UCL Université catholique de Louvain

Université partenaire de l'Académie universitaire 'Louvain'

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

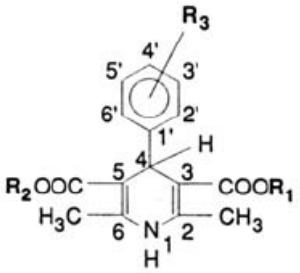
RSA vues dans d'autres parties du cours:

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 …

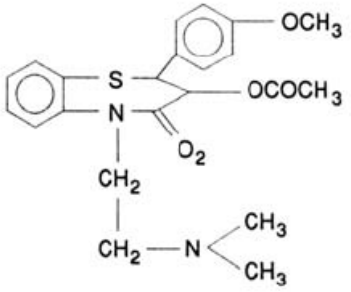
* avec l'aide (éclairée) des professeurs Poupaert, Depovere et Sonveaux 

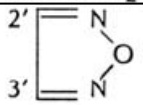
Antagonistes calciques

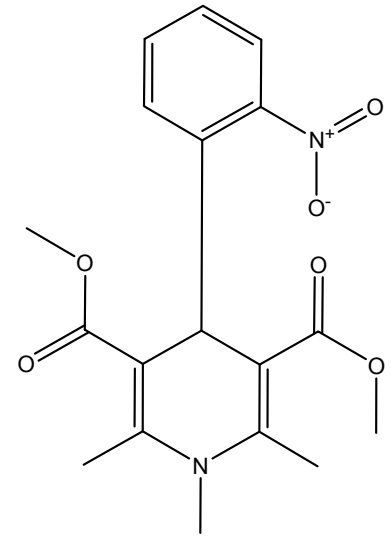
dihydropyridines (structure générale)

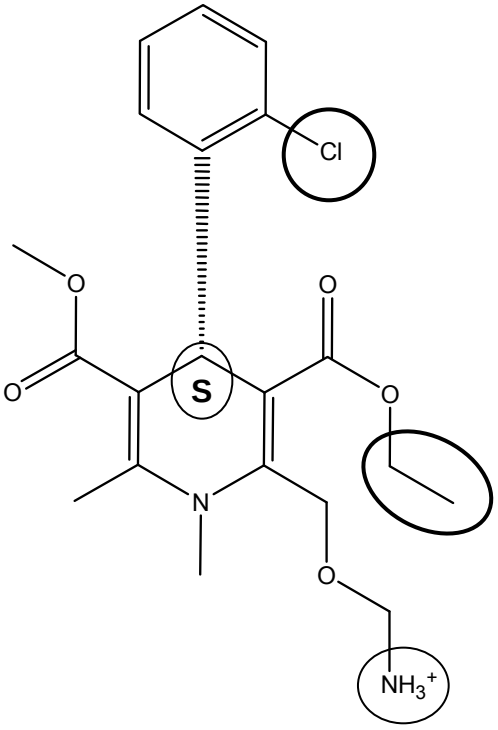


diltiazem



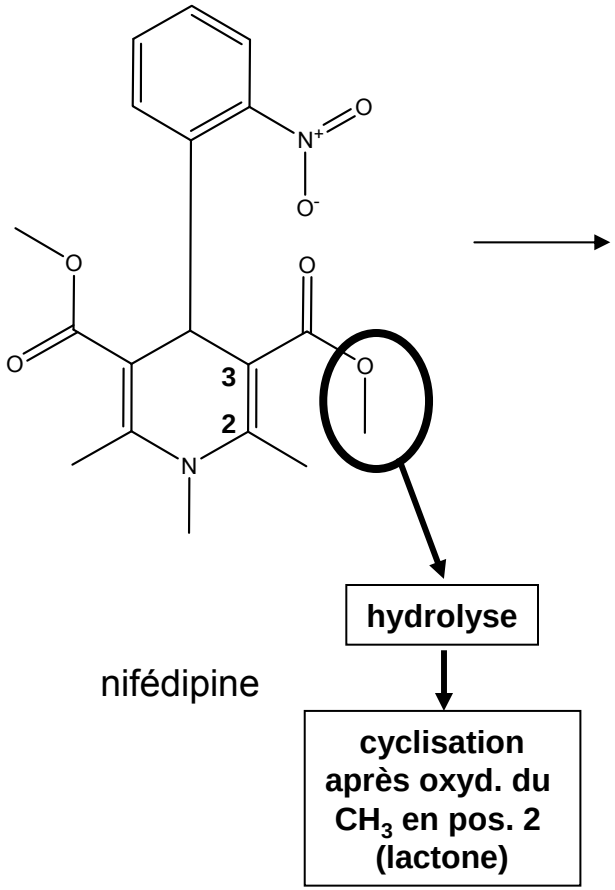
	R_1	R_2	R_3
nifédipine	CH_3	CH_3	2'-NO_2
nimopidine	$(CH_2)_2OCH_3$	$CH(CH_3)_2$	3'-NO_2
nitrendipine	C_2H_5	CH_3	3'-NO_2
nilupidine	$CH_2CH_2H_3$	$C_3H_7O(CH_2)_2$	2'-NO_2
félodipine	CH_3	C_2H_5	2',3-dichloro
nisoldipine	CH_3	isobutyl	2'-NO_2
nicardipine	(phénylméthyl-méthylamino)éthyl	CH_3	2'-NO_2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



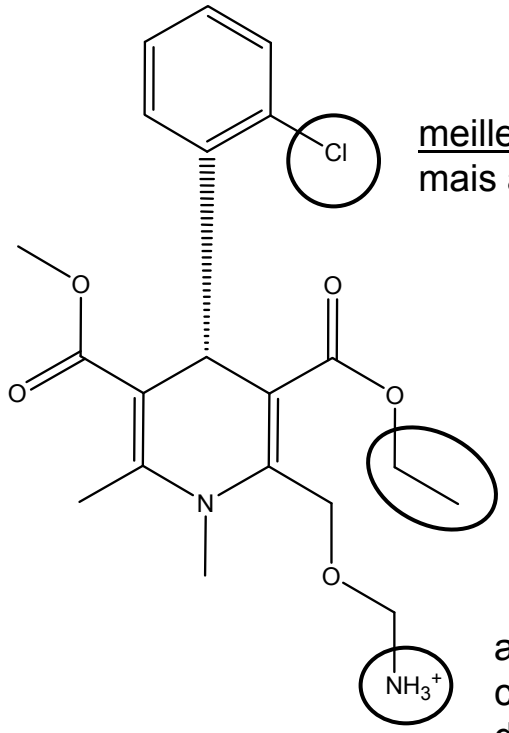


Dia 6 de Mr Feron – corrigée ce 24-01-10 pour la nimodipine

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



nifédipine



amlodipine

meilleure stabilité
mais augmentation de la lipophilie

meilleure résistance à l'hydrolyse mais aumentation de la lipophilie

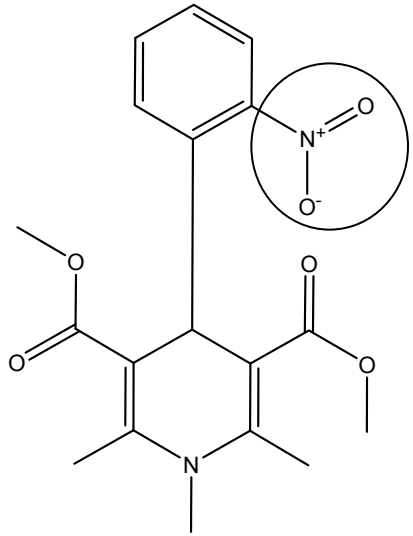
addition d'une charge pour compenser l'augmentation de lipophilie

Antagonistes calciques: charge (à pH 7) et lipophilie

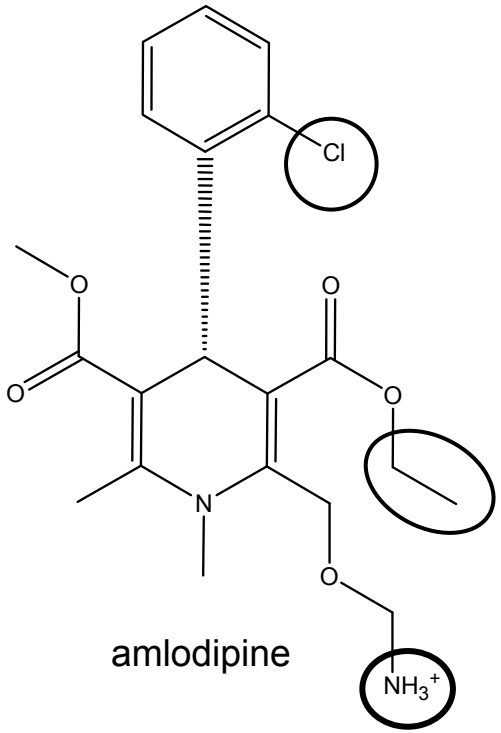
(en relation avecv la $t_{1/2}$ et la pénétration dans le SNC)

	$t_{1/2}$	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

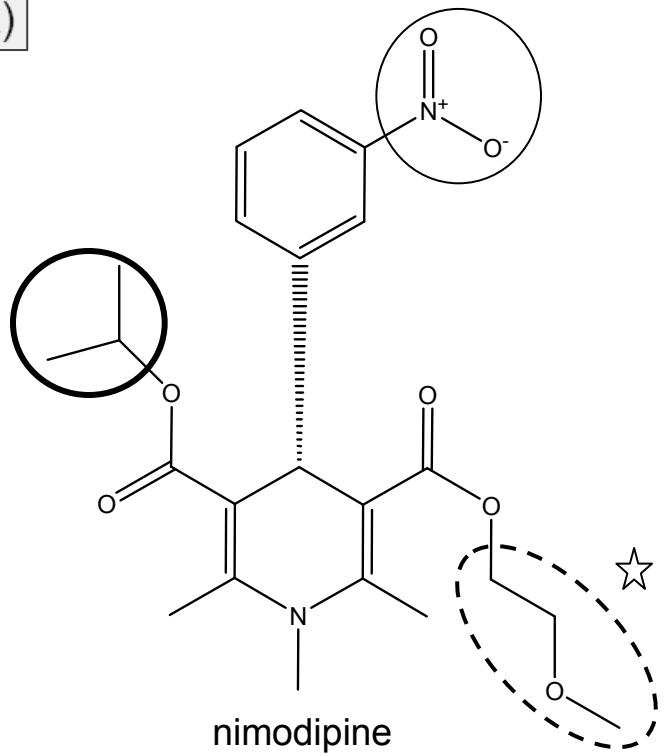
** nimodipine: très lipophile (⇒ spasmes artériels cérébraux)



nifédipine



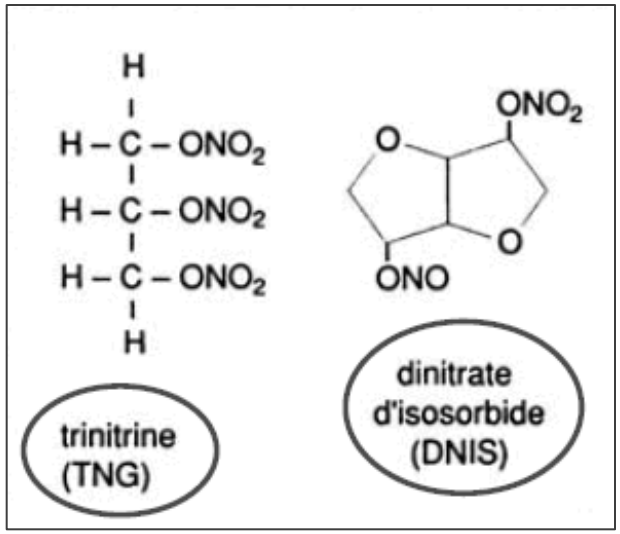
amlodipine

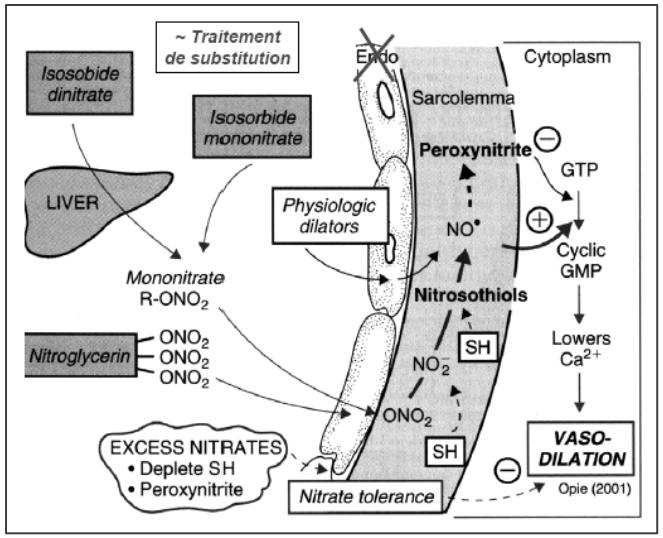


nimodipine

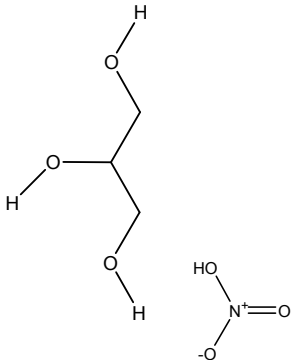
!! Dia 6 de Mr Feron corrigée ce 24-01-10

