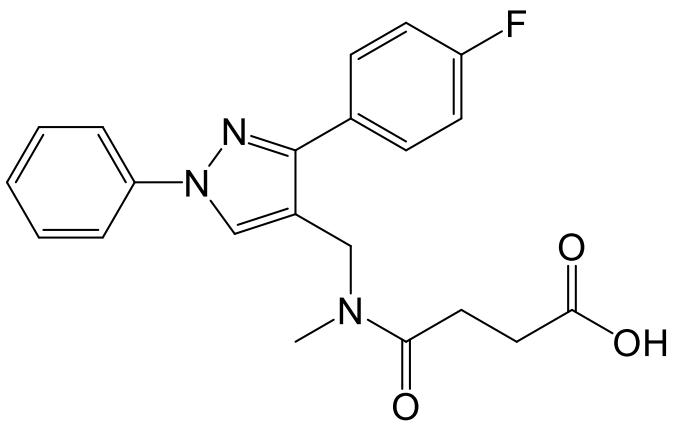
Welke verbindingen voldoen aan farmacofoor-model?



1

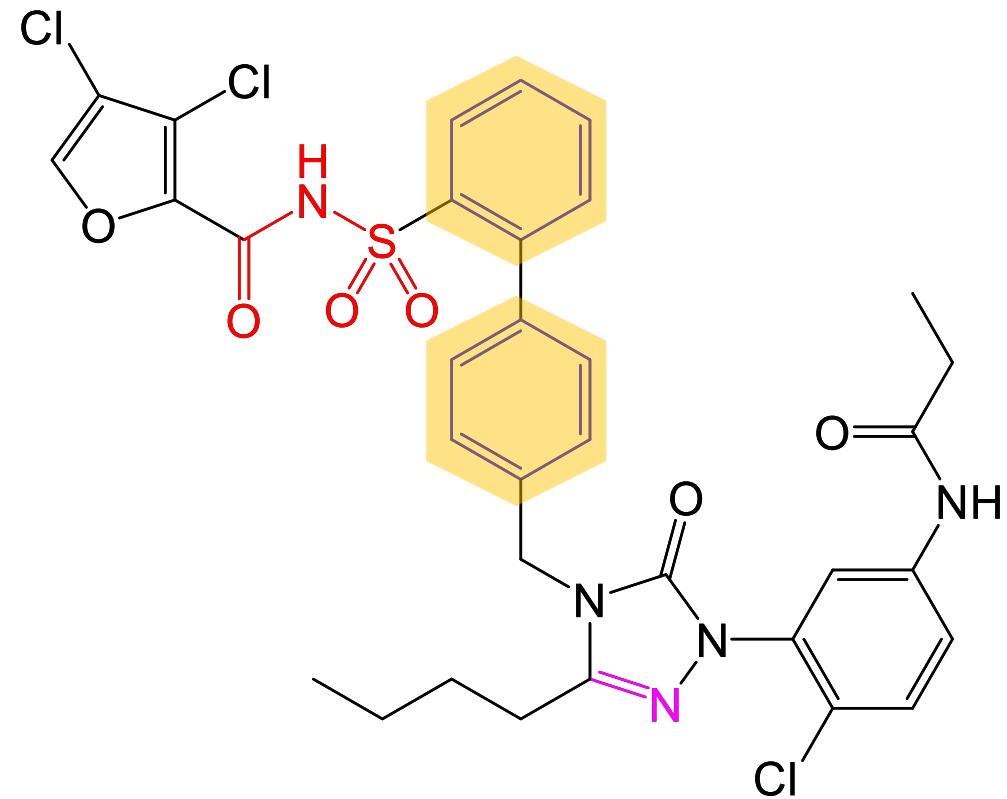
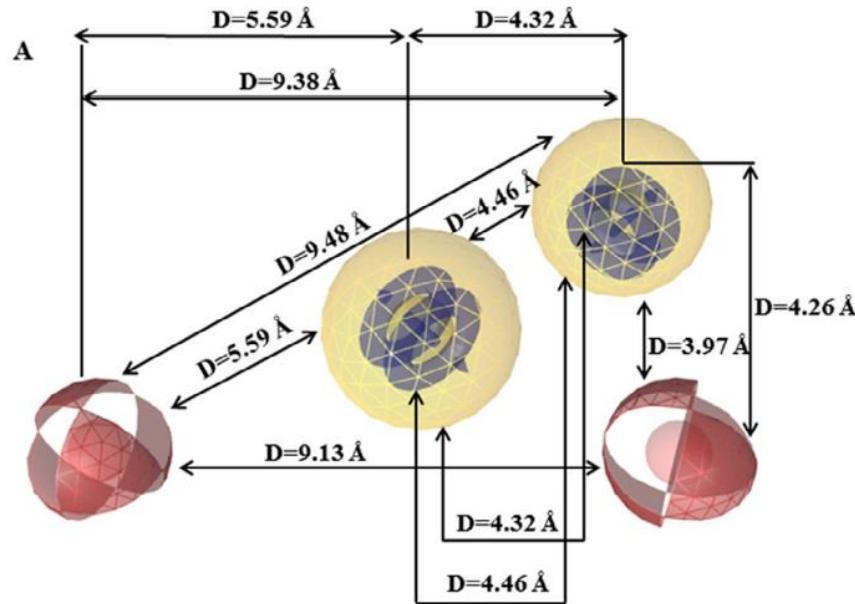


2



3

Welke verbindingen voldoen aan farmacofoor-model?

