# FARM 2219 : Pharmacologie spéciale

## Relations structure-activité: quelques notions utiles (ou éclairantes) *

**1 février 2010**

1. antagonistes du $Ca^{++}$
2. dérivés nitrés
3. β-adrénergiques
4. sartans
5. statines
6. ézétimibe

**20 mai 2010**

7. spironolactone
8. opiacés et codéine
9. tricycliques
10. neuroleptiques
11. sumatriptan

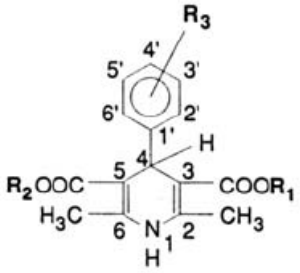
RSA vues dans d'autres parties du cours:

AINS (et coxibs) – antihistaminiques (H1 et H2) – antibiotiques – antiviraux – inhibiteurs de la pompe à proton – agents procinétiques – antiémétiques (sétrons) – antagonistes muscariniques (respiratoire) – morphiniques – hypnosédatifs – antidépresseurs – agents anti-parkinsoniens – neuroleptiques – anesthésiques locaux – stéroïdes (cort. et sex.) – diphosphonates – insulines – glitazones …

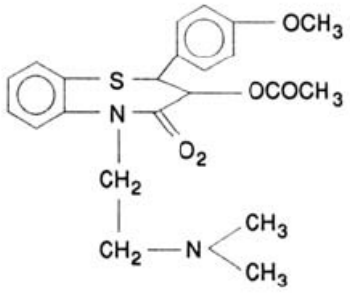
* avec l'aide (éclairée) des professeurs Poupaert, Depovere et Sonveaux 

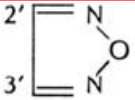
# Antagonistes calciques

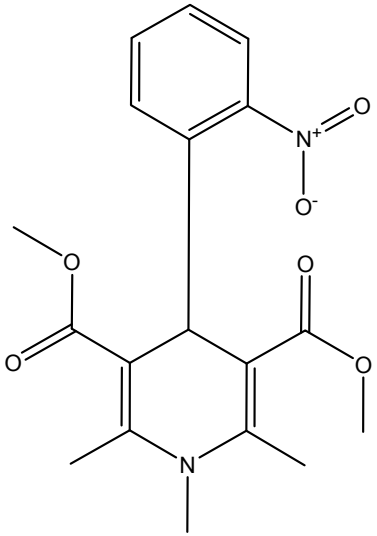
dihydropyridines (structure générale)

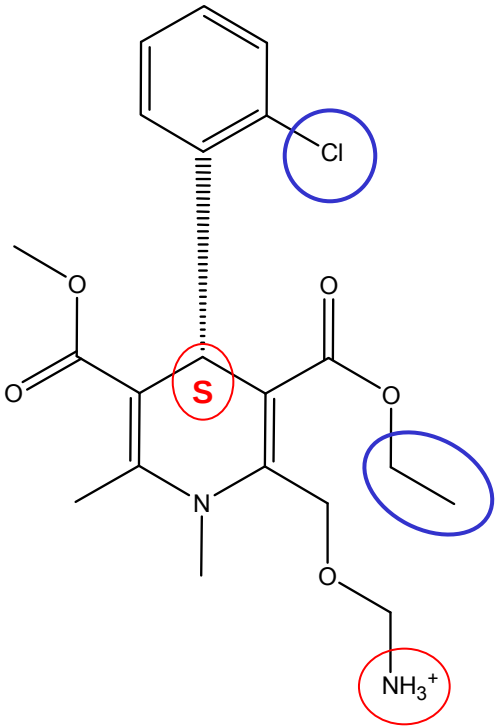


diltiazem



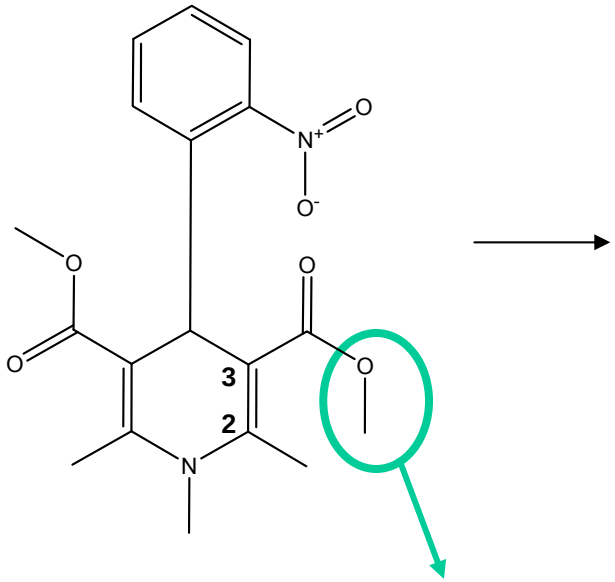
| | $R_1$ | $R_2$ | $R_3$ |
|---|---|---|---|
| nifédipine | $CH_3$ | $CH_3$ | 2'-$NO_2$ |
| nimopidine | $(CH_2)_2OCH_3$ | $CH(CH_3)_2$ | 3'-$NO_2$ |
| nitrendipine | $C_2H_5$ | $CH_3$ | 3'-$NO_2$ |
| nilupidine | $CH_2CH_2H_3$ | $C_3H_7O(CH_2)_2$ | 2'-$NO_2$ |
| félodipine | $CH_3$ | $C_2H_5$ | 2',3-dichloro |
| nisoldipine | $CH_3$ | isobutyl | 2'-$NO_2$ |
| nicardipine | (phénylméthyl-méthylamino)éthyl | $CH_3$ | 2'-$NO_2$ |
| amlodipine | $C_2H_5$ | $CH_3$ | 2'-Cl-2-$CH_2O(CH_2)_2NH_2$ |
| isradipine | $CH(CH_3)_2$ | $CH_3$ |  |
| lacidipine | $C_2H_5$ | $C_2H_5$ | 2'$CHCHCO_2C(CH_3)_3$ |





Dia 6 de Mr Feron – corrigée ce 24-01-10 pour la nimodipine

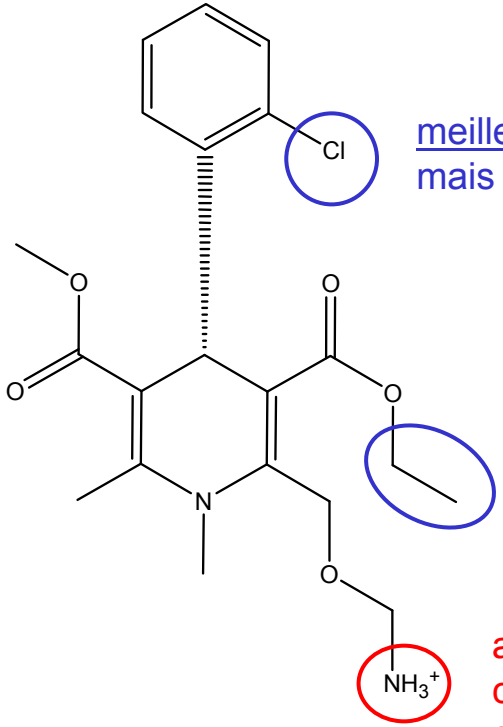
# Antagonistes calciques; pourquoi des $t_{1/2}$ différents ?




nifédipine

hydrolyse

cyclisation après oxyd. du $CH_3$ en pos. 2 (lactone)




amlodipine

meilleure stabilité
mais augmentation de la lipophilie

meilleure résistance à l'hydrolyse mais aumentation de la lipophilie

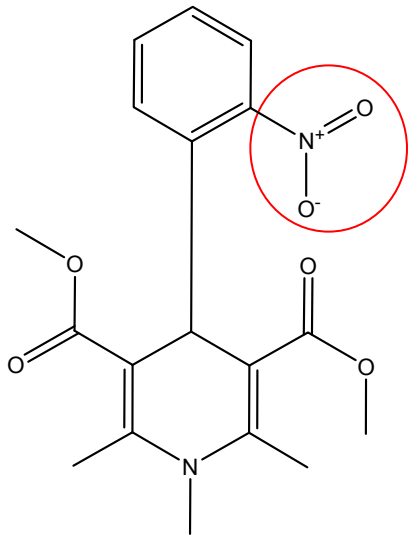
addition d'une charge pour compenser l'augmentation de lipophilie

# Antagonistes calciques: charge (à pH 7) et lipophilie

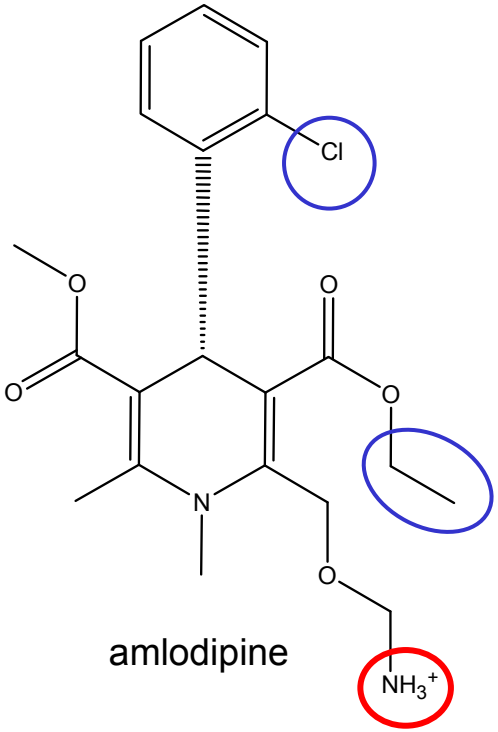
(en relation avecv la $t_{1/2}$ et la pénétration dans le SNC)

| | $t_{1/2}$ | log P | log D pH7 | pKa |
|---|---|---|---|---|
| nifedipine | 3 h | 2.96 | 2.97 | 2.69 |
| amlodipine | 45h | 4.16 | 2.21 | **8.97** |
| nimodipine | 2h | 3.85 | **3.85** | 2.77 |

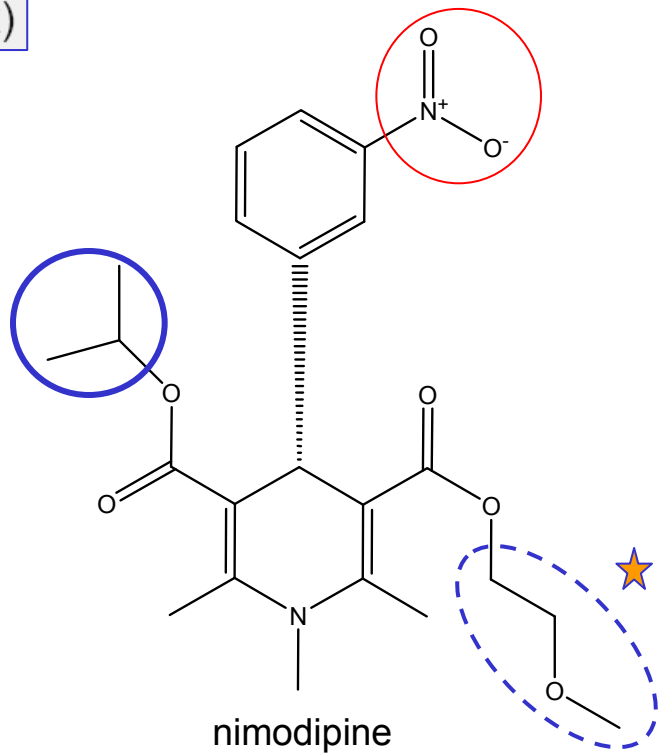
** nimodipine: très lipophile (⇒ spasmes artériels cérébraux)