Dérivés nitrés: pourquoi des rapides et des lents ?



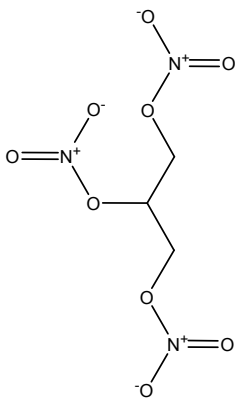


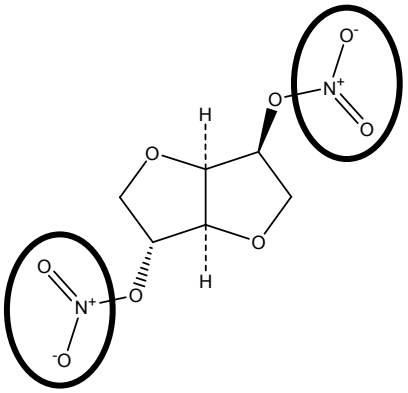
autocatalyse !

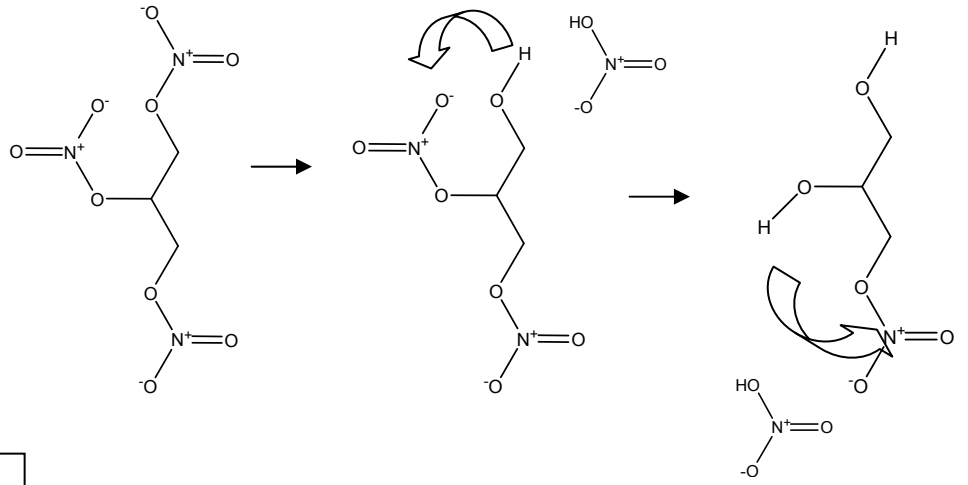


rapide

lent

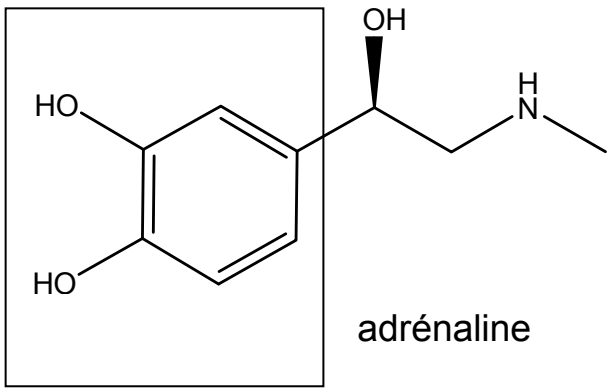






!! erreur dans la dia 9 (F.) - Fig 14.1 (Shorderet) – c'est -ONO_2 2 x

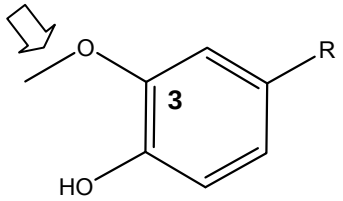
β-mimétiques - β-bloquants: importance du catéchol



adrénaline

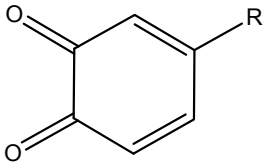
catéchol

dégradation rapide par la COMT



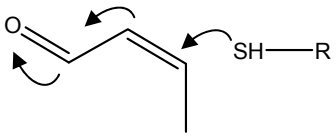
aussi pour la dopamine !

oxydation en *o*-quinone



aussi pour le paracétmol !

sequestration du CoASH et du glutathion

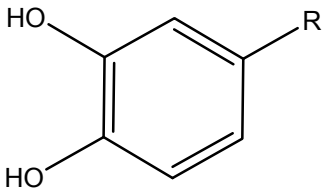


accepteur de Michaël …

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

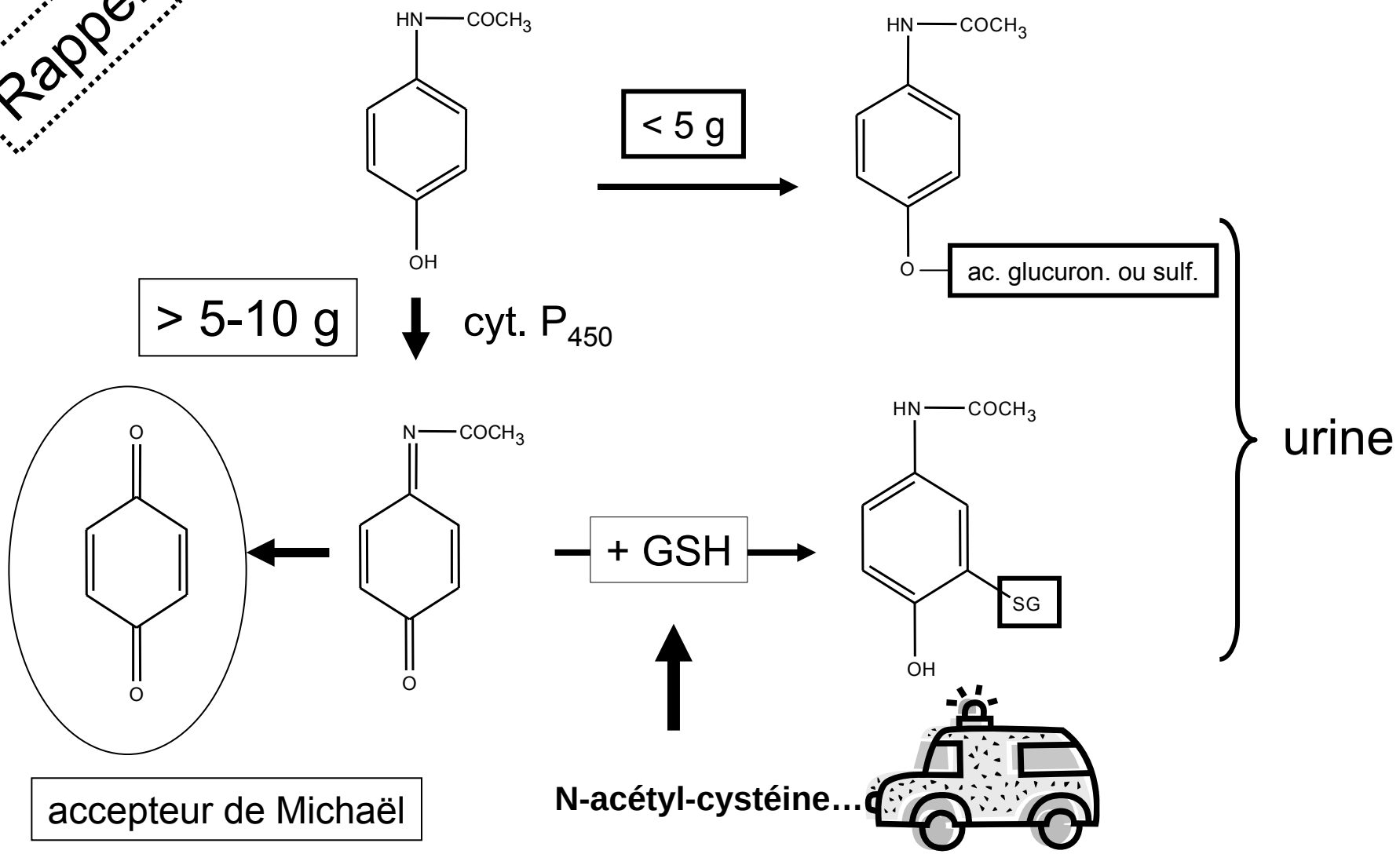
H-donneur/accepteur →

H-donneur/accepteur →

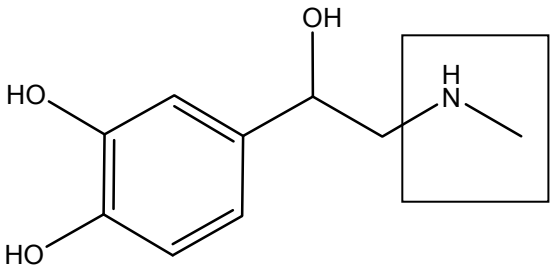


Metabolisme hépatique du paracétamol et toxicité ...