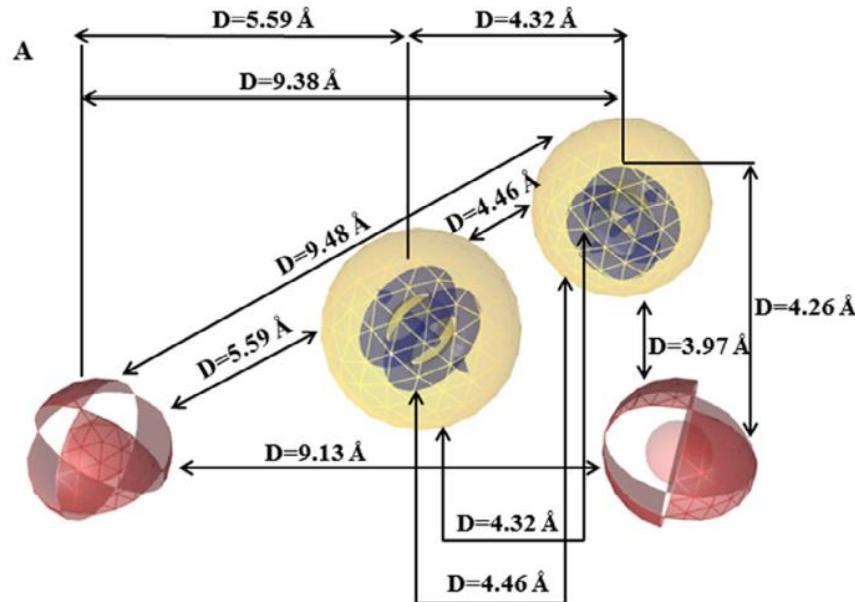


■ 2 Waterstofbrug accepterende eenheden

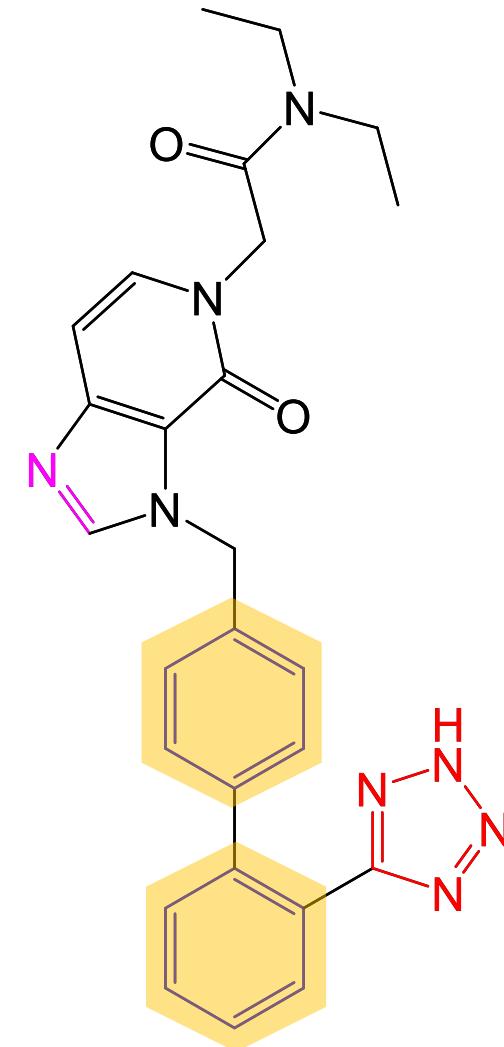
■ 2 Aromatische ringstructuren (bifenylskelet)