nifédipine



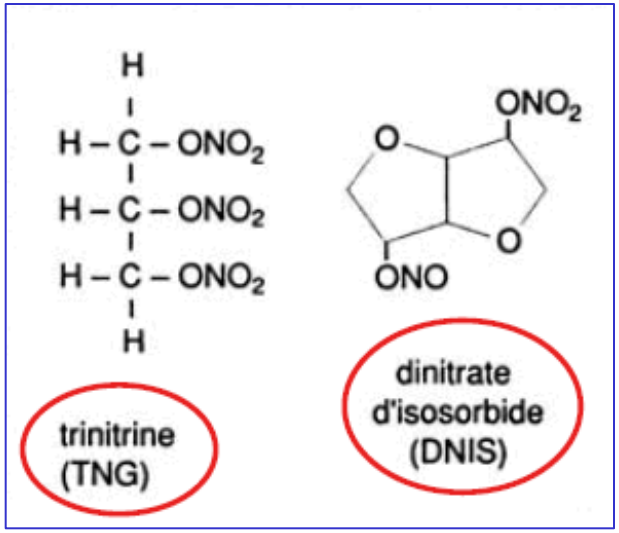
amlodipine

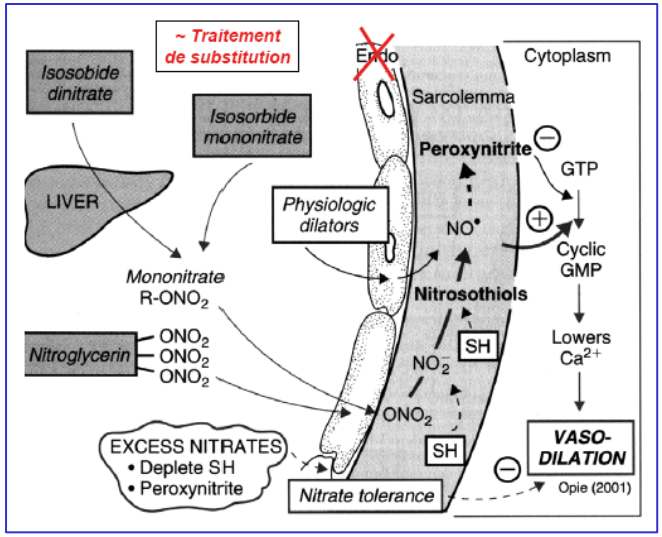


nimodipine

!! Dia 6 de Mr Feron corrigée ce 24-01-10

# Dérivés nitrés: pourquoi des rapides et des lents ?

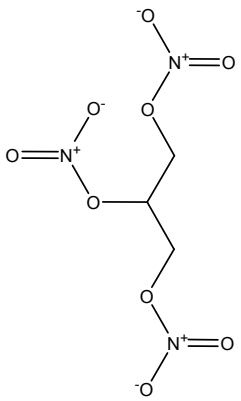


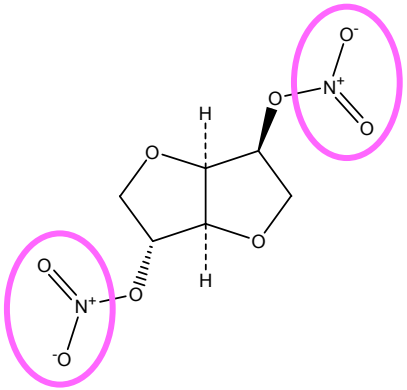



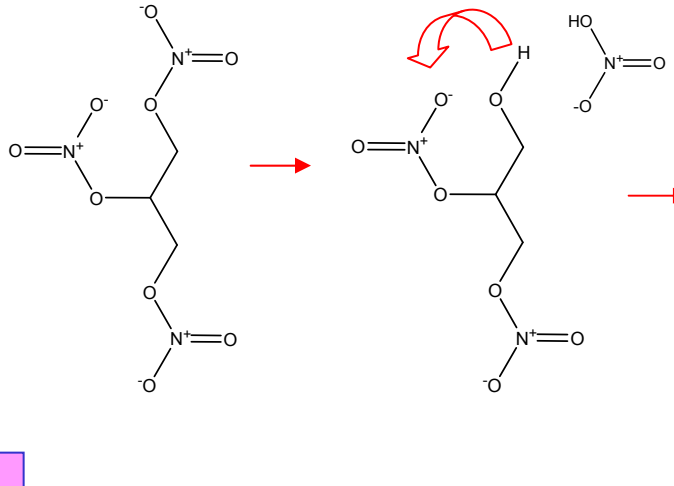

autocatalyse !

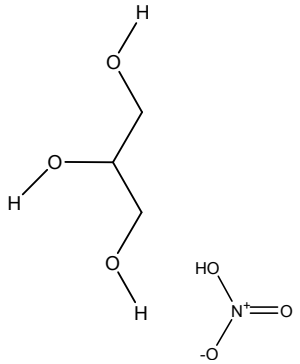
rapide

lent



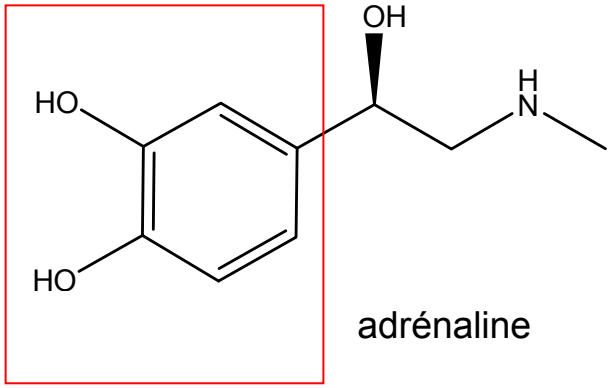






!! erreur dans la dia 9 (F.) - Fig 14.1 (Shorderet) – c'est -$ONO_2$ 2 x

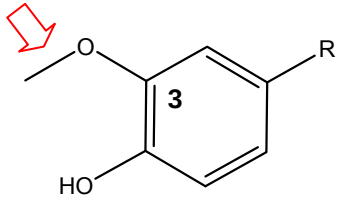
# β-mimétiques - β-bloquants: importance du catéchol




adrénaline

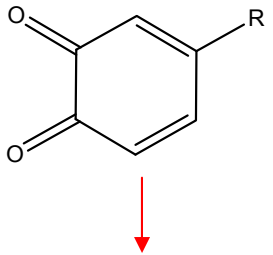
**catéchol**

dégradation rapide par la COMT



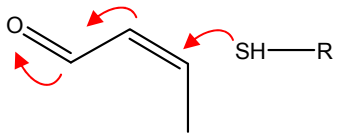

**aussi pour la dopamine !**

oxydation en *o*-quinone




**aussi pour le paracétmol !**

**sequestration du CoASH et du glutathion**

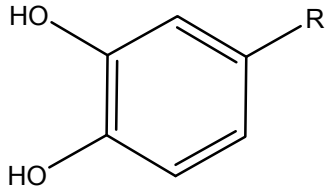



accepteur de Michaël …

C'est pourquoi les β-mimétiques et β-bloquants développés comme médicaments éviteront cette structure, mais essayeront d'en garder les éléments importants…