Rappel

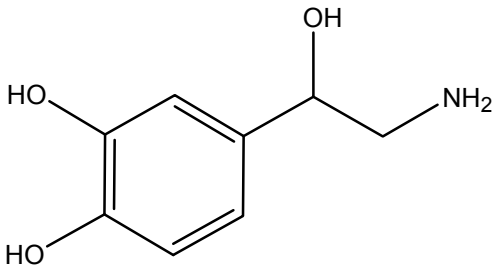


β-mimétiques - β-bloquants: inhiber la dégradation…

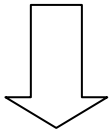


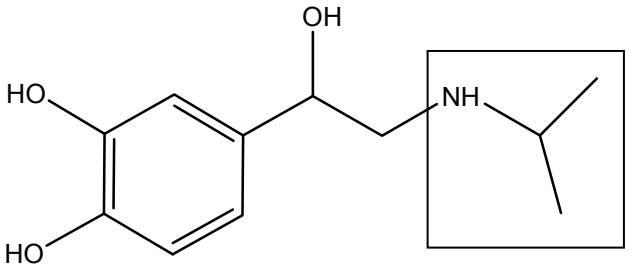
adrénaline

déalkylation



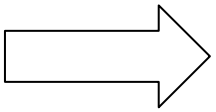
noradrénaline





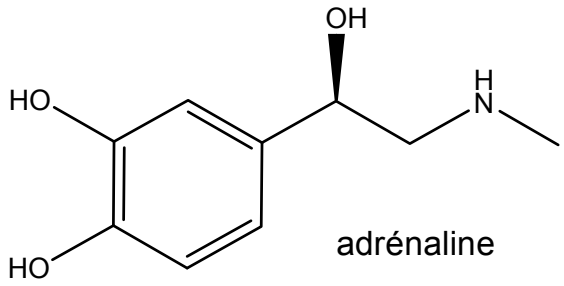
isoprotérénol

déalkylation moins aisée

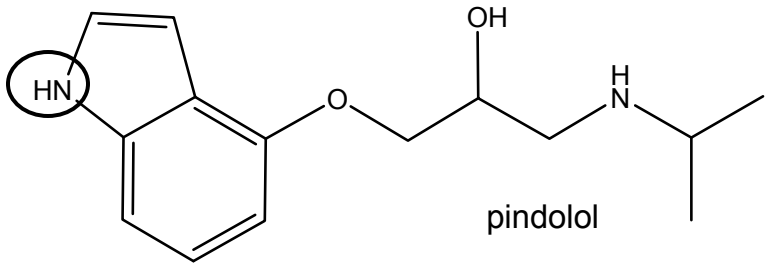


- un groupe isopropyle sera souvent utilisé pour améliorer la stabilité (et renforcer l'activité β)
- un *t*-butye rendra la molécule non-dégradable par déalkylation (absence de CH en α du N

β-bloquants et activité sympathicomimétique intrinsèque

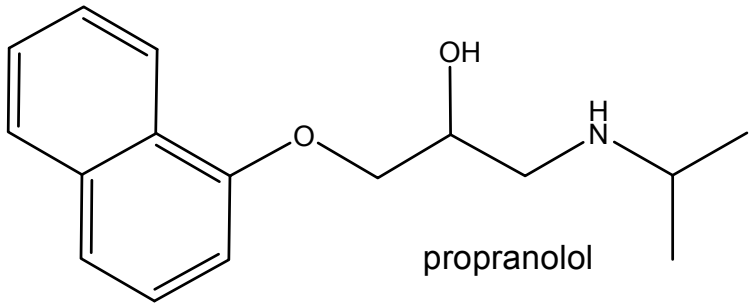


adrénaline

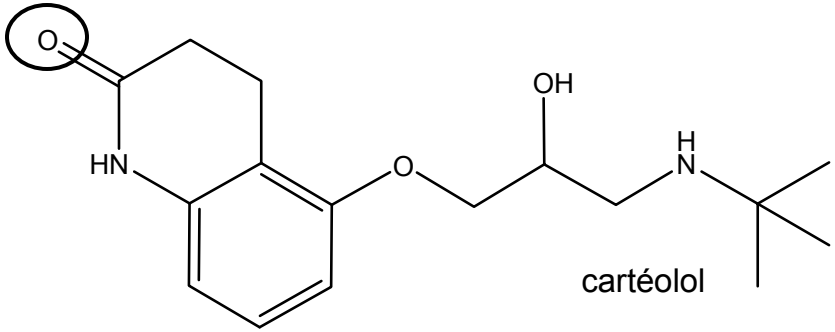


pindolol

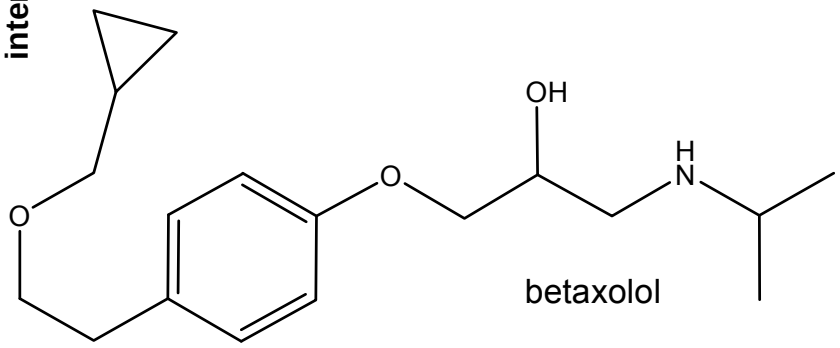
interactions hydrophobes



propranolol



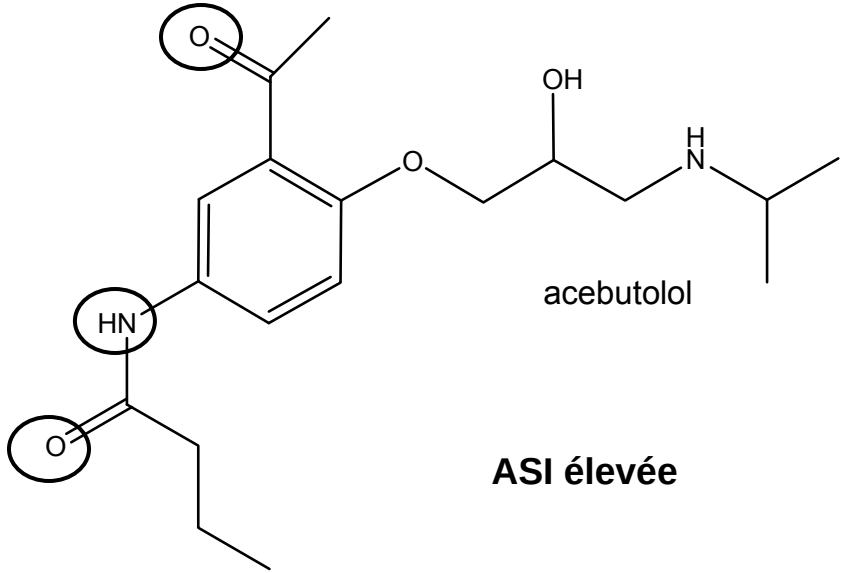
cartéolol



betaxolol

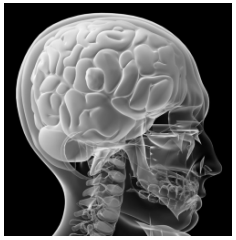
cycle virtuel
non hydroxylable

ASI faible ou nulle

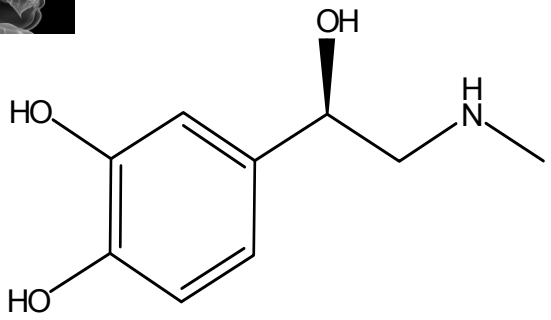


acebutolol

ASI élevée

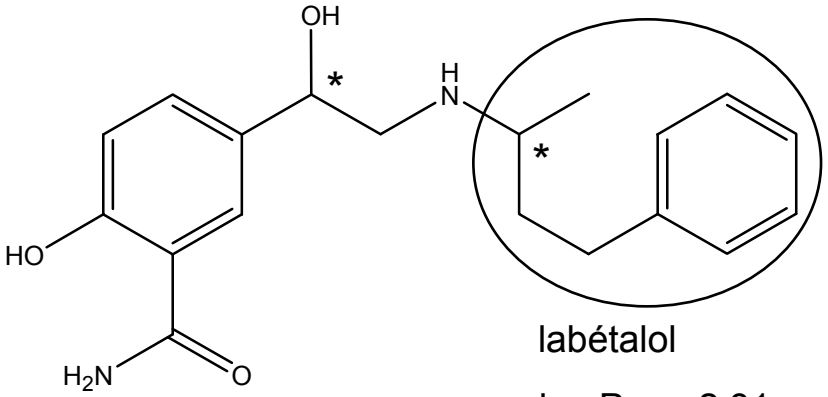


β-bloquants et lipophilie [a]