■ 2 Hydrofobe fragmenten

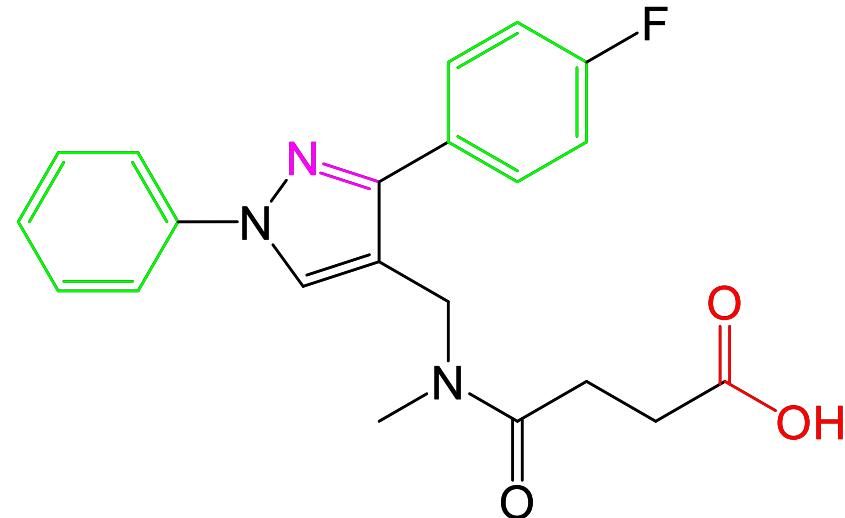
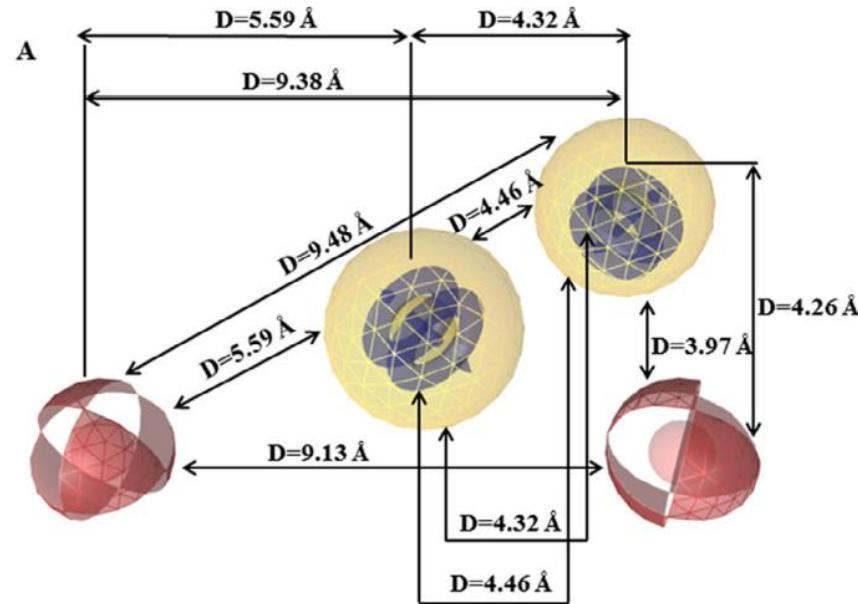
Welke verbindingen voldoen aan farmacofoor-model?