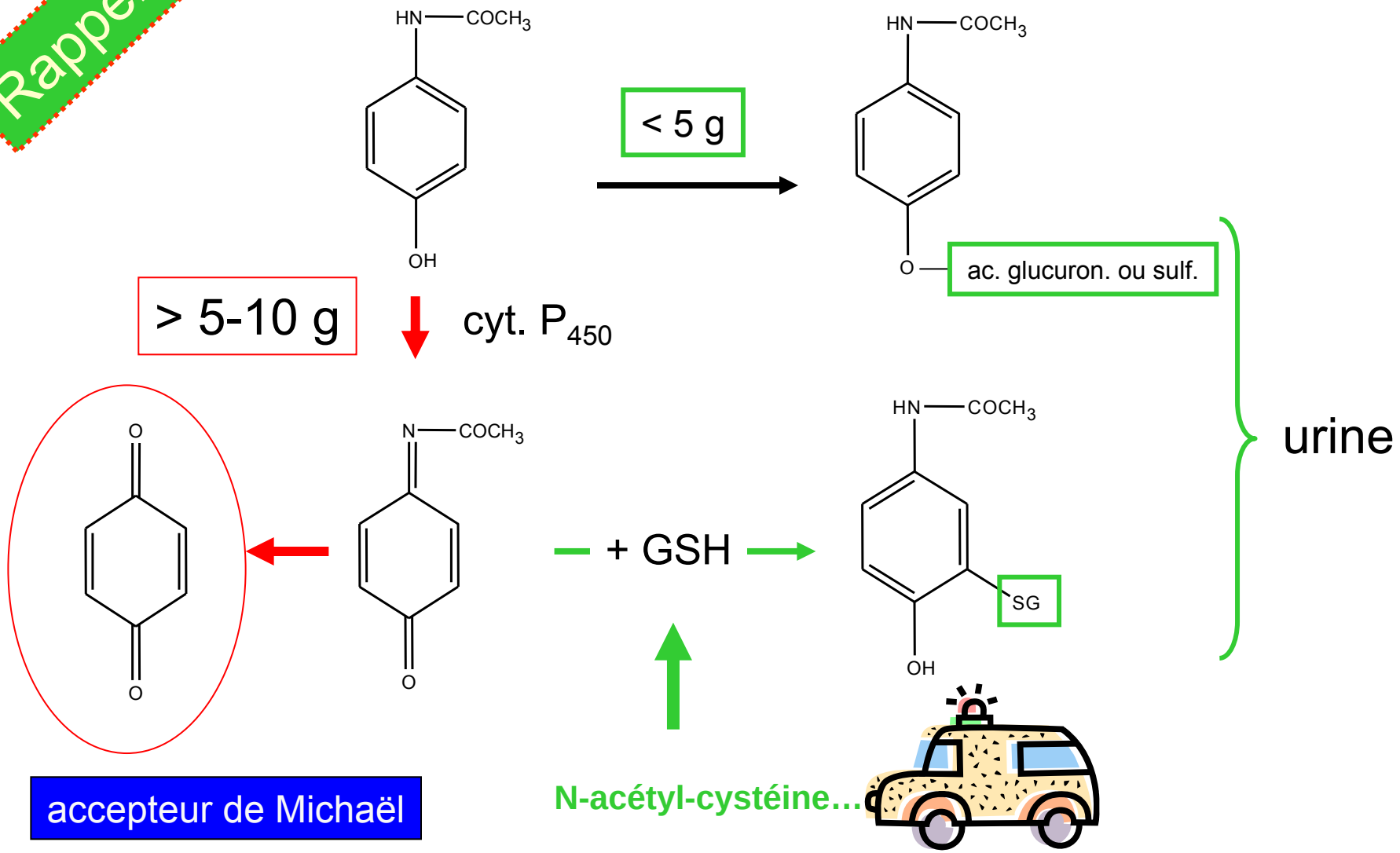
**H-donneur/accepteur** →

**H-donneur/accepteur** →

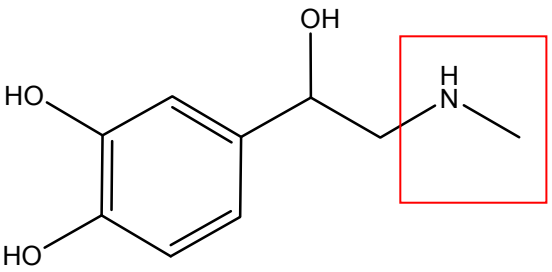


# Metabolisme hépatique du paracétamol et toxicité ...

Rappel

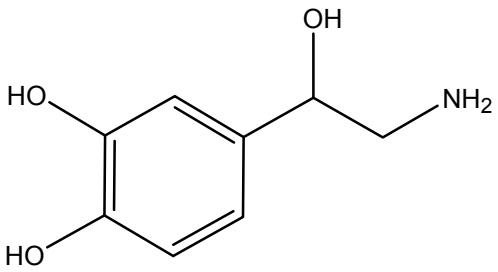


# β-mimétiques - β-bloquants: inhiber la dégradation…

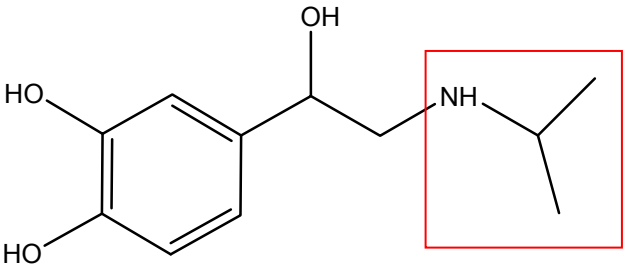



adrénaline

déalkylation




noradrénaline

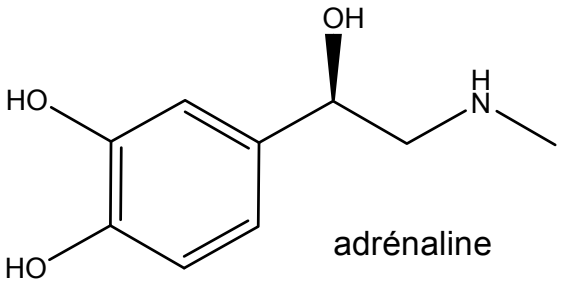



isoprotérénol

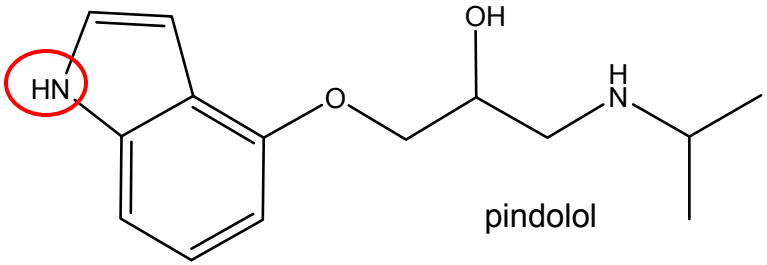
déalkylation moins aisée

- un groupe isopropyle sera souvent utilisé pour améliorer la stabilité (et renforcer l'activité β)
- un *t*-butye rendra la molécule non-dégradable par déalkylation (absence de CH en α du N

# β-bloquants et activité sympathicomimétique intrinsèque

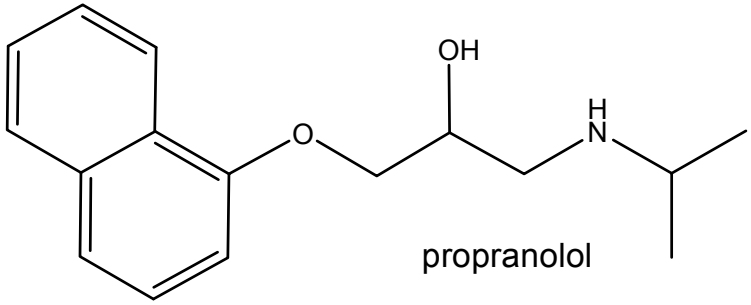



adrénaline

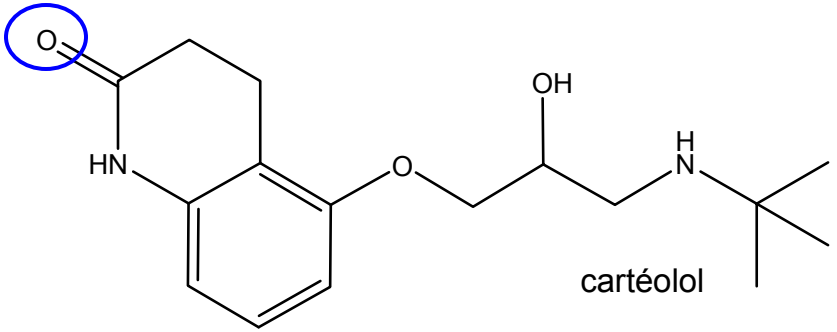



pindolol

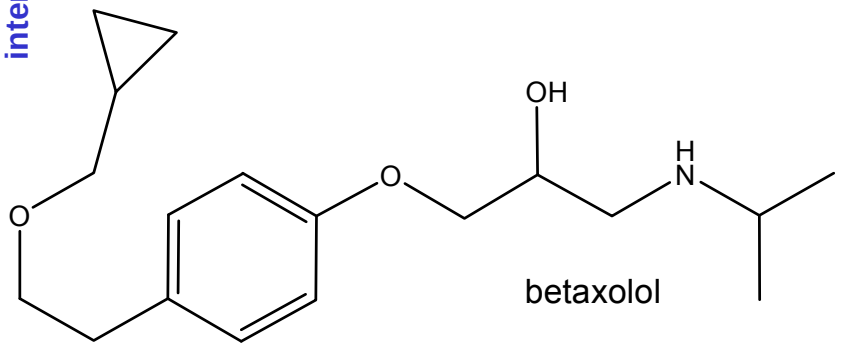
interactions hydrophobes




propranolol



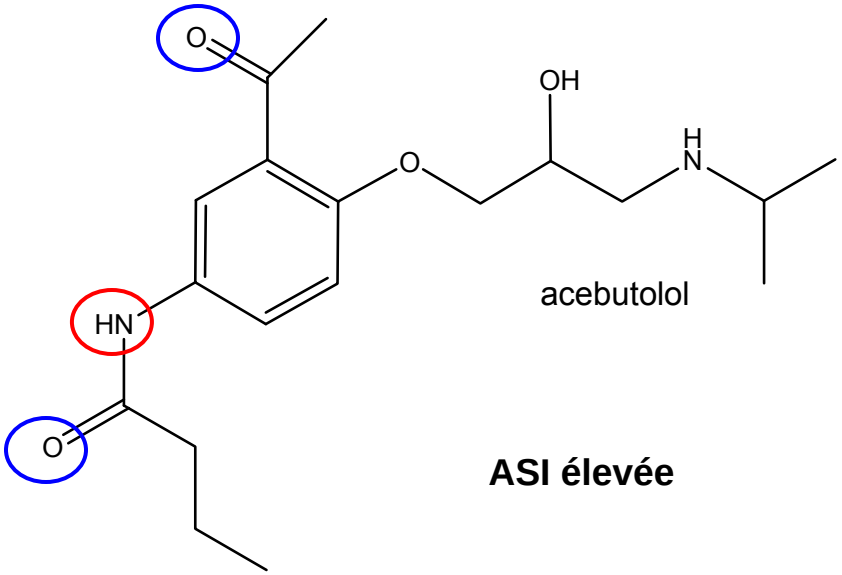

cartéolol




betaxolol

cycle virtuel
non hydroxylable

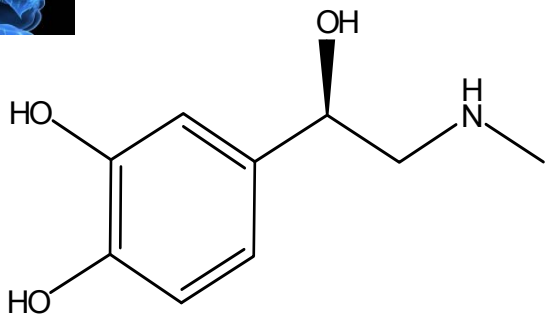
**ASI faible ou nulle**




acebutolol

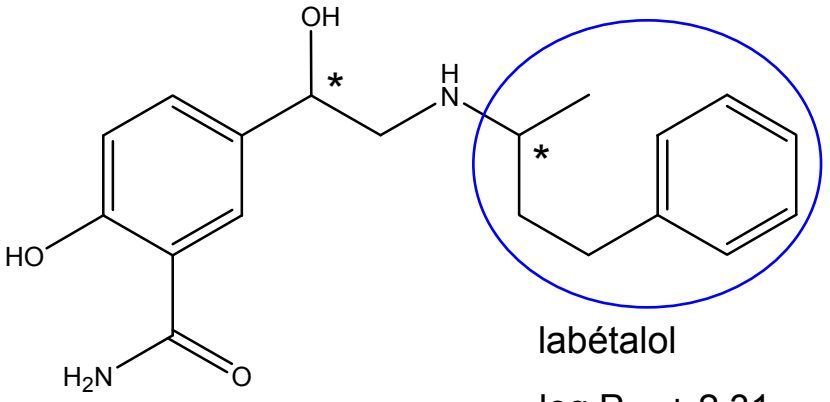
**ASI élevée**

# β-bloquants et lipophilie [a]



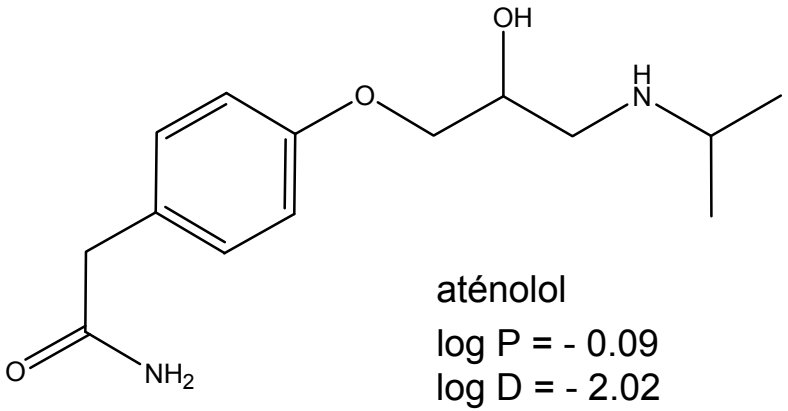

L-adrénaline

log P = - 0.63
log D = - 2.75



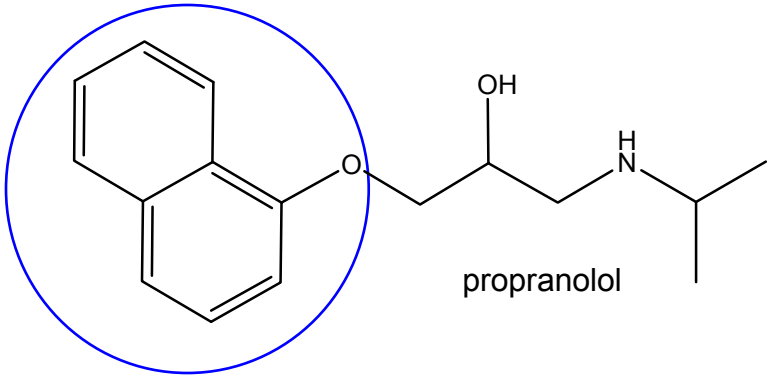

labétalol

log P = + 2.31
log D = + 0.33
SNC forte




aténolol

log P = - 0.09
log D = - 2.02
SNC faible

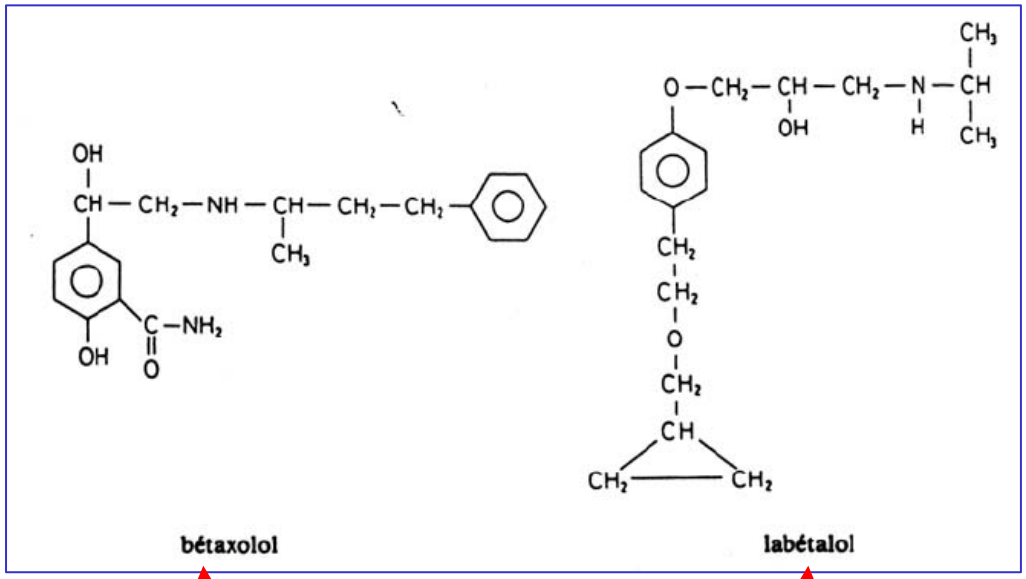



propranolol

log P = + 3.09
log D = + 1.00
SNC forte

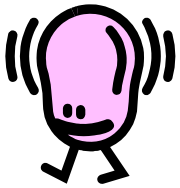
[a] les valeurs de log D sont celles à pH 7