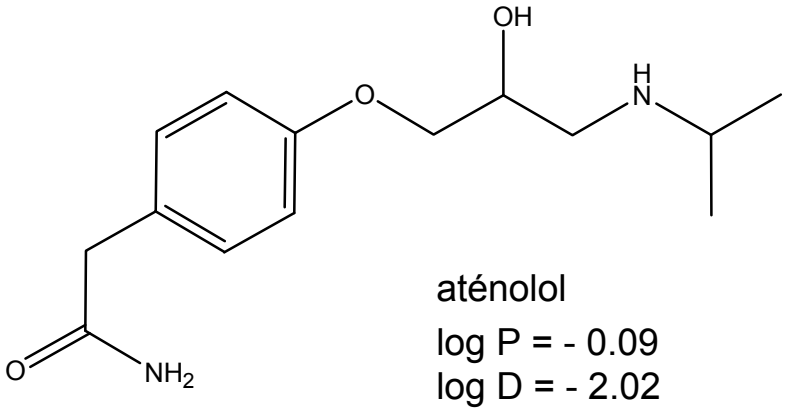
L-adrénaline

log P = - 0.63
log D = - 2.75



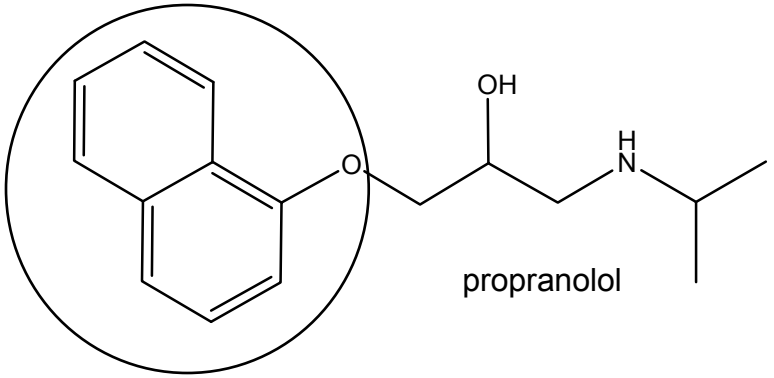
labétalol

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



aténolol

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

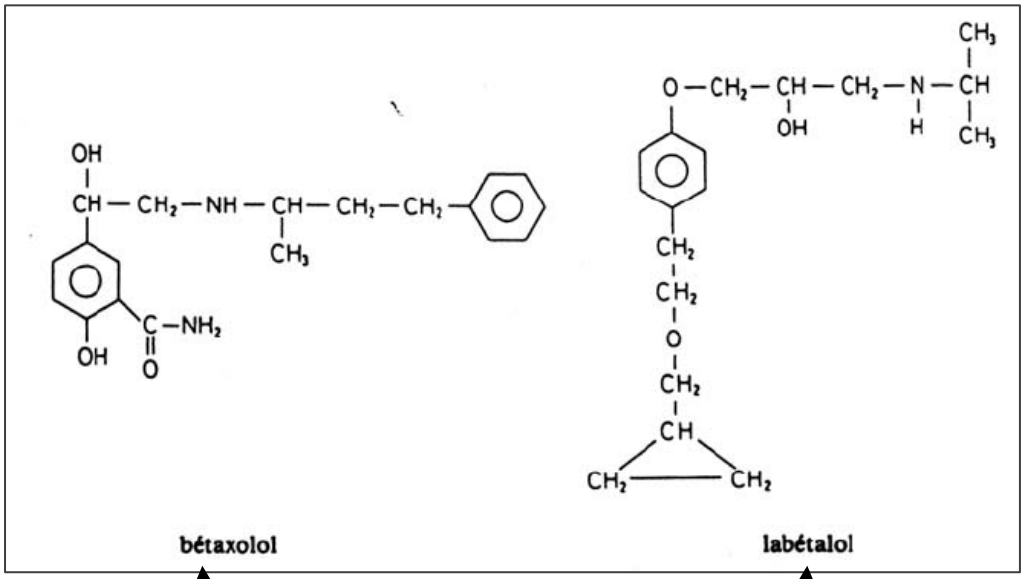


propranolol

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

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

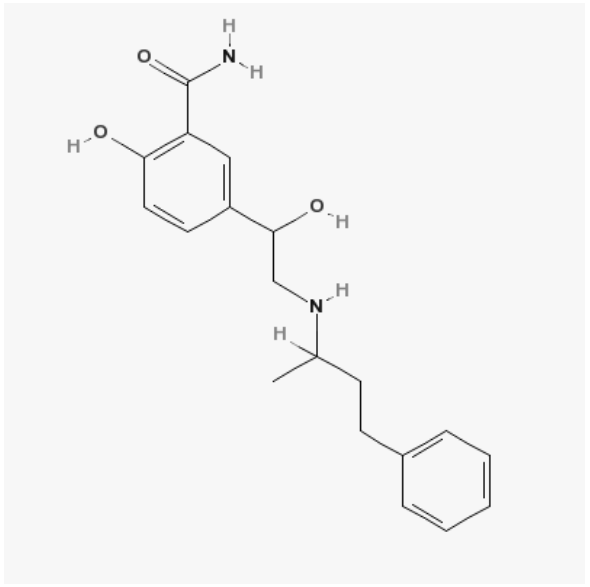
β-bloquants: une petite erreur…



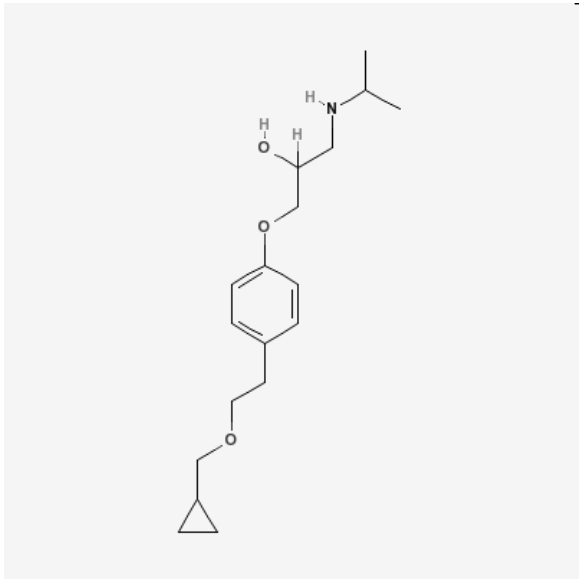
légendes inversées…

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

Corrigé par Mr Feron ce 24-01-10

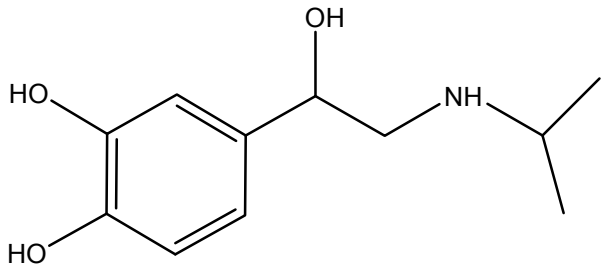


labetalol; Labetolol; Ibidomide …
IUPAC: 2-hydroxy-5-[1-hydroxy-2-(4-phenylbutan-2-ylamino)ethyl]benzamide

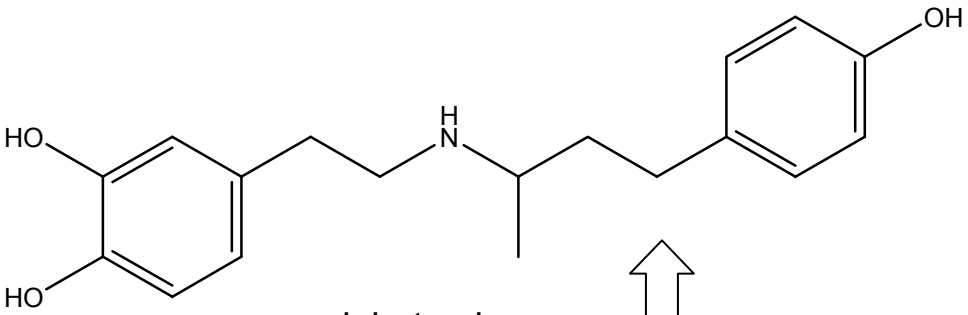


betaxolol; Betazolol; Betoptic …
IUPAC: 1-[4-[2-(cyclopropylmethoxy)ethyl]phenoxy]-3-(propan-2-ylamino)propan-2-ol

β-mimétiques β1 et β2

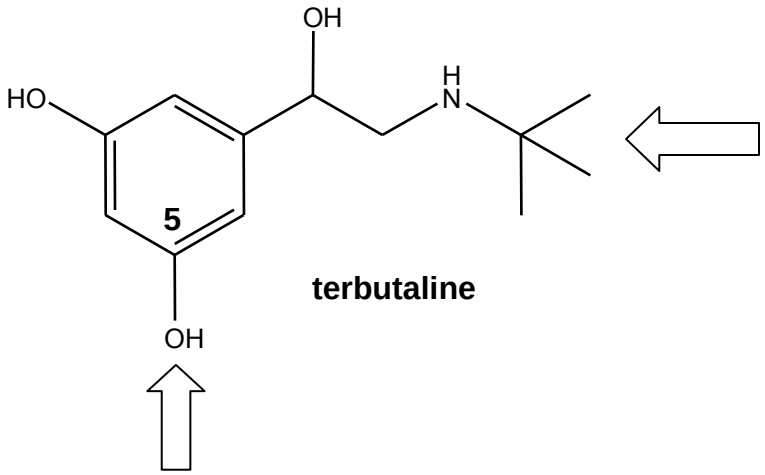


isoprotérénol



dobutamine

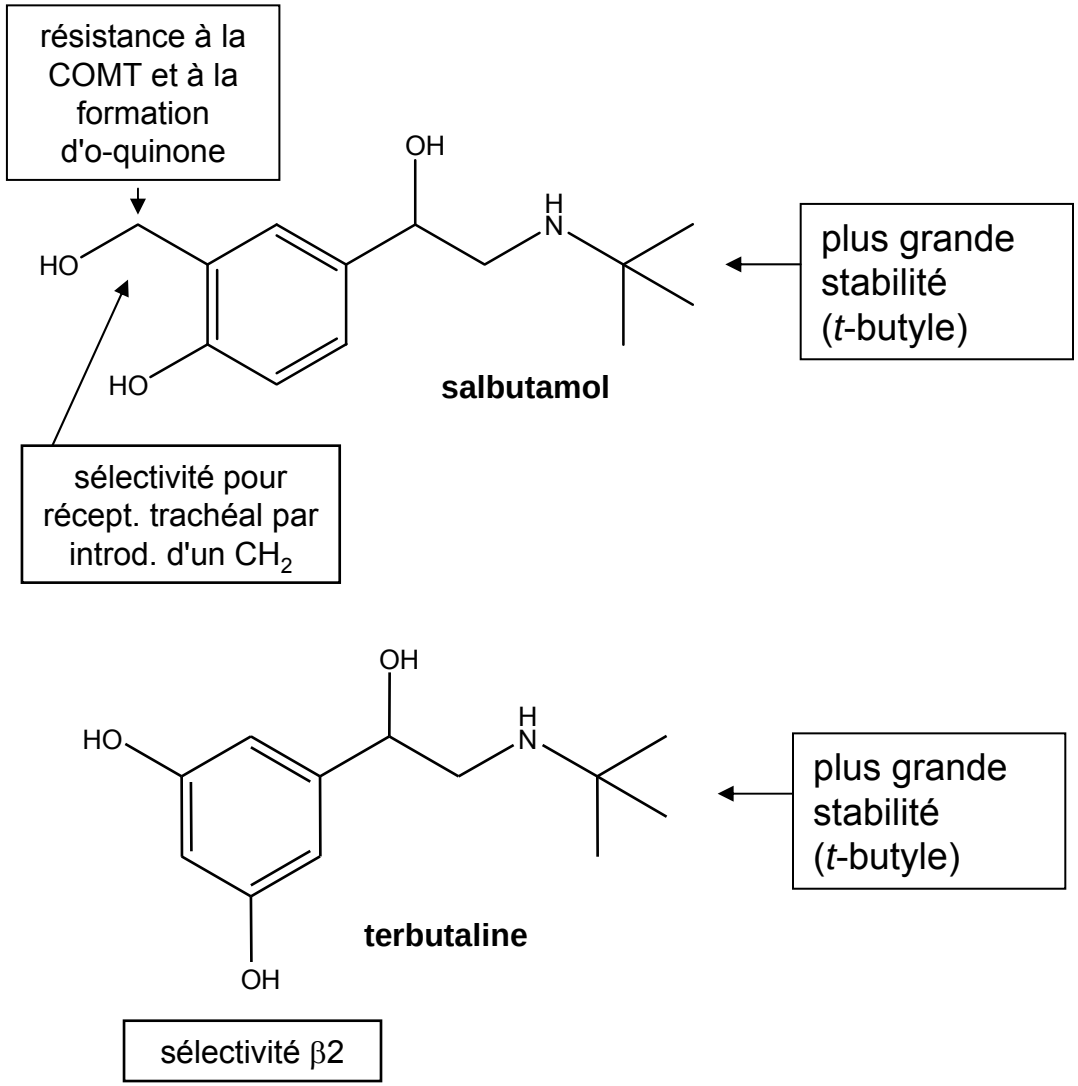
renforce l'activité β



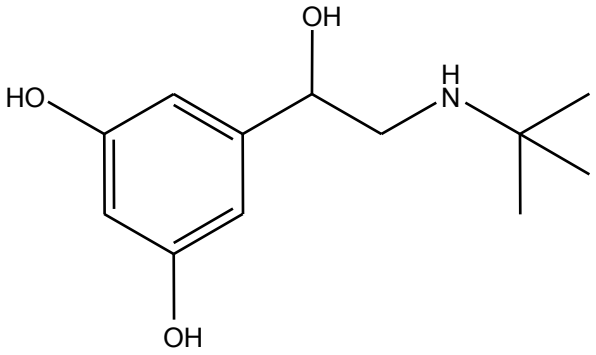
terbutaline

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

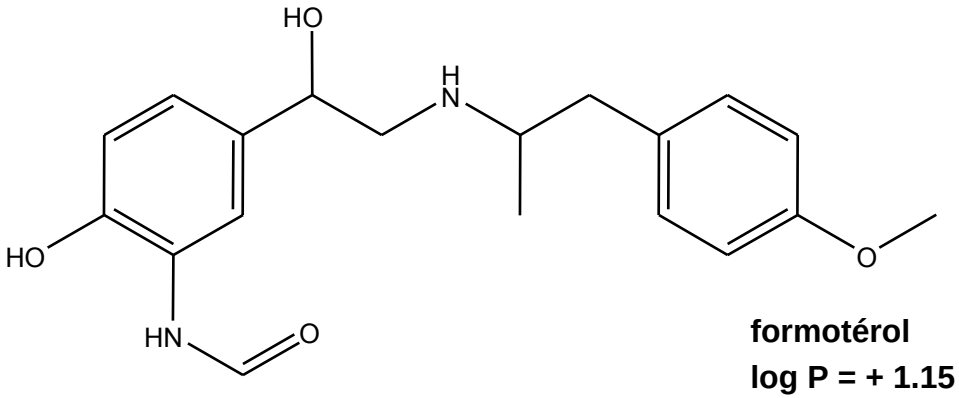
β_2-mimétiques: construire des molécules (suffisamment) spécifiques et stables