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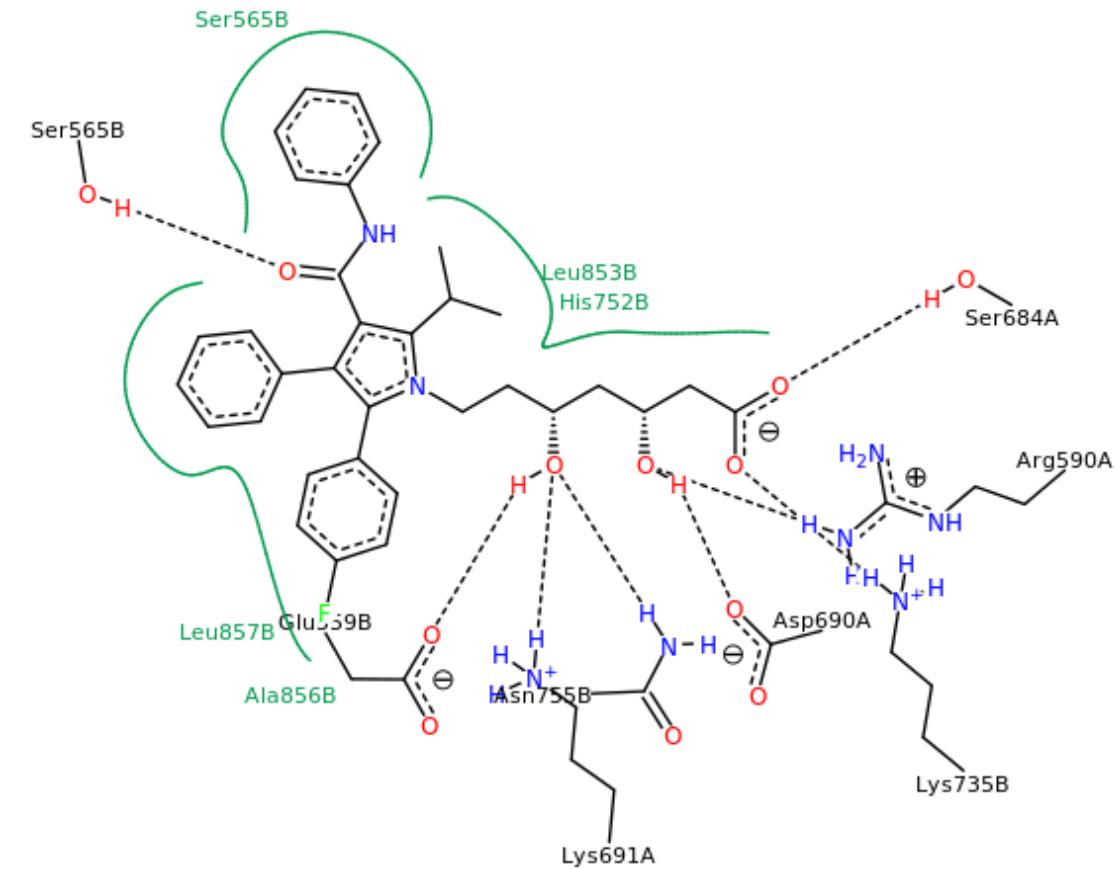
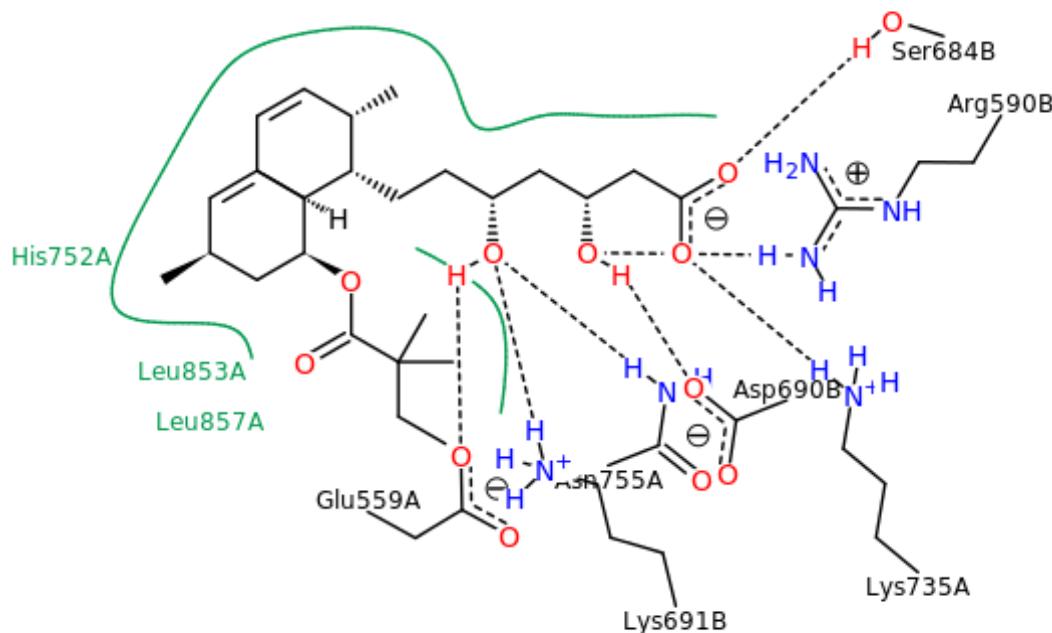