# β-bloquants: une petite erreur…

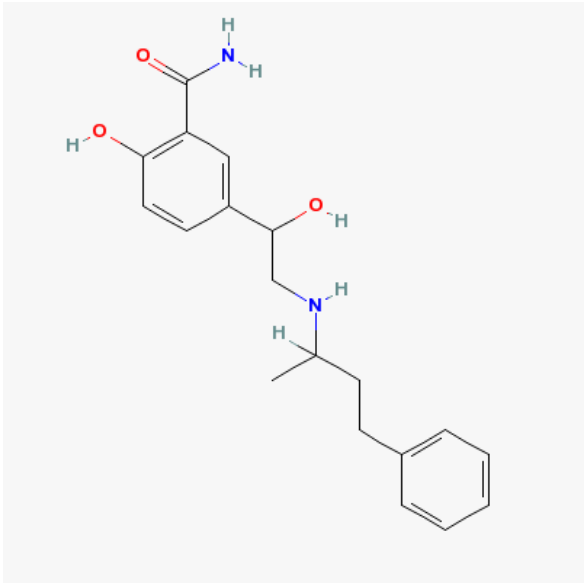



légendes inversées…

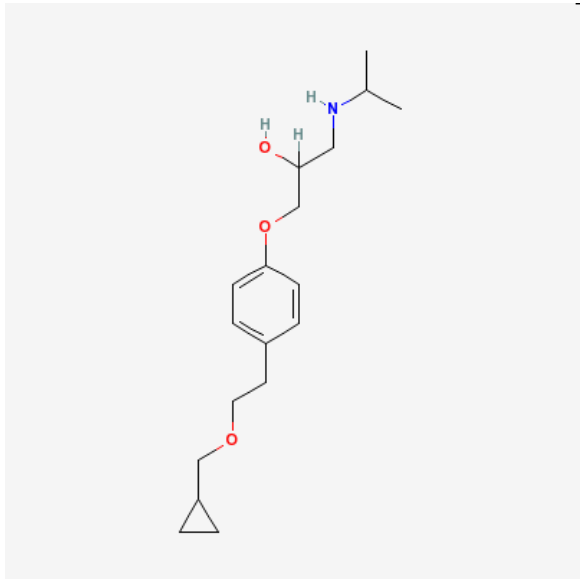
!! faute dans la dia 3 (F.) - Fig 3 (Shorderet)



Corrigé par Mr Feron ce 24-01-10

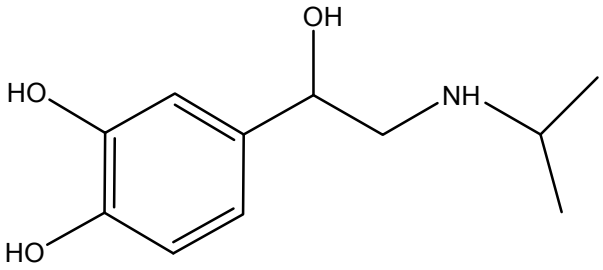


labetalol; Labetolol; Ibidomide …
**IUPAC**: 2-hydroxy-5-[1-hydroxy-2-(4-phenylbutan-2-ylamino)ethyl]benzamide

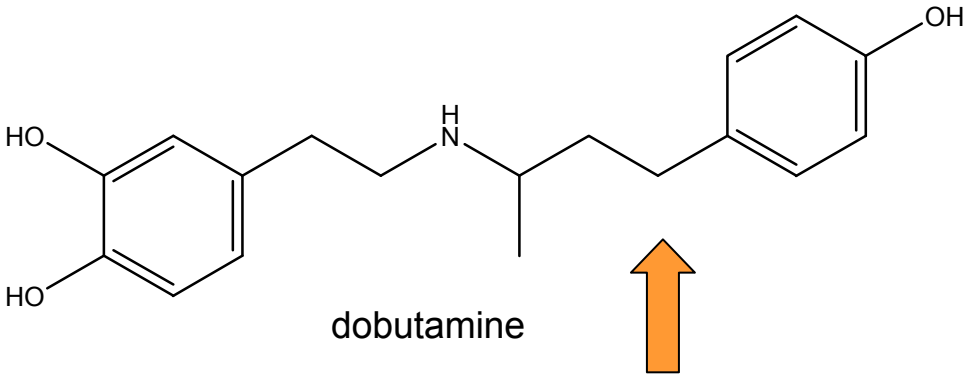


betaxolol; Betazolol; Betoptic …
**IUPAC**: 1-[4-[2-(cyclopropylmethoxy)ethyl]phenoxy]-3-(propan-2-ylamino)propan-2-ol

# β-mimétiques
# β1 et β2

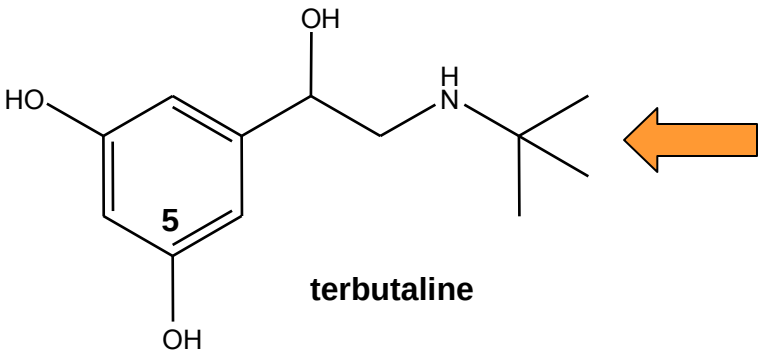



isoprotérénol




dobutamine

renforce
l'activité β

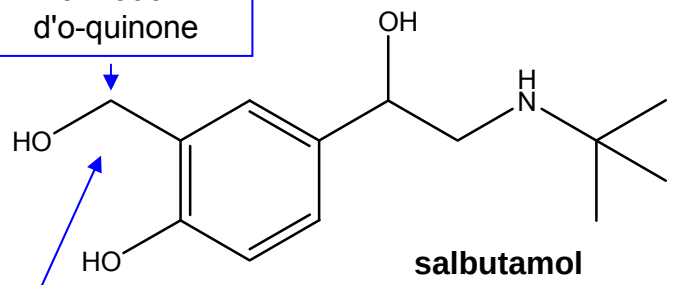



**terbutaline**

5 –OH confère une sélectivité β2
(salbutamol = exception [voir dia suivante])

# $\beta_2$-mimétiques: construire des molécules (suffisamment) spécifiques et stables

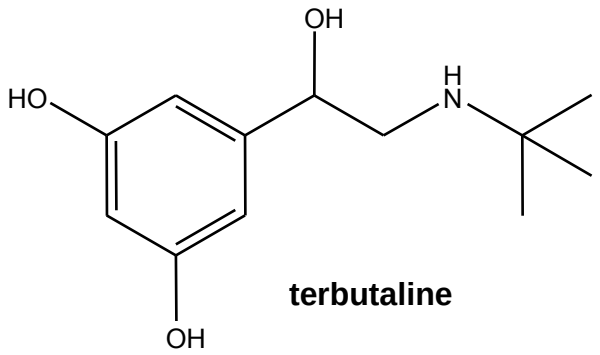
résistance à la COMT et à la formation d'o-quinone




**salbutamol**

plus grande stabilité (*t*-butyle)

sélectivité pour récept. trachéal par introd. d'un $CH_2$

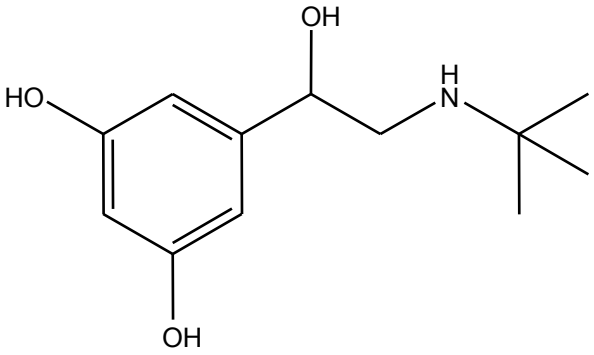



**terbutaline**

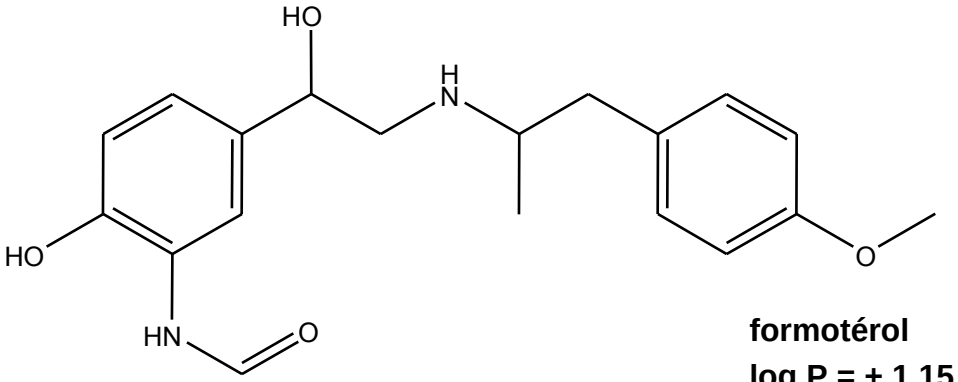
plus grande stabilité (*t*-butyle)