β_2-mimétiques: augmenter la durée d'action

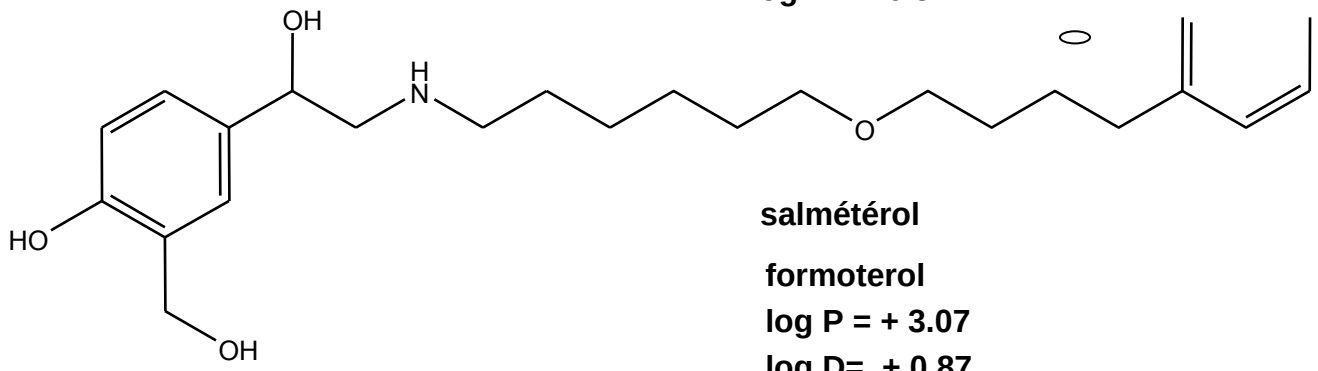


terbutaline
log P = + 0.477
log D = - 1.67



Nous verrons cela en avril …

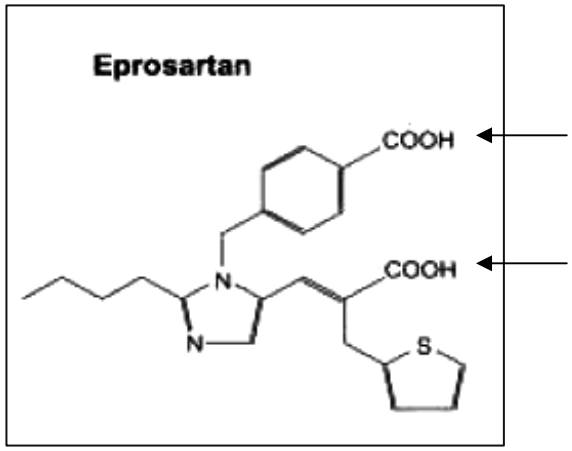
formotérol
log P = + 1.15
log D = - 0.31



salmétérol

formoterol
log P = + 3.07
log D= + 0.87

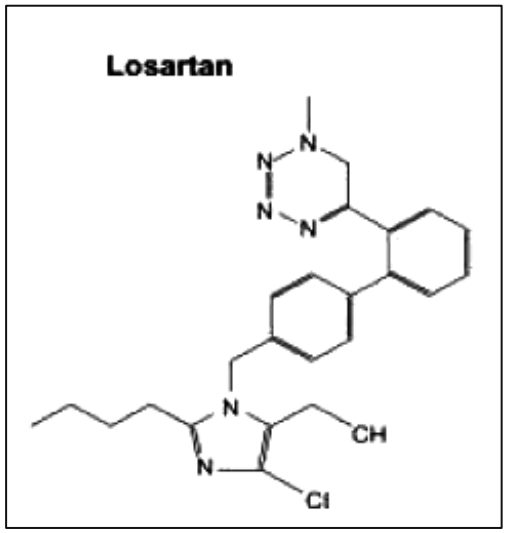
Sartans: toute une famille autour d'un tétrazole…



Les premiers sartans sont des dianions

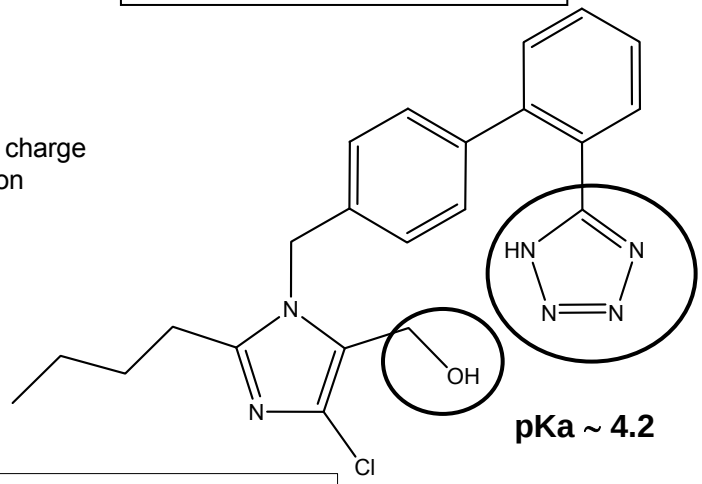
Mais un de ceux-ci a été vite remplacé par un **tétrazole *** (et l'autre, parfois, par une autre permettant des **ponts H**)

* 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

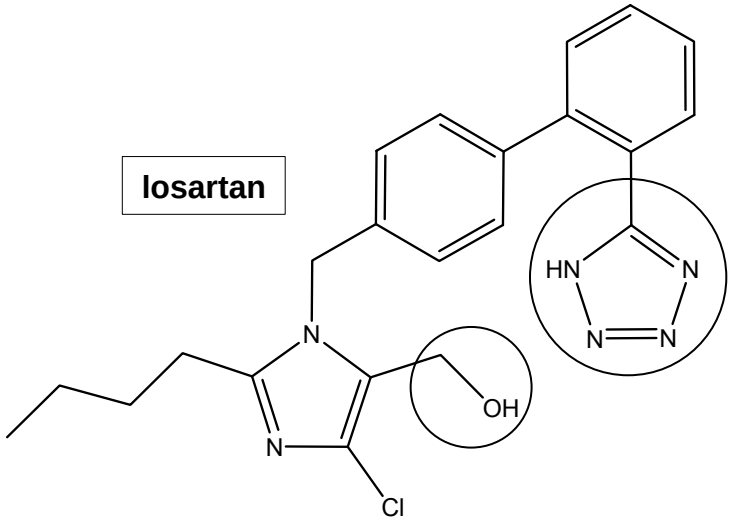


pKa ~ 4.2

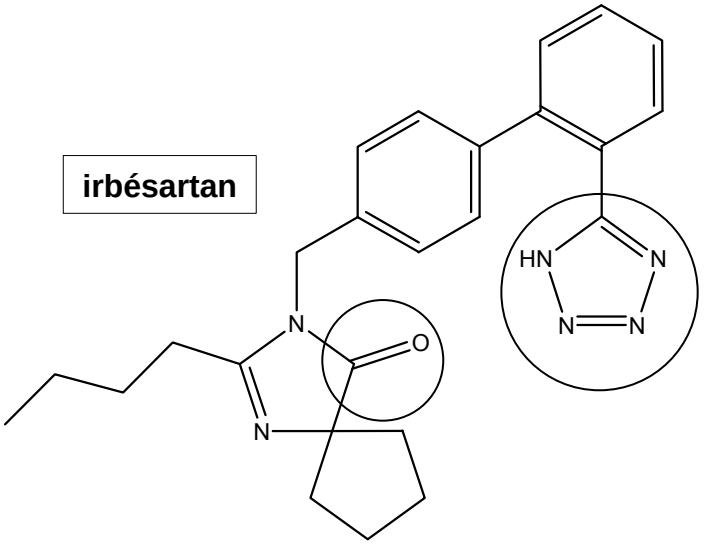
losartan (vraie structure)

Sartans

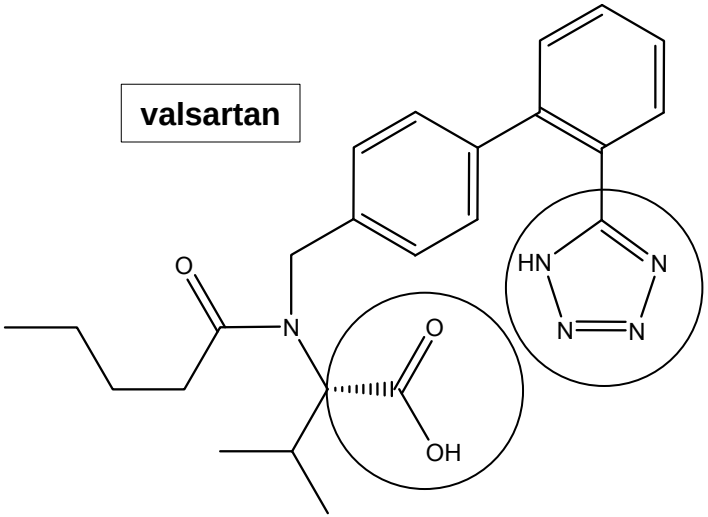
losartan



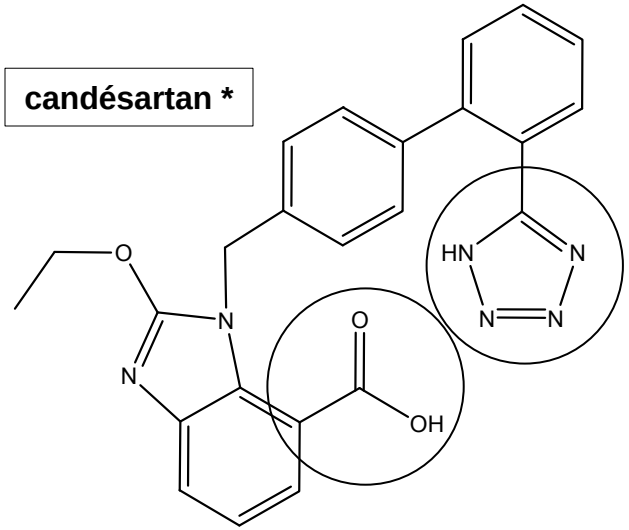
irbésartan



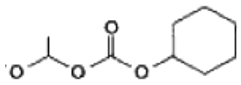
valsartan



candésartan *

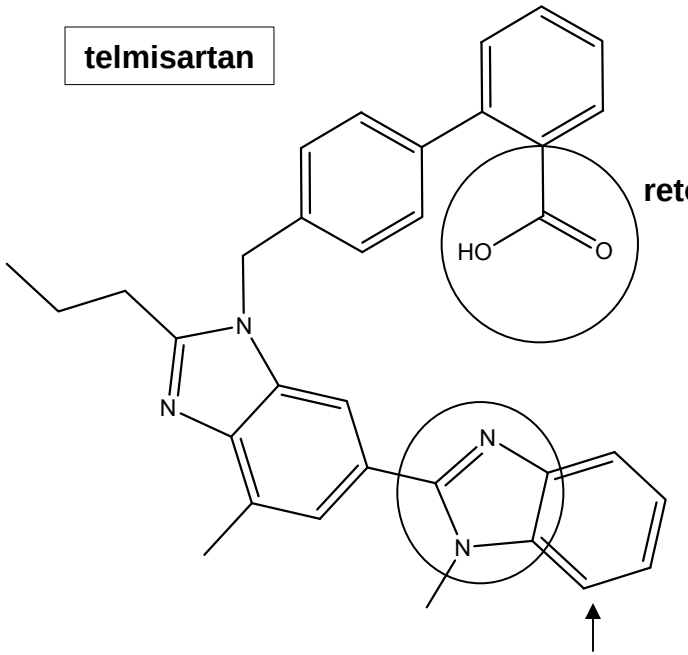


* commerc. sous forme de prodrogue
(cilexétil substituant le COOH)