Welke verbindingen voldoen aan farmacofoor-model?

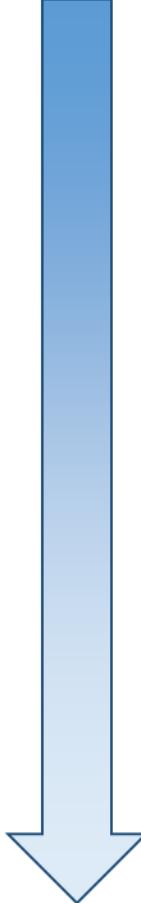


- 2 Waterstofbrug accepterende eenheden
- 2 Aromatische ringstructuren (bifenylskelet)
- 2 Hydrofobe fragmenten

Vraag: Met welke interacties bindt het farmacon aan HMG-CoA-reductase?

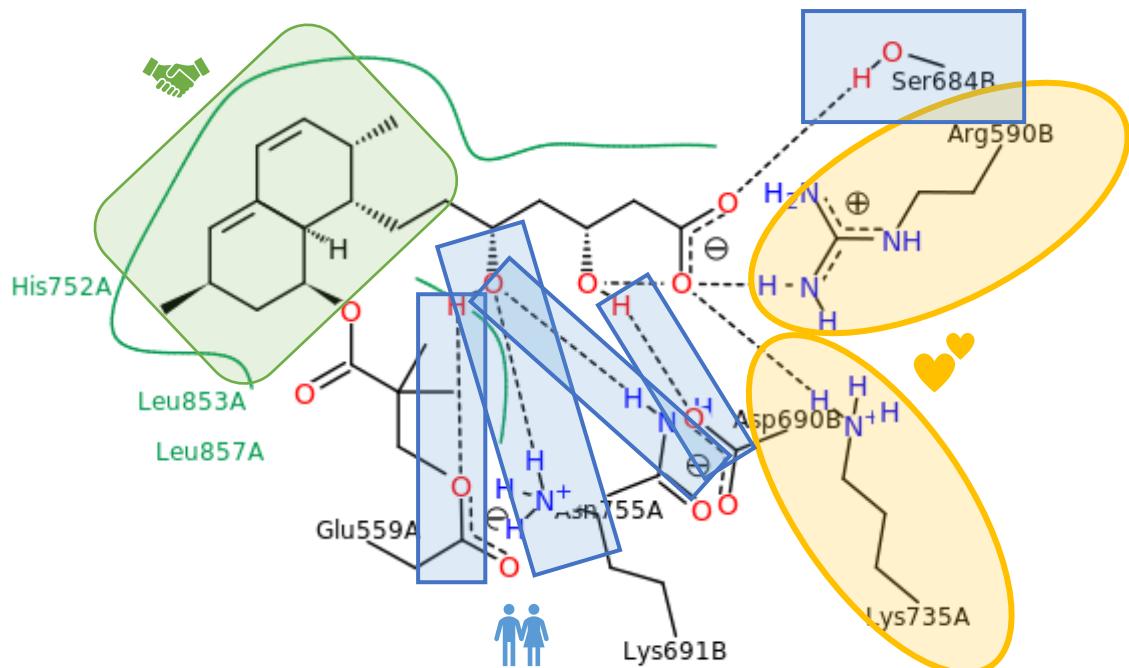


Welke receptor bindingsinteracties zijn er?

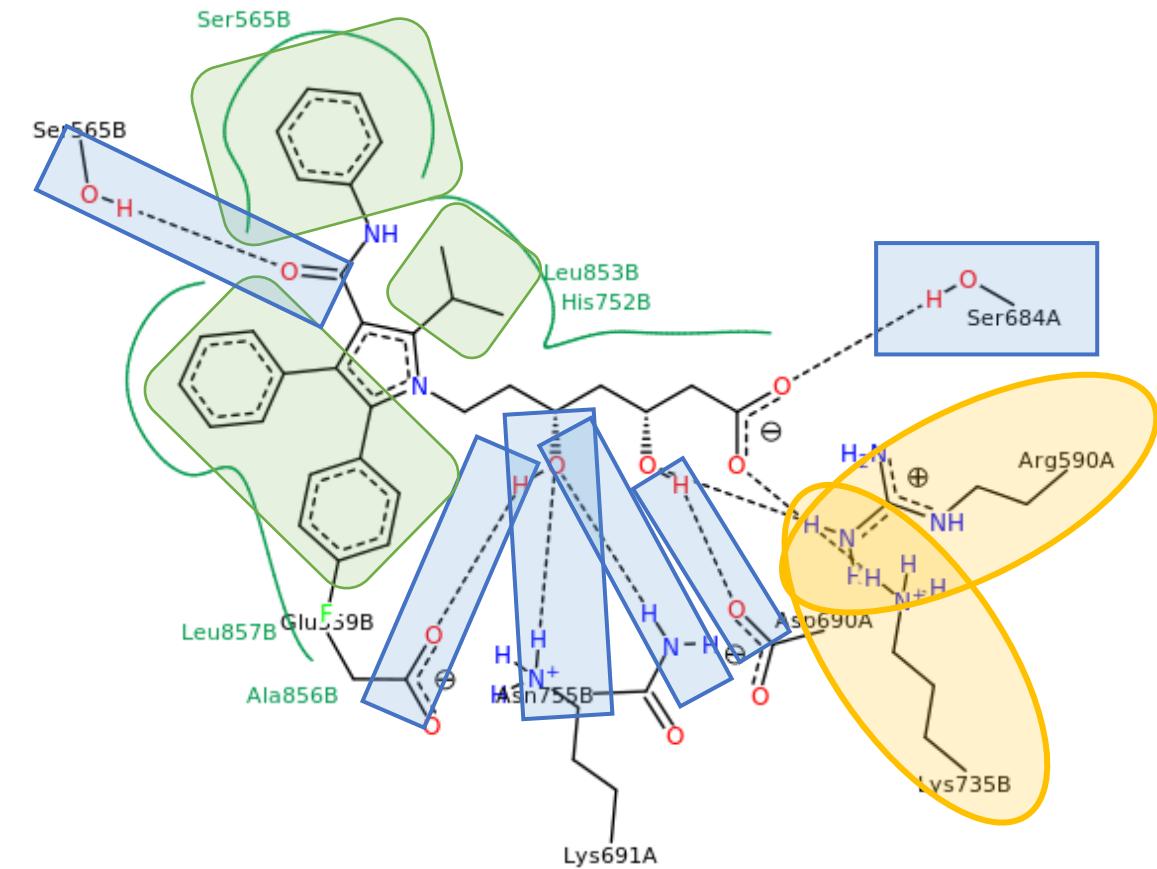


	Covalent	
	Ionogeen	
	Waterstofbrug	
	Ion-dipool	
	Dipool-dipool	
	Hydrofoob	

Vraag: Met welke interacties bindt het farmacon aan HMG-CoA-reductase?