sélectivité $\beta$2

# $\beta_2$-mimétiques: augmenter la durée d'action

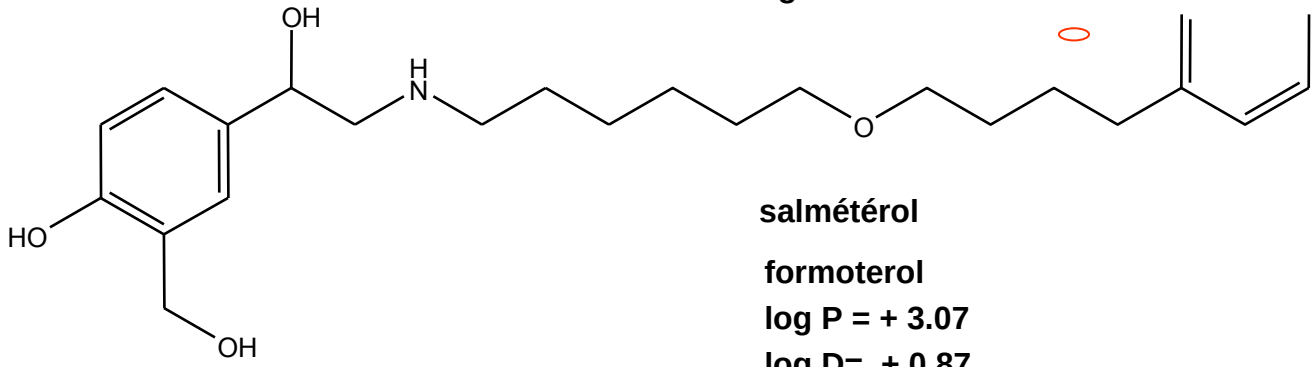



**terbutaline**
**log P = + 0.477**
**log D = - 1.67**



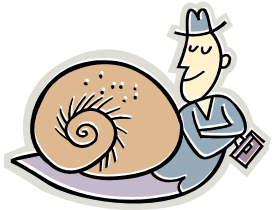

**formotérol**
**log P = + 1.15**
**log D = - 0.31**

Nous verrons cela en avril …

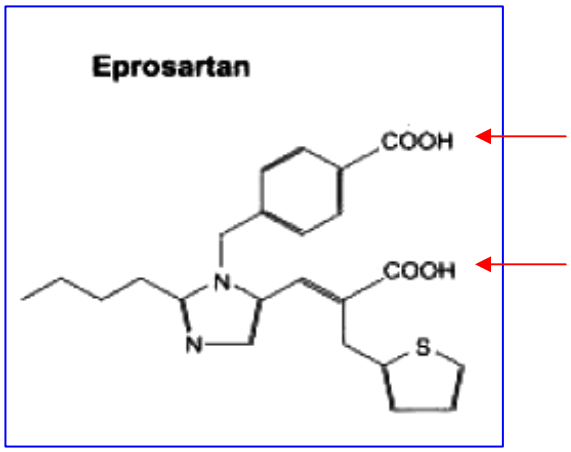



**salmétérol**

**formoterol**
**log P = + 3.07**
**log D= + 0.87**



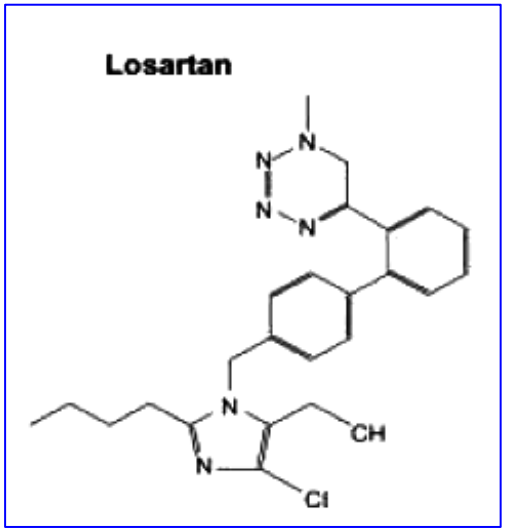
# Sartans: toute une famille autour d'un tétrazole…




Les premiers sartans sont des dianions

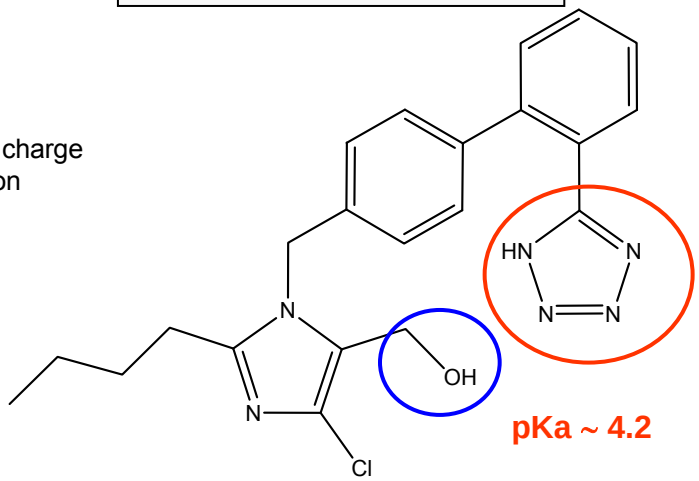
Mais un de ceux-ci a été vite remplacé par un **tétrazole *** (et l'autre, parfois, par une autre permettant des **ponts H**)

* bioisostère du COOH mais diminution de la charge et pas de possibilité de glucuronoconjugaison




attention, erreur systématique à la dia 7 (F.) pour la struct. du tétrazole

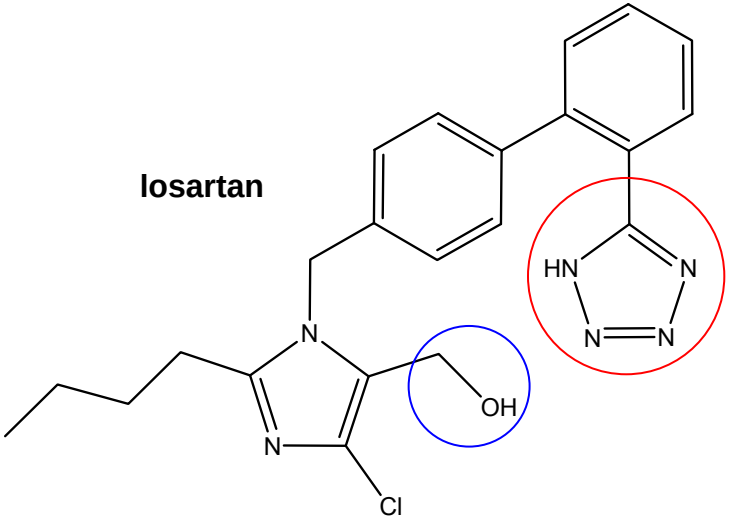
corrigée ce 24-01-10 par Mr Feron



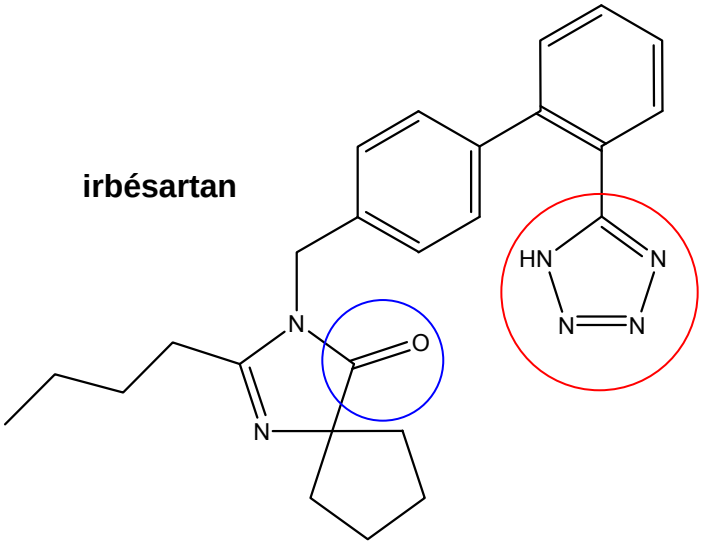

losartan (vraie structure)

# Sartans

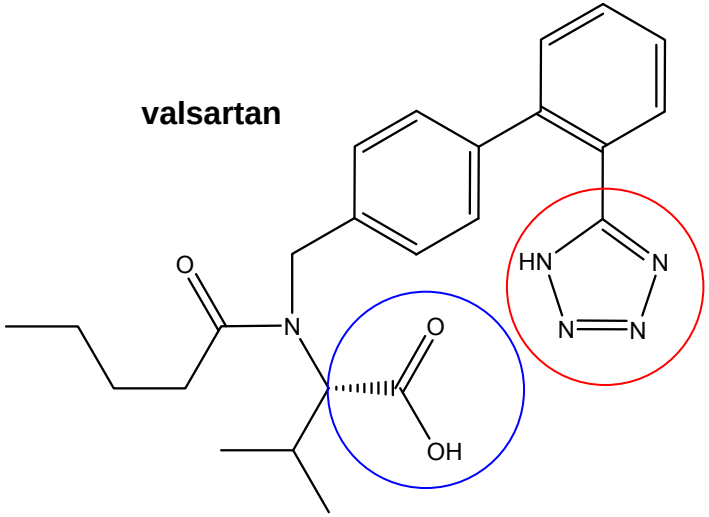
**losartan**



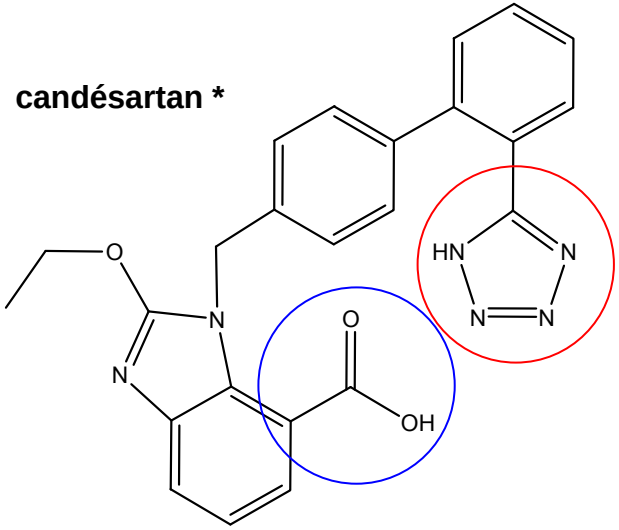

**irbésartan**



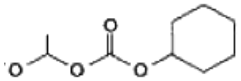

**valsartan**




**candésartan ***

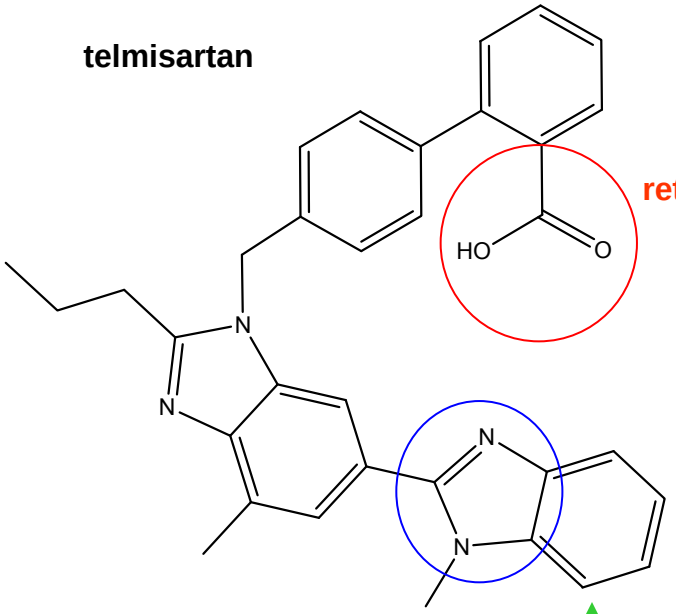



* commerc. sous forme de prodrogue
(cilexétil substituant le COOH)