Sartans

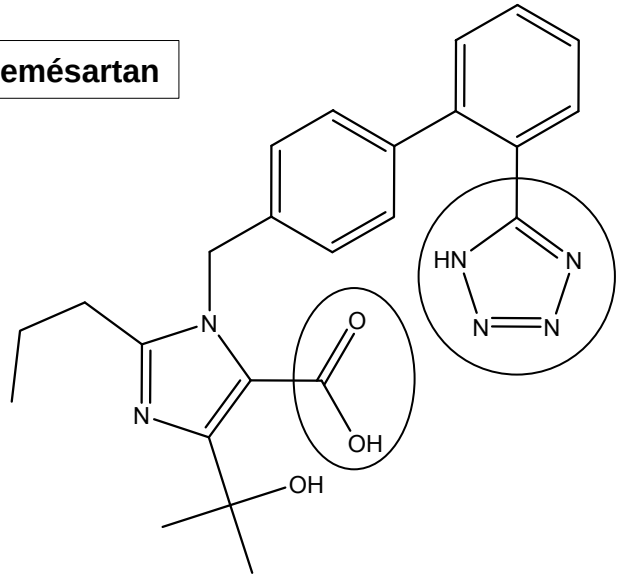
telmisartan



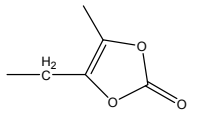
retour aux origines…

longue demi-vie (~ 24h)

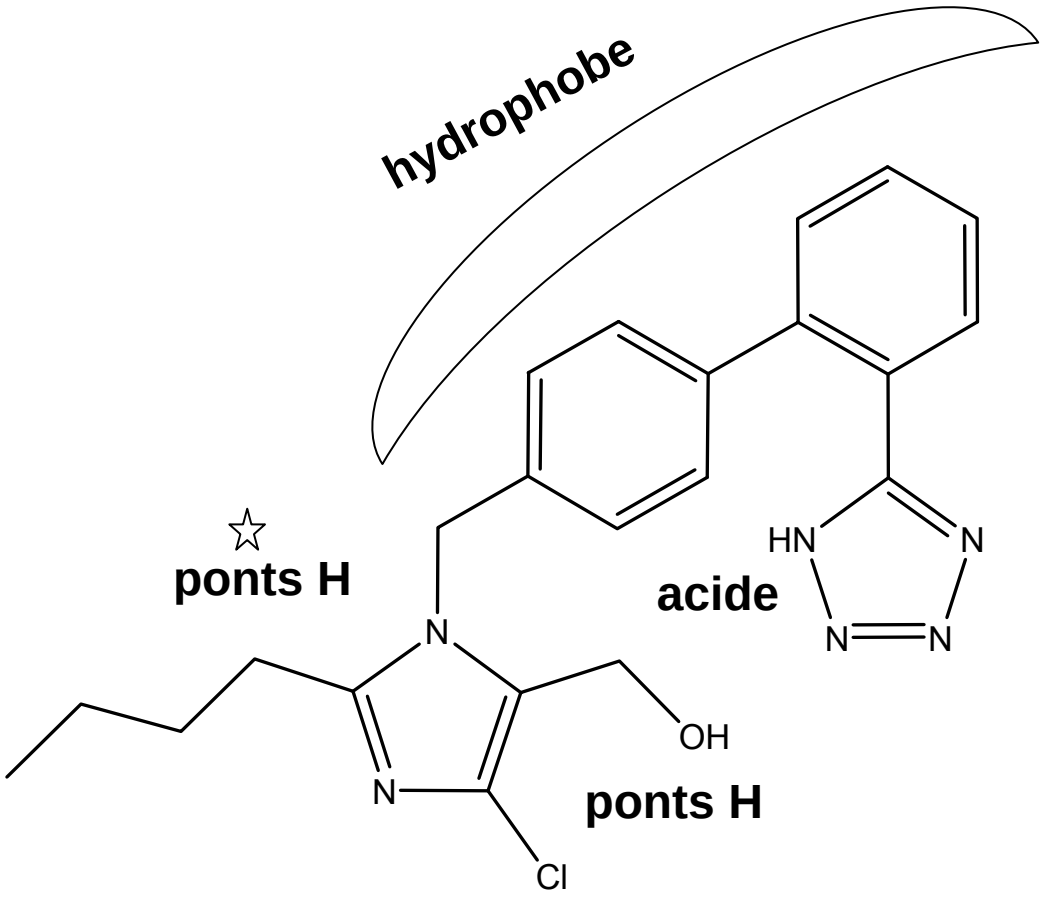
olemésartan



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



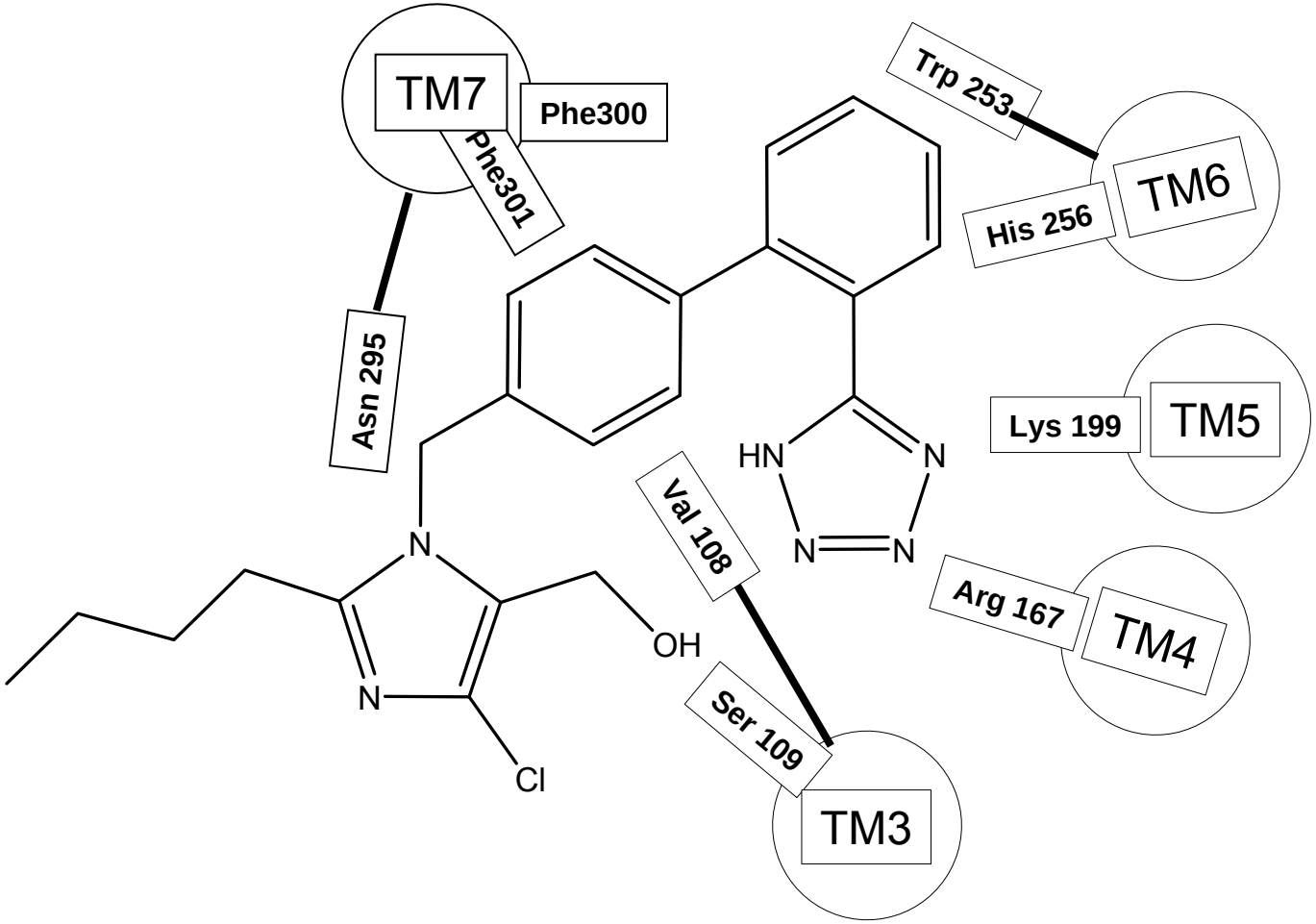
Sartans: une certaine idée du pharmacophore ...



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

disponible sur i-campus

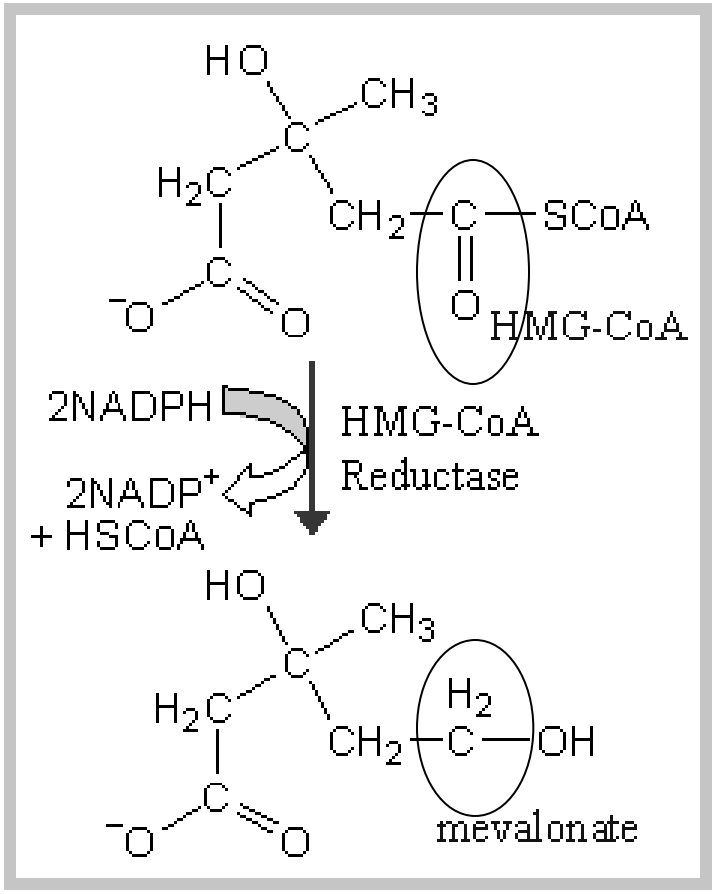
Sartans: pourquoi tous sur le même pharmacophore ?