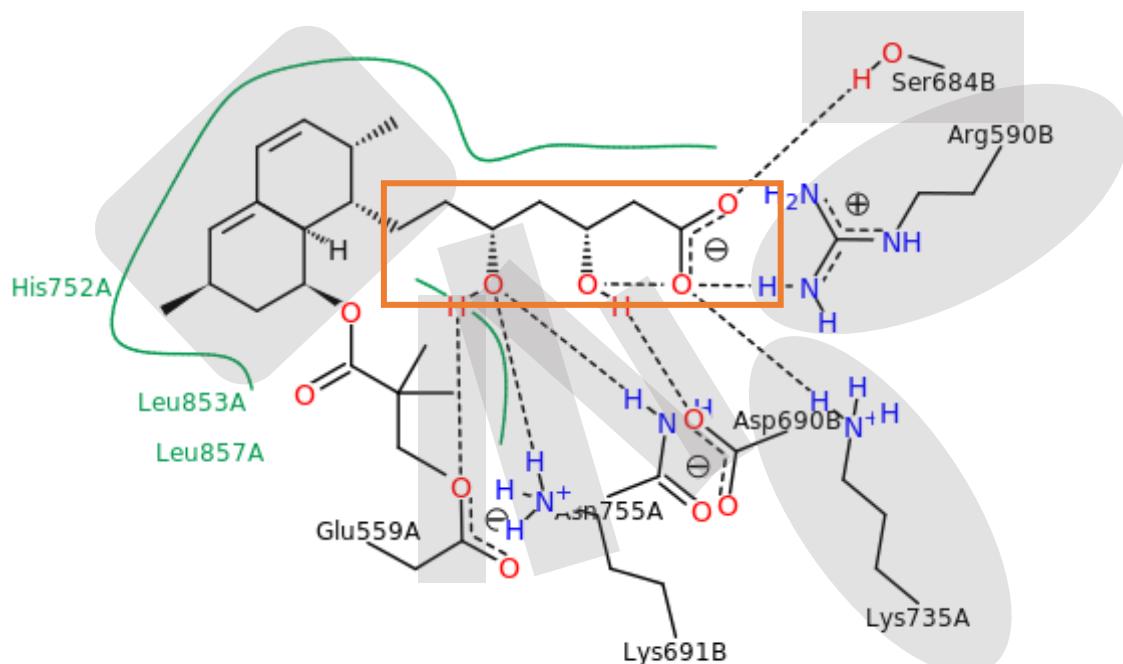


simvastatine

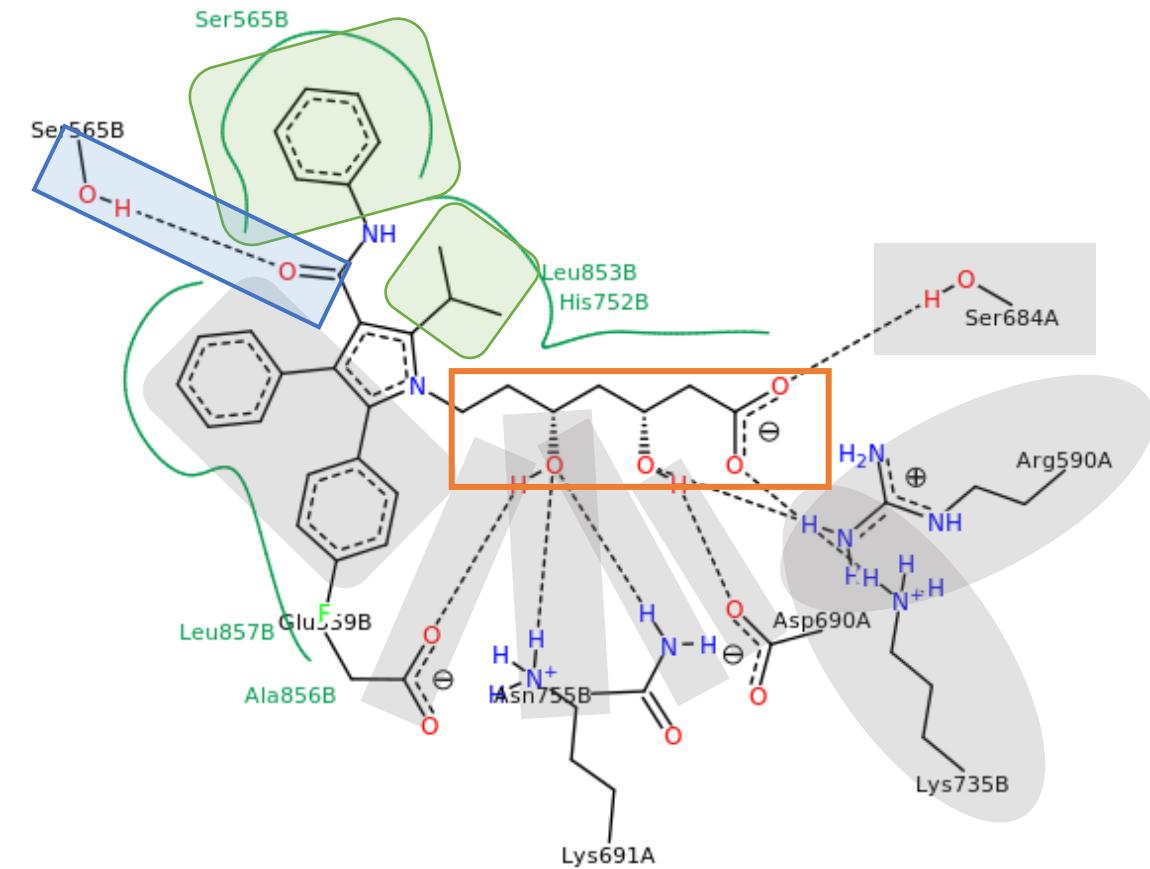


atorvastatine

Vraag: Definieer het *farmacofoor* van statines

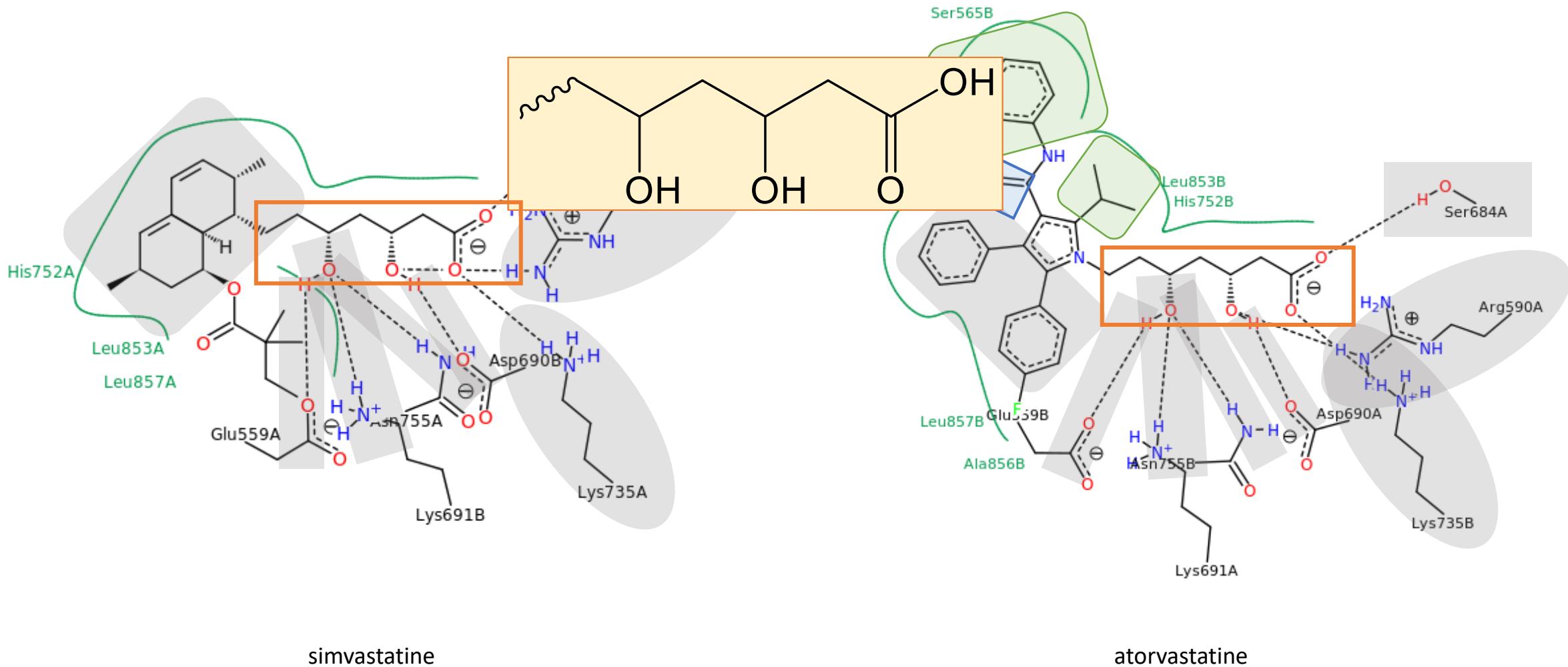


simvastatine

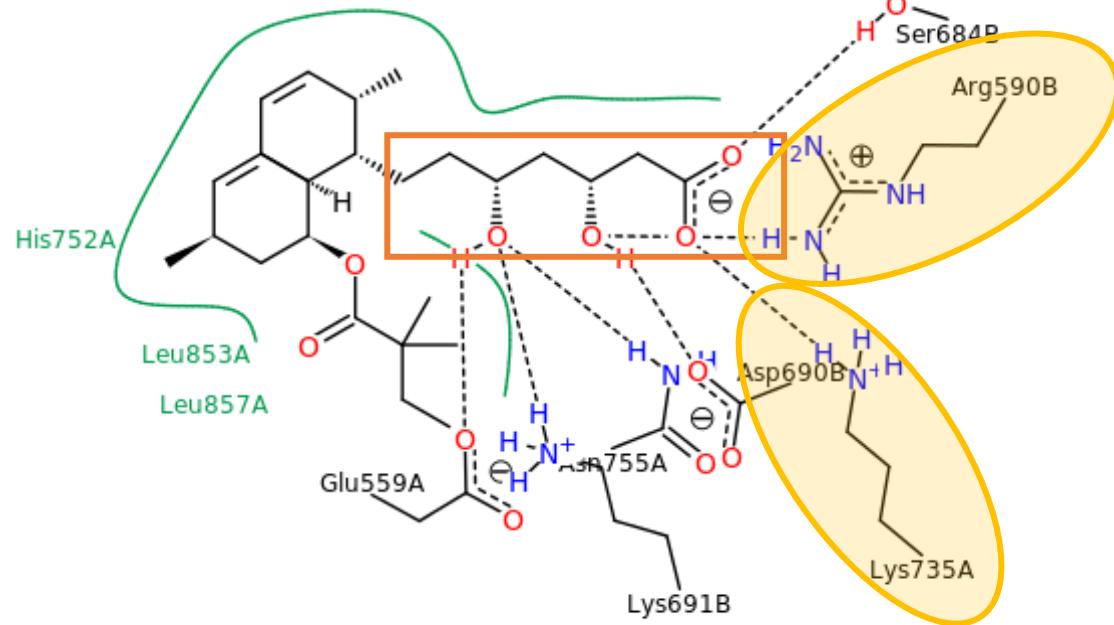


atorvastatine

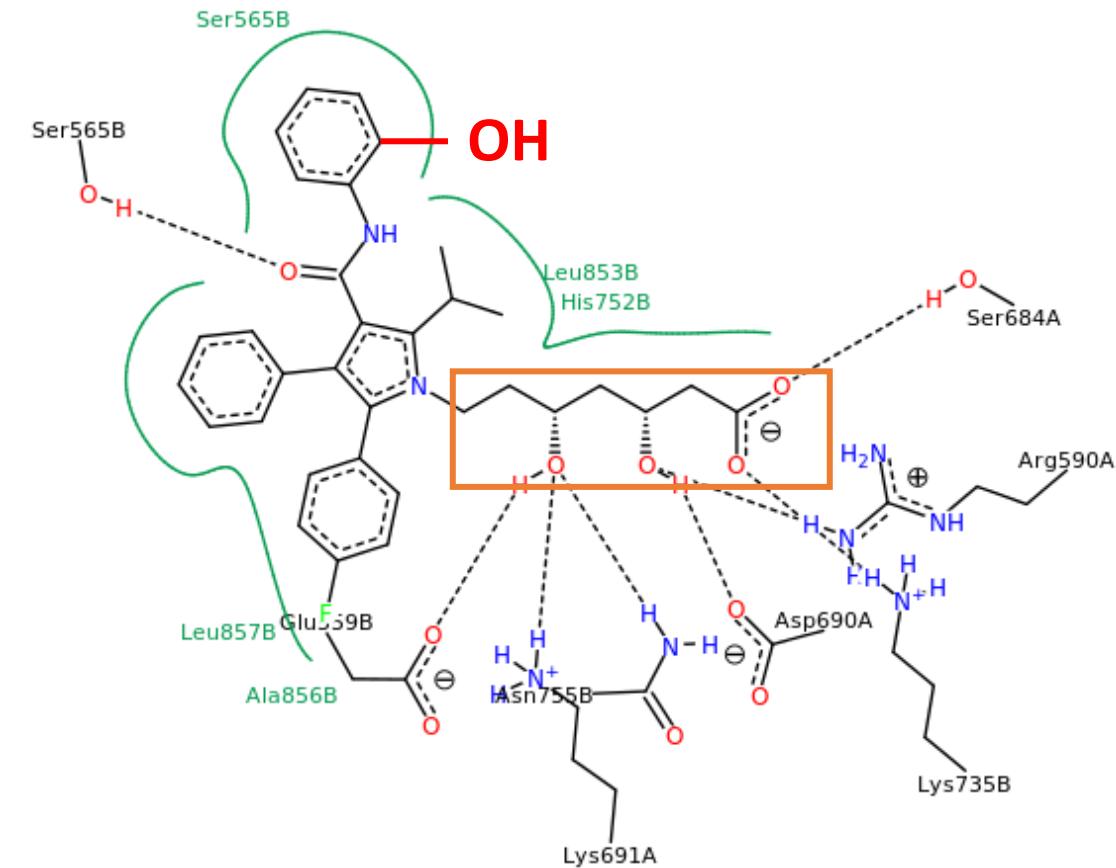
Vraag: Definieer het *farmacofoor* van statines



Vraag: Hoe beïnvloedt een verandering aan de structuur de activiteit/affiniteit van het farmacon?



simvastatine



atorvastatine

En verder?

- **Responsiecollege:** **Vrijdag 6 december @ 11:00 uur:**
 - Vragen van te voren opsturen (voor woensdag 4 december 9:00 uur)
- **Discussieforum Teams:**
 - Help elkaar: zelf vragen stellen en beantwoorden
- **Cursuswijzer BA-102:**
 - Zie Blackboard course content
- **Kennisclips Chemie**
- **Boeken, o.a:**
 - Pandit, Pharmaceutical Sciences
 - Barber, Pharmaceutical Chemistry
 - Stryer, Biochemistry