# Sartans

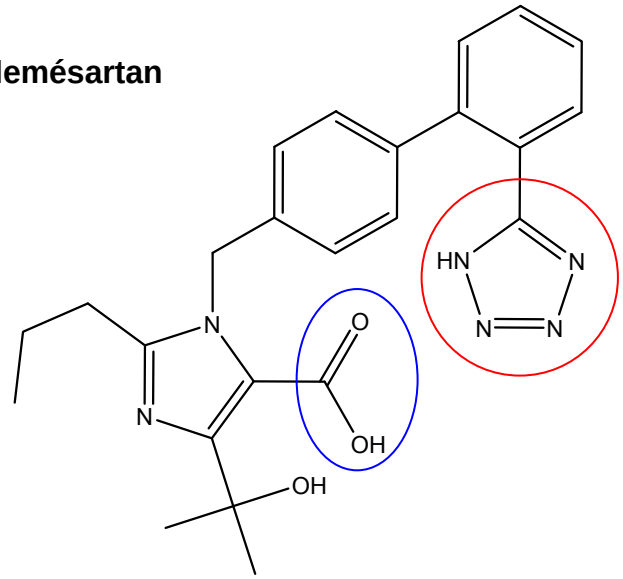
**telmisartan**



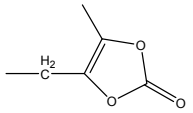

**retour aux origines…**

**longue demi-vie (~ 24h)**

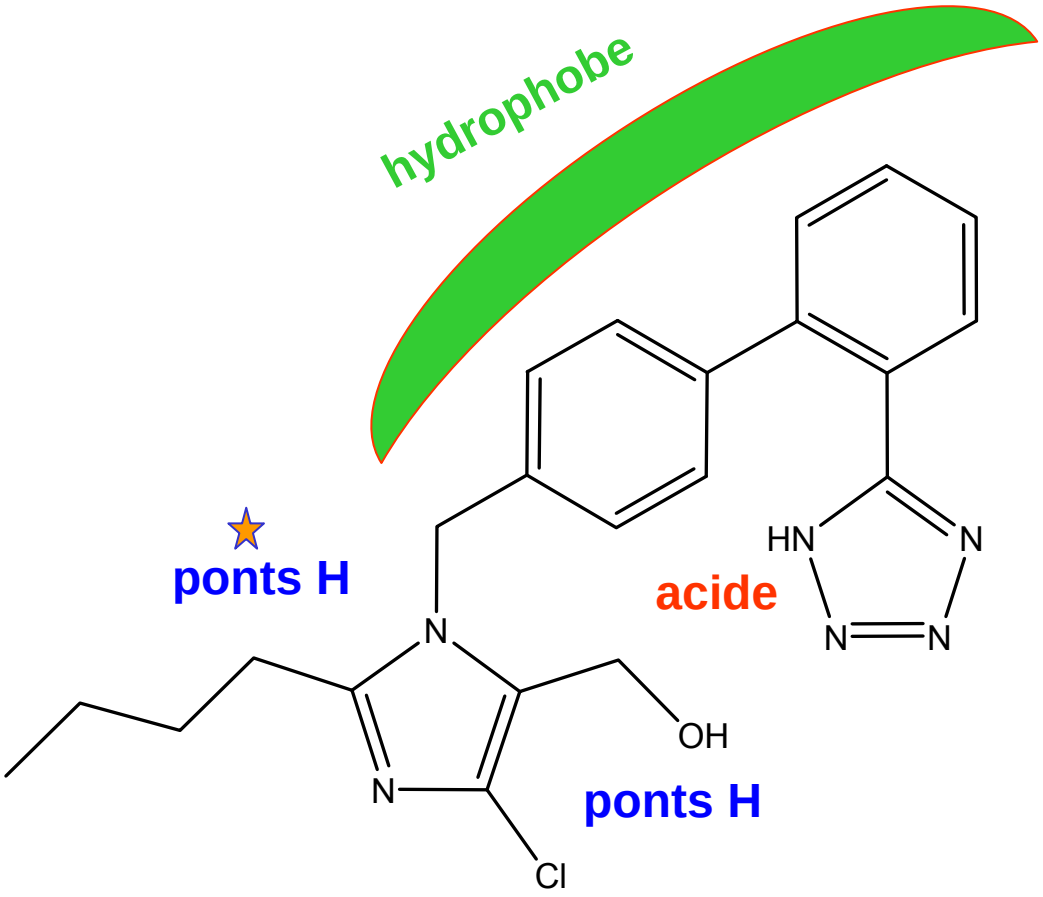
**olemésartan**




* commerc. sous forme de prodrogue (medoxomil substituant le COOH)



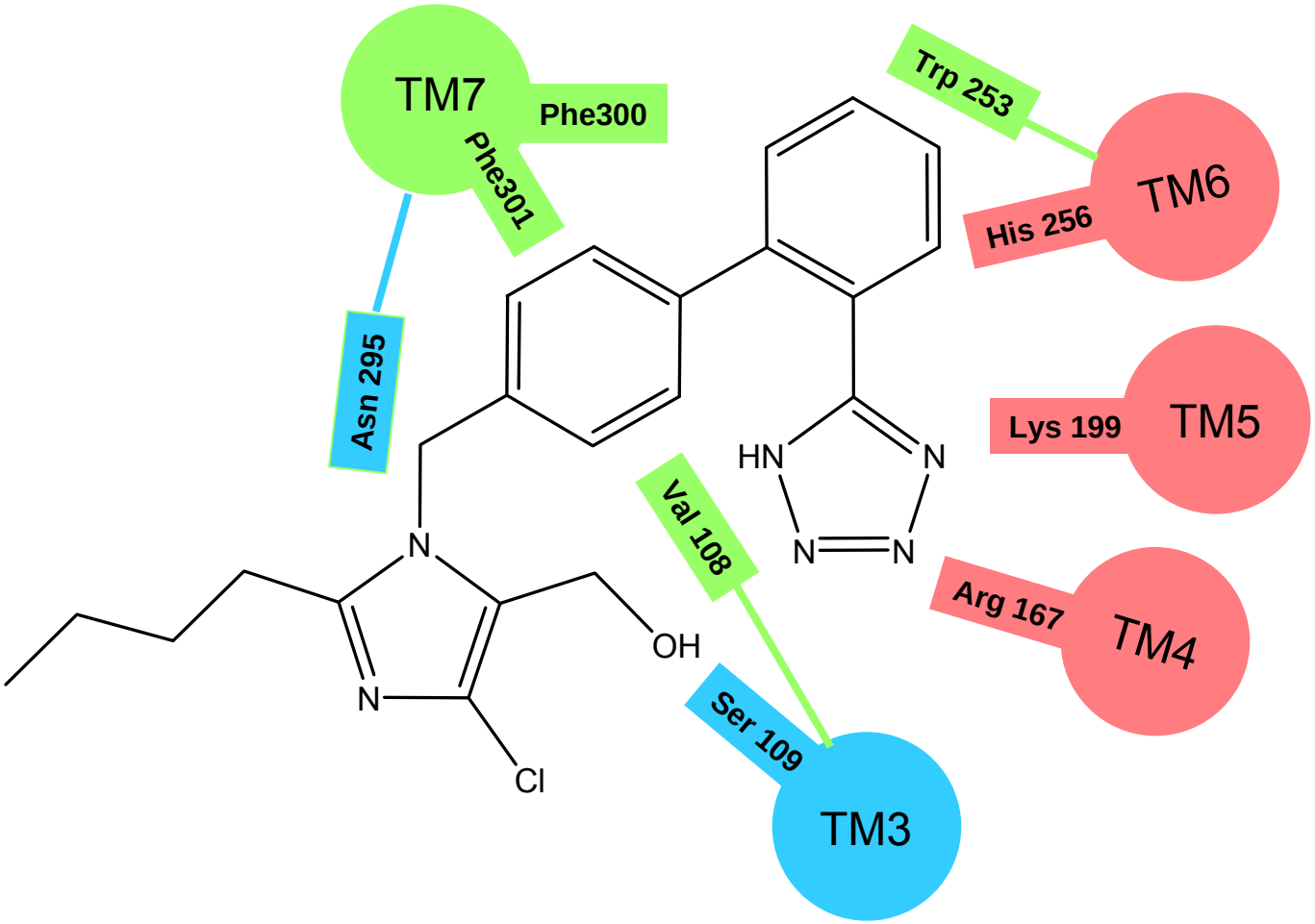
# Sartans: une certaine idée du pharmacophore ...




Aulakh et al., An update on non-peptidic angiotensin receptor inhbitors. Life Sci. 2007; 81:615-639

disponible sur i-campus

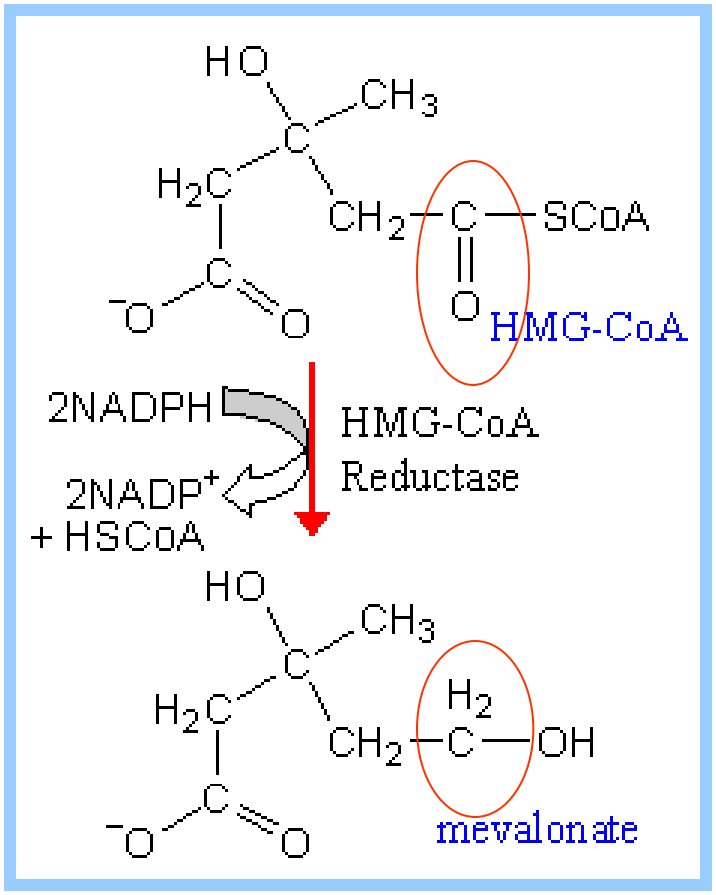
# Sartans: pourquoi tous sur le même pharmacophore ?




Aulakh et al., An update on non-peptidic angiotensin receptor inhbitors. Life Sci. 2007; 81:615-639

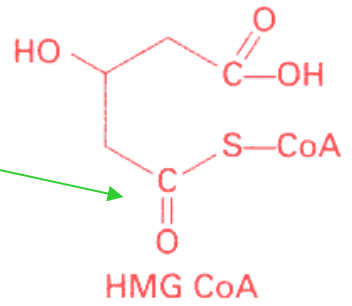
disponible sur i-campus

# The statins (as inhibitors of the HMG-CoA reductase…)

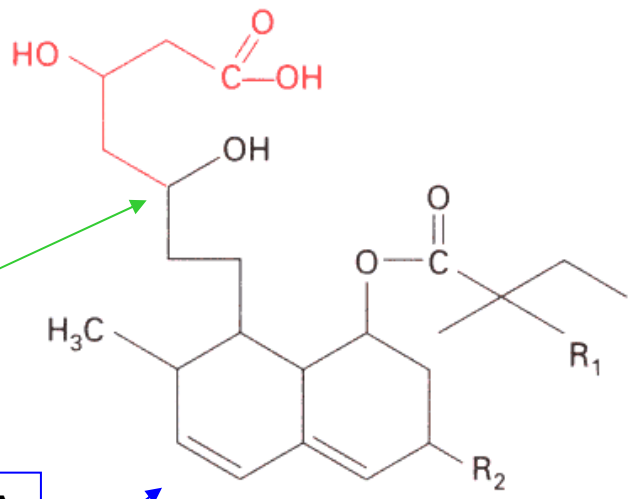



Reduction

substrate



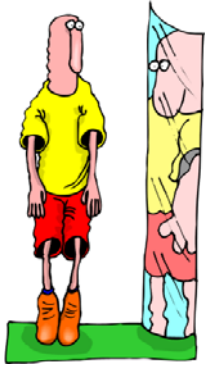

inhibitor

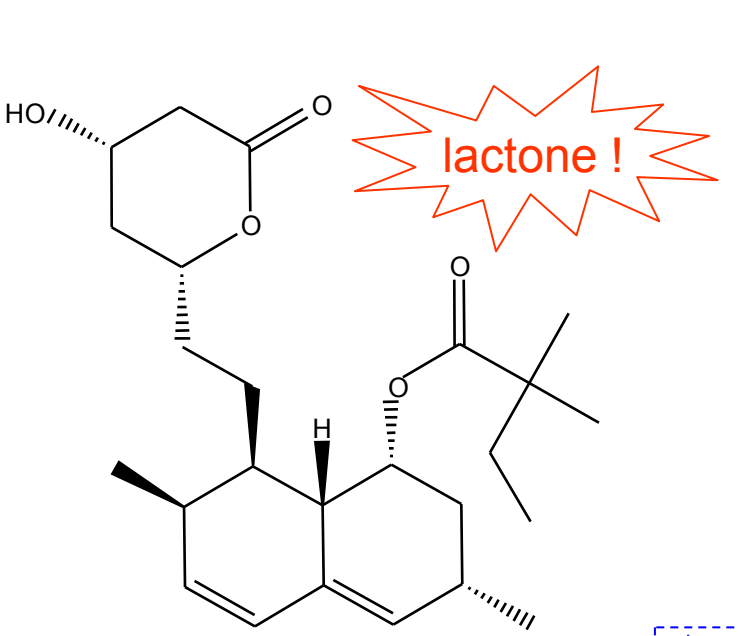



mimics CoA and allows membrane anchoring

| | $R_1$ | $R_2$ |
|---|---|---|
| Simvastatin | $CH_3$ | $CH_3$ |
| Pravastatin | (H) | OH |