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

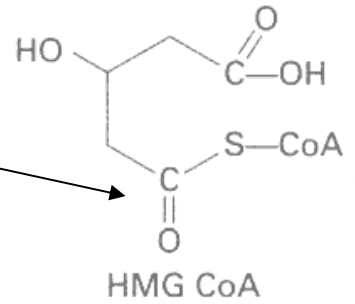
disponible sur i-campus

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

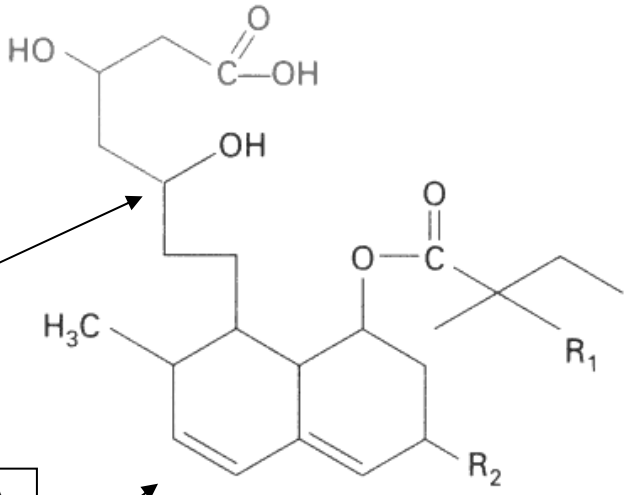


Reduction

substrate



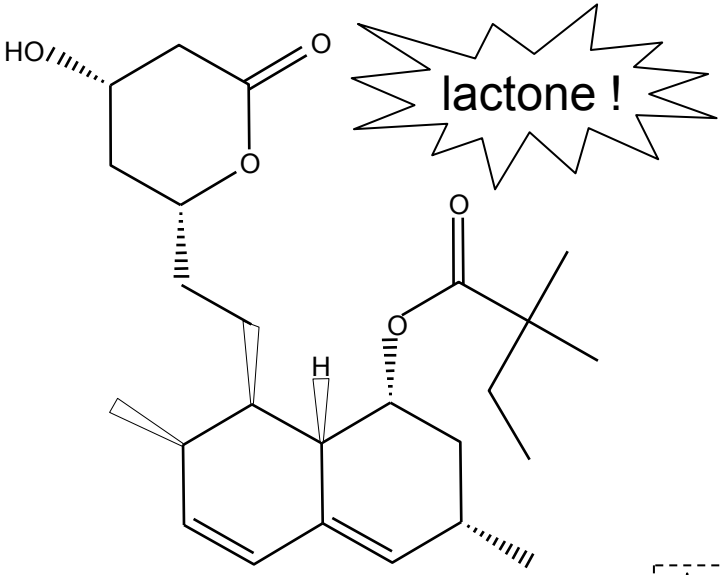
inhibitor



mimics CoA and allows membrane anchoring

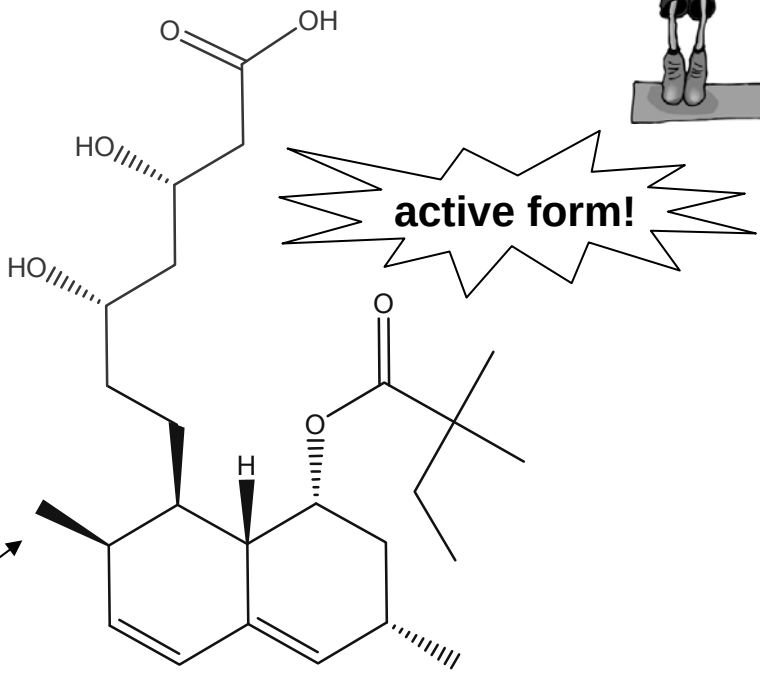
	R_1	R_2
Simvastatin	CH_3	CH_3
Pravastatin	(H)	OH

You said "statins" ?