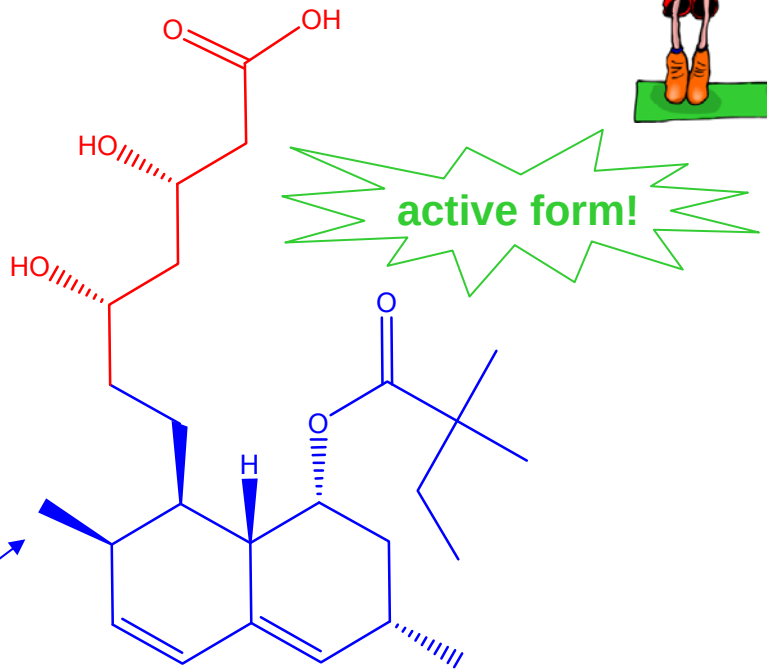
# You said "statins" ?






lactone !

simvastatin

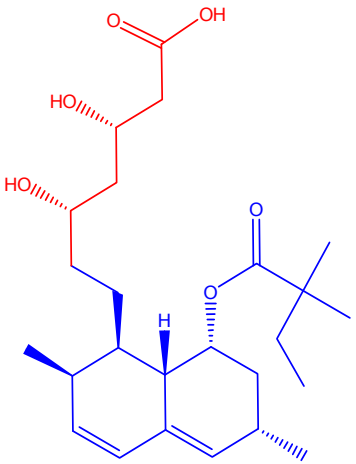



active form!

simvastatin hydroxy acid

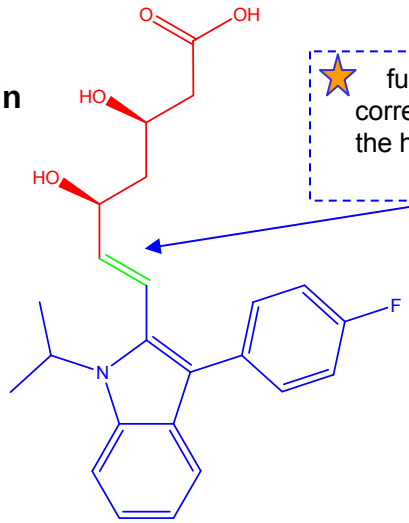
**prevents free rotation of the hydroxyacid chain**

# Here is the family (as available for you in Belgium)…



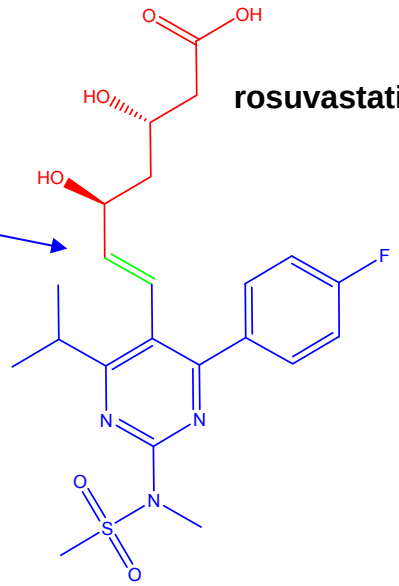
**simvastatin hydroxy acid**

**fluvastatin**

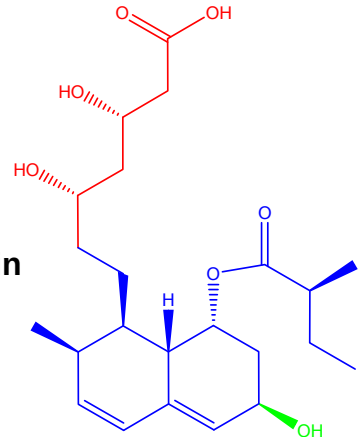


further forces a correct orientation of the hydroxyacid side chain

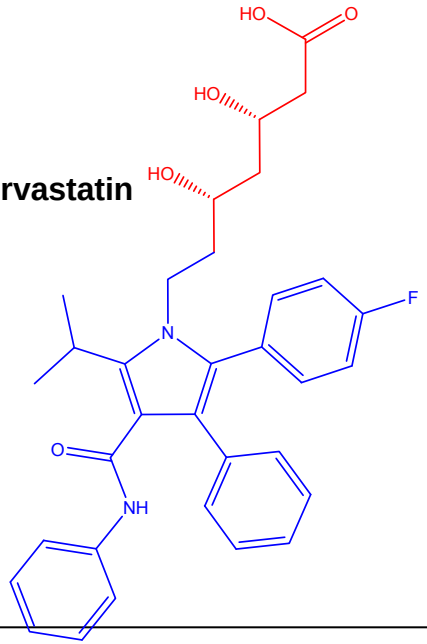
**rosuvastatin**



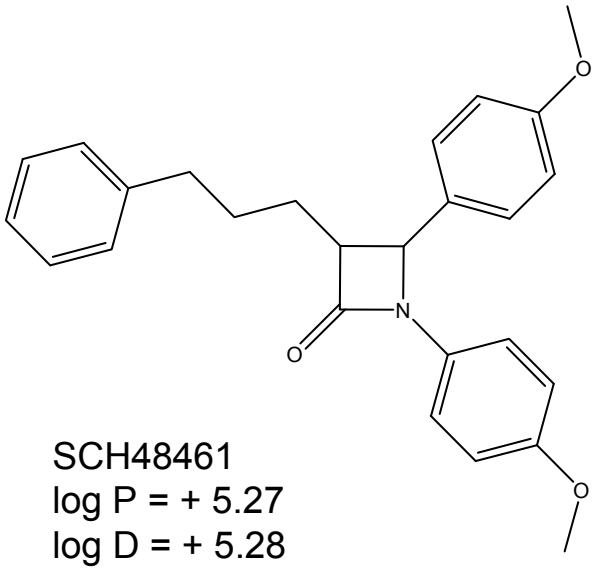
**pravastatin**



**atorvastatin**



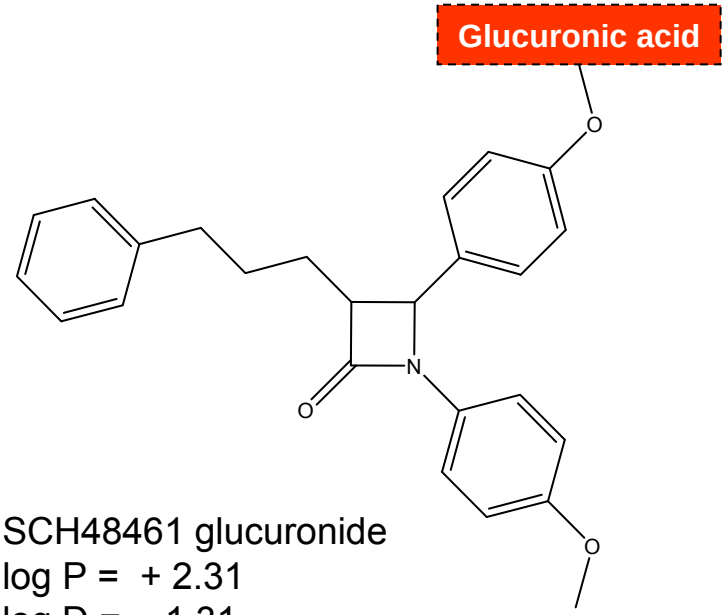
# The story of ezetimibe



SCH48461
log P = + 5.27
log D = + 5.28

weak cholesterol uptake inhbitor

**absobtion,**
**liver metabolism,**
**and bile excretion**

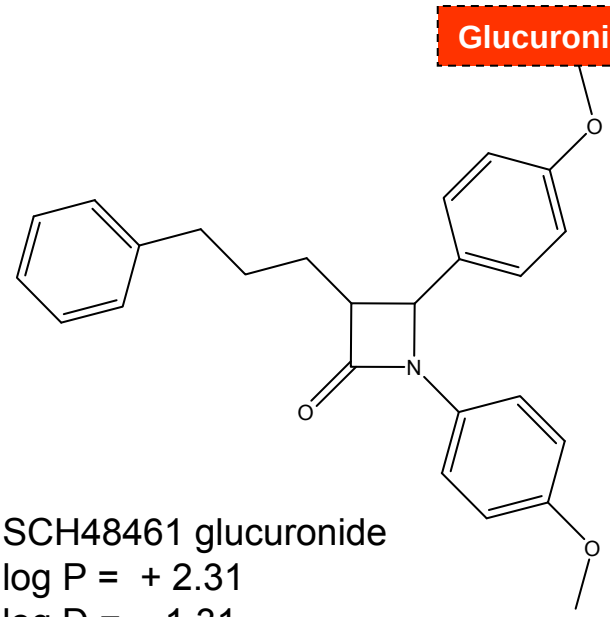



SCH48461 glucuronide
log P = + 2.31
log D = - 1.31

potent cholesterol upake inhibitor

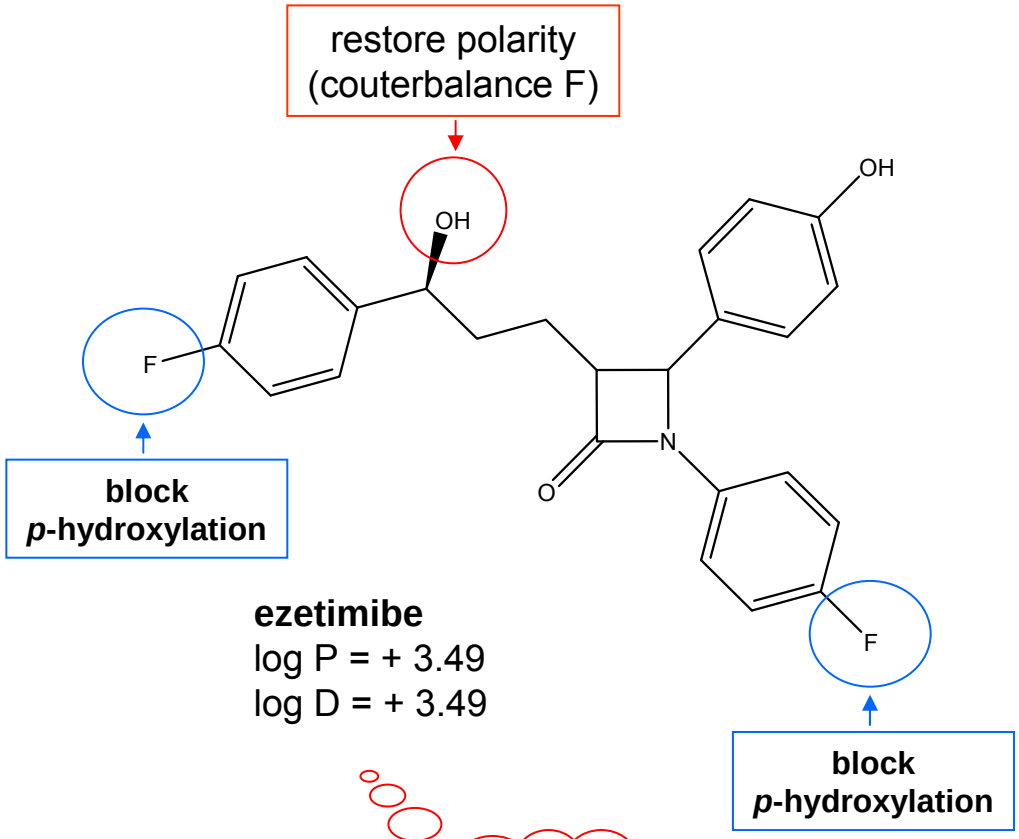
Journal of pharmacology and experimental therapeutics (1997), 283(1), 157-63.

# From a metabolite to a drug

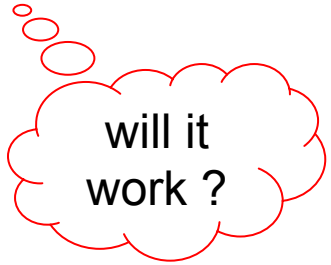



SCH48461 glucuronide
log P = + 2.31
log D = - 1.31

potent cholesterol upake inhibitor

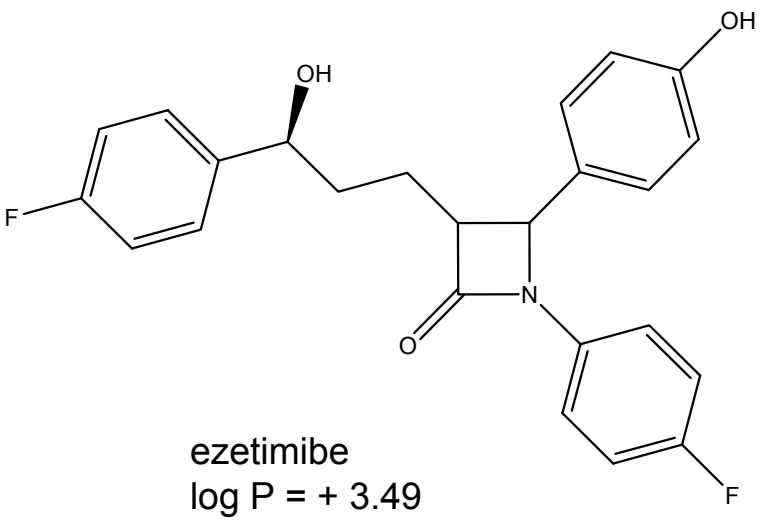



**ezetimibe**
log P = + 3.49
log D = + 3.49




Journal of medicinal chemistry (1998), 41(6), 973-80.

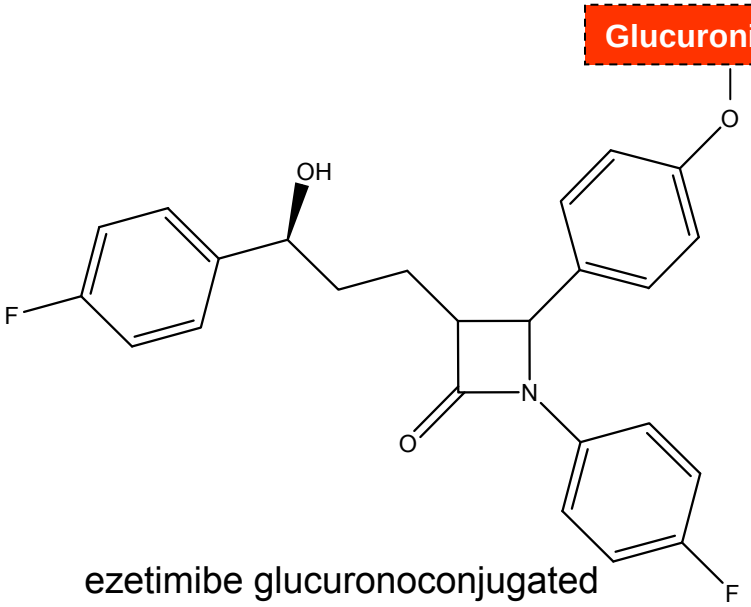
# Here is how…




ezetimibe
log P = + 3.49
log D = + 3.49

resorbtion
metabolism

Glucuronic acid




ezetimibe glucuronoconjugated
log P = + 1.18
log D = - 2.44

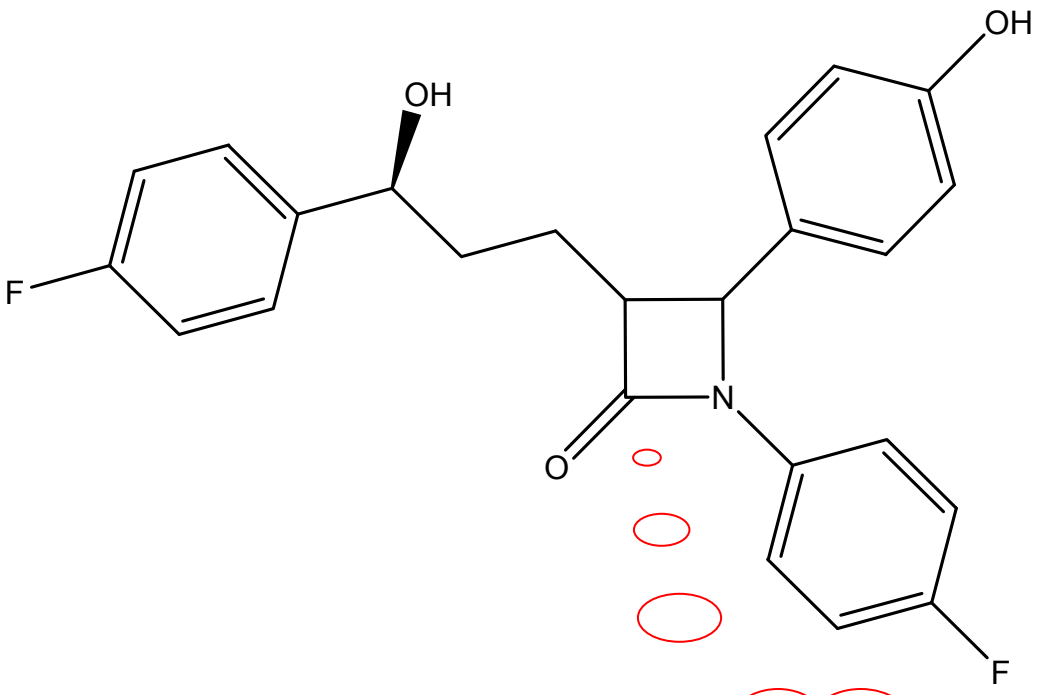
intestine

enterohepatic cyle

Here is how !

British journal of pharmacology (2000), 129(8), 1748-54
Clinical therapeutics (2001), 23(6), 871-85
Drug metabolism and disposition (2002), 30(4), 430-7

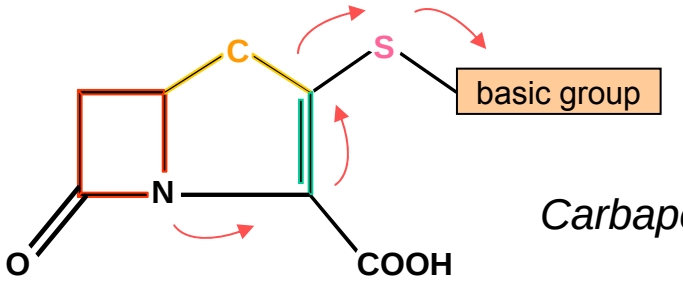
# But is the molecule stable ?




is this not a β-lactam ?

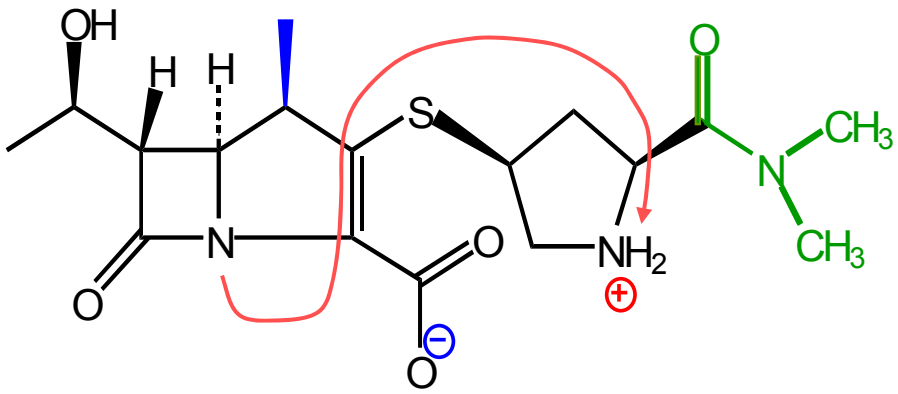
# β-lactams are unstable because of anchimeric assistance …

example for carbapenems (very unstable)




*Carbapenem*

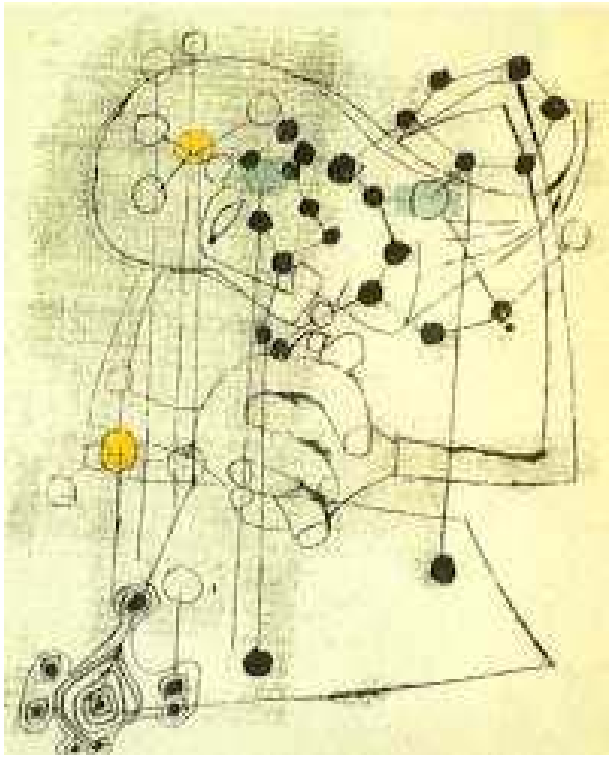
greater intrinsic activity due to larger instability of the β-lactam ring because of C1-C2 double bond and **electrocapturing effect of the basic group**




**meropenem**

1β-methyl, C2-pyrrolidylthio-dimethylcarbamoyl

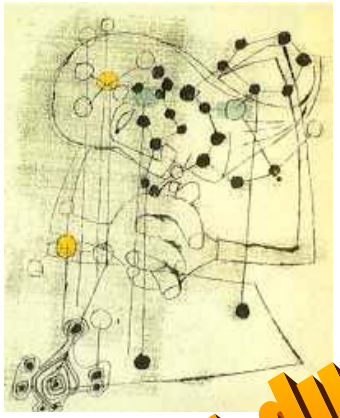
# Le médicament …



"Scientist" by Ben Shahn
New Jersey State Museum,
Trenton, N.J.

est une structure chimique (ou biologique) qui guérit …

# Le médicament …



… et ceci, du chercheur …

… au pharmacien


… et à la pharmacienne !!

est une structure chimique (ou biologique) qui guérit …