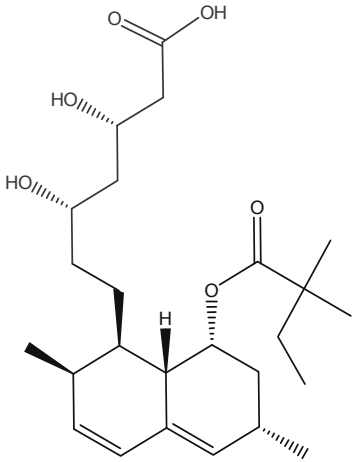
simvastatin

☆ **prevents free rotation of the hydroxyacid chain**



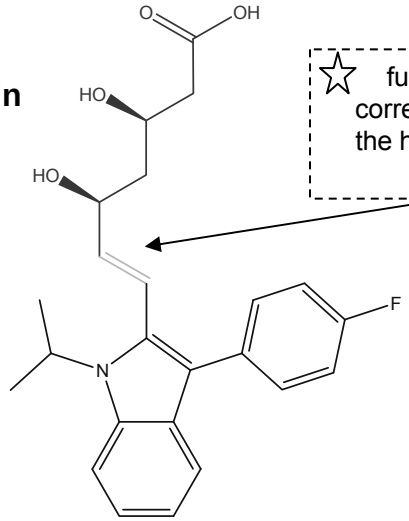
simvastatin hydroxy acid

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



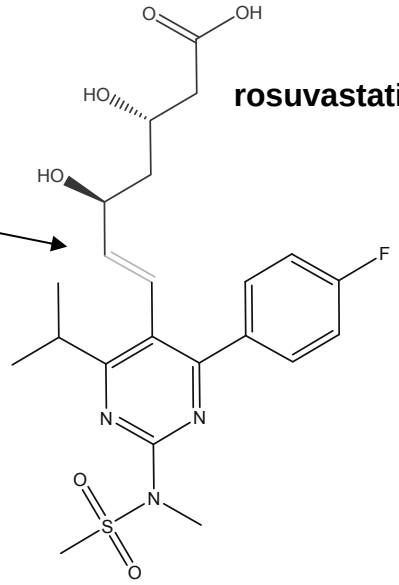
simvastatin hydroxy acid

fluvastatin

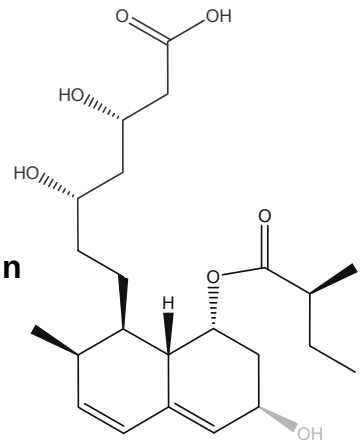


☆ further forces a correct orientation of the hydroxyacid side chain

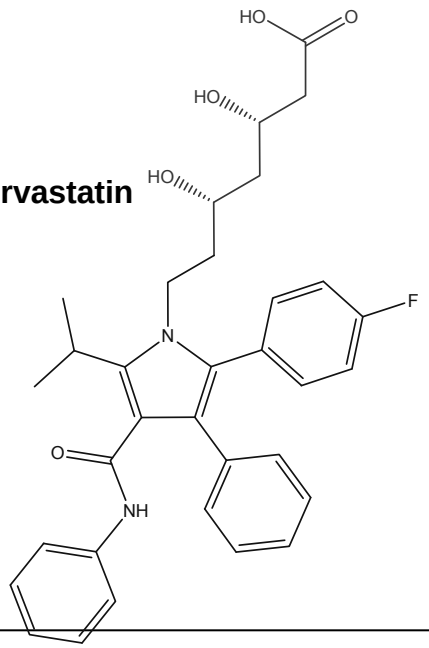
rosuvastatin



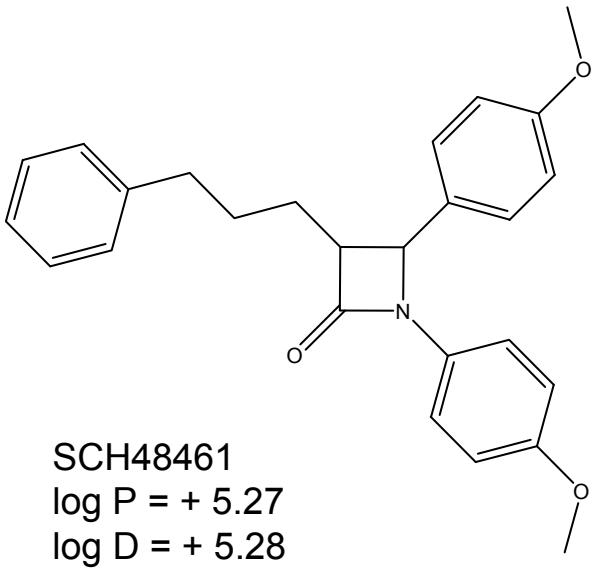
pravastatin



atorvastatin



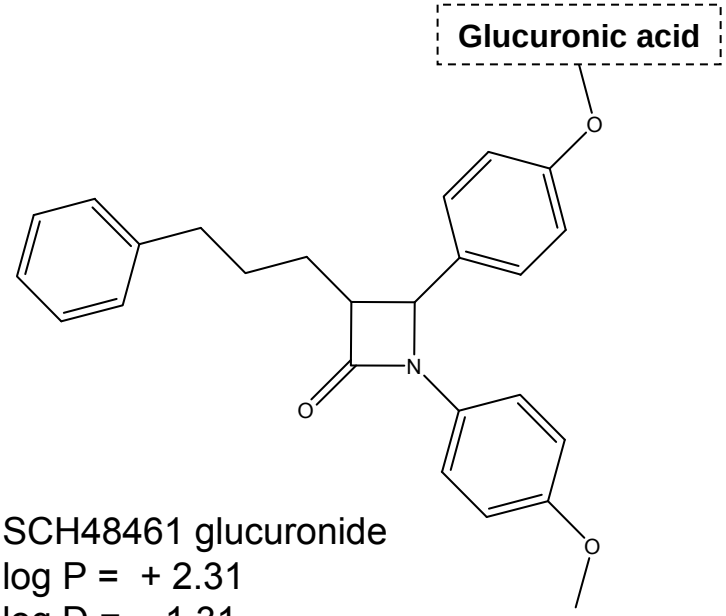
The story of ezetimibe



SCH48461
log P = + 5.27
log D = + 5.28

weak cholesterol uptake inhbitor

absobtion,
liver metabolism,
and bile excretion

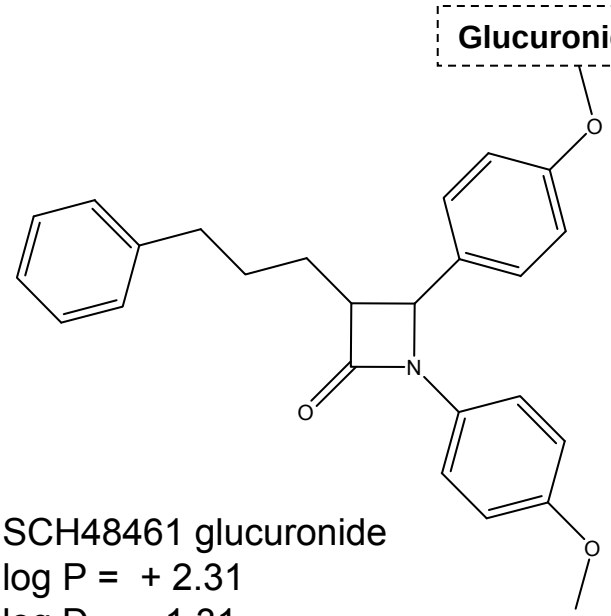


SCH48461 glucuronide
log P = + 2.31
log D = - 1.31

potent cholesterol upake inhibitor

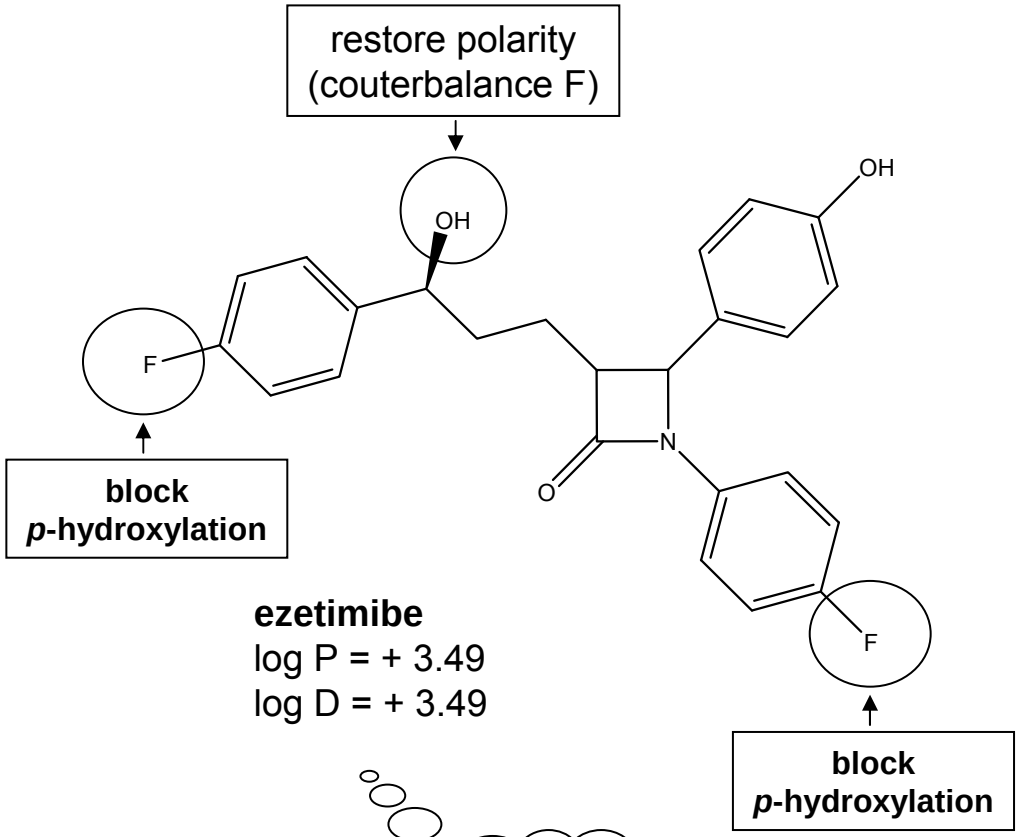
Journal of pharmacology and experimental therapeutics (1997), 283(1), 157-63.

From a metabolite to a drug

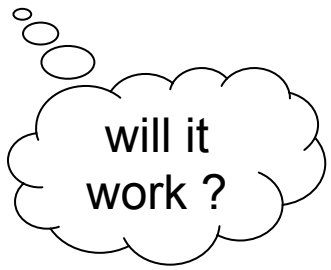


SCH48461 glucuronide
log P = + 2.31
log D = - 1.31

potent cholesterol upake inhibitor

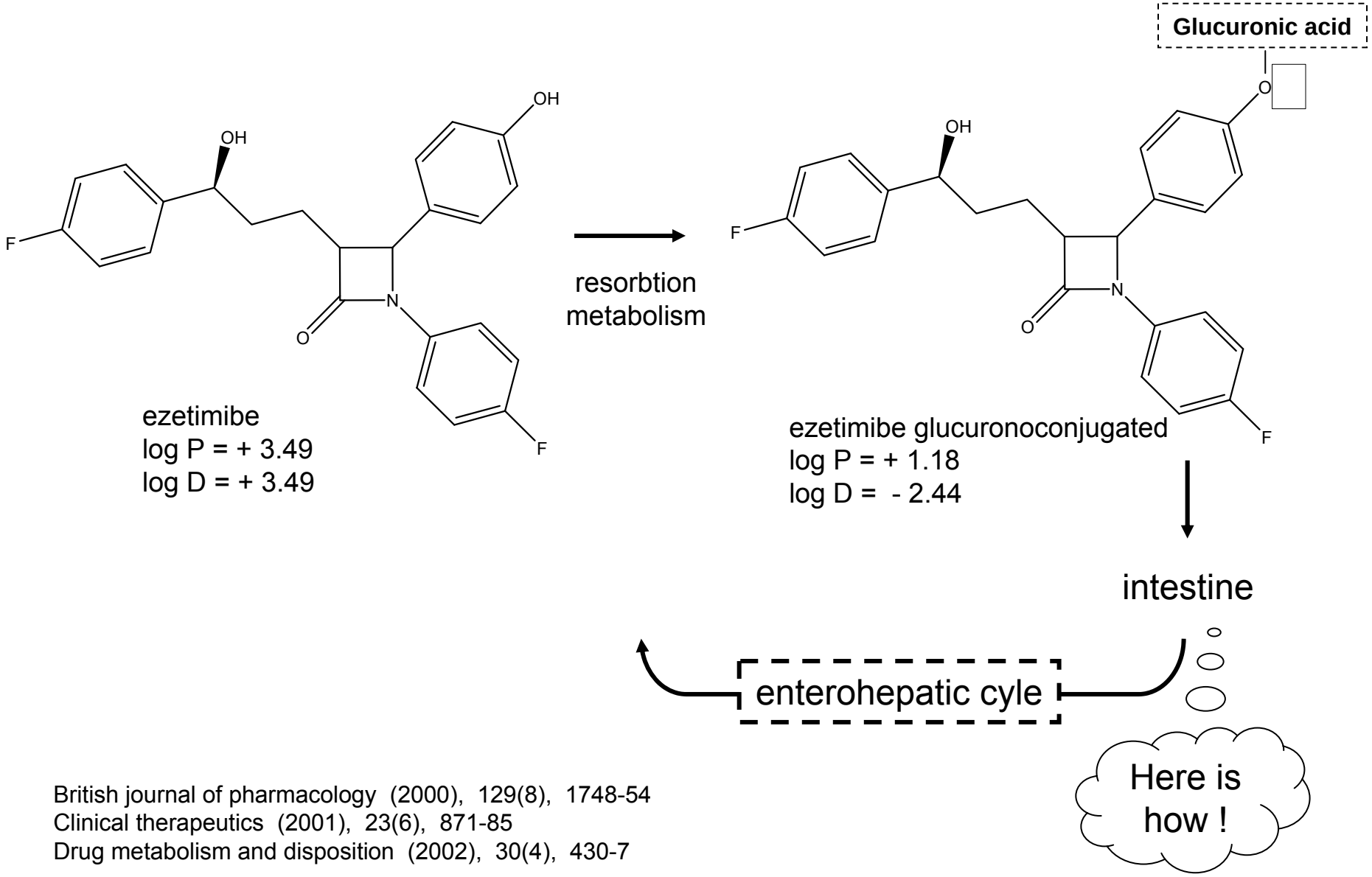


ezetimibe
log P = + 3.49
log D = + 3.49



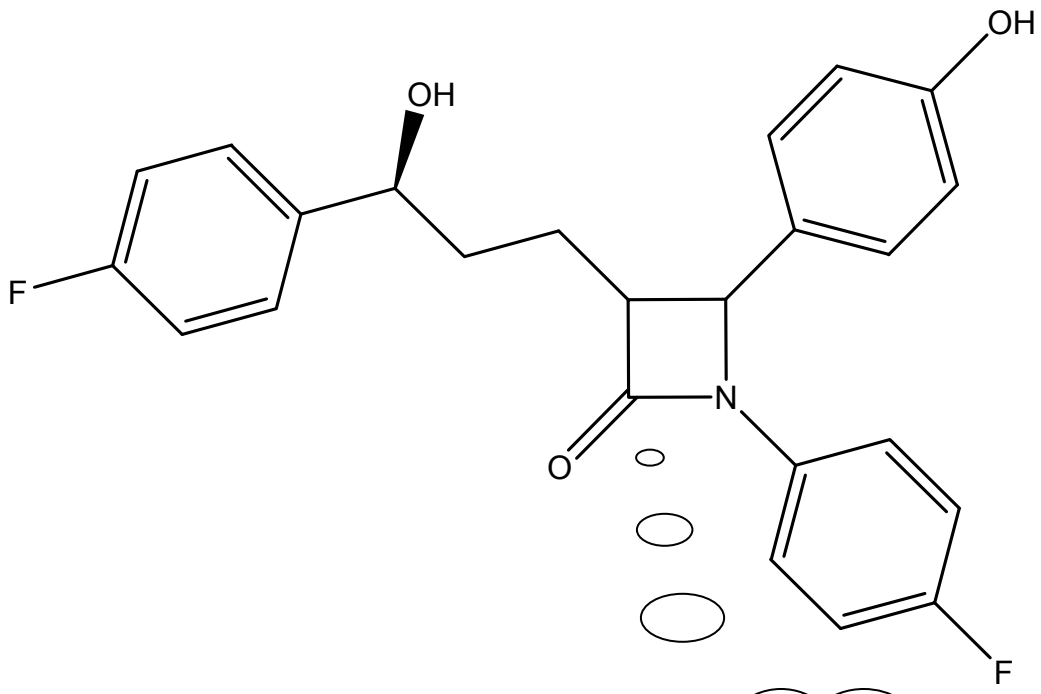
Journal of medicinal chemistry (1998), 41(6), 973-80.

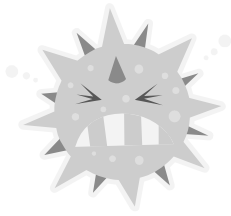
Here is how…



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 ?

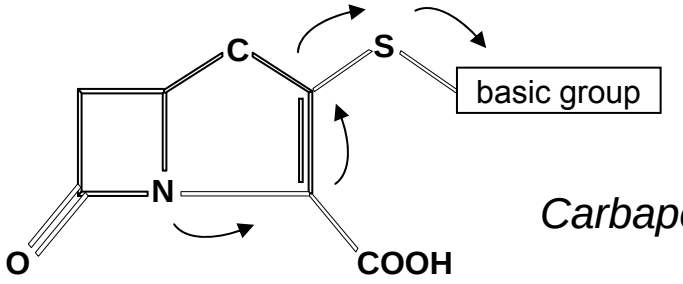




is this not a β-lactam ?

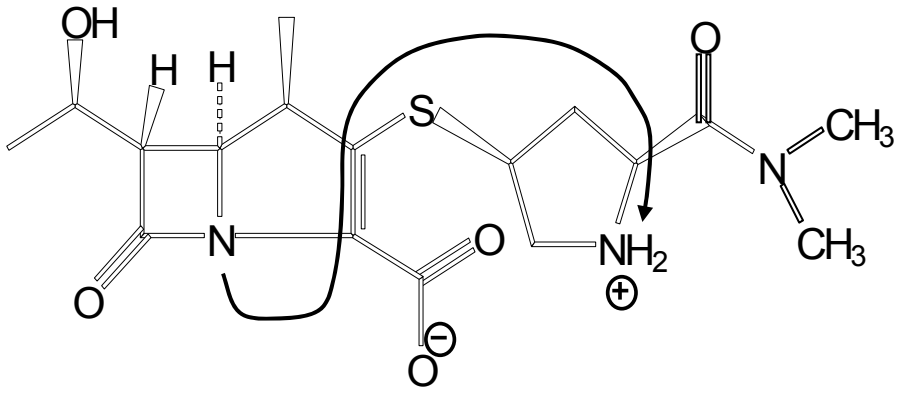
β-lactams are unstable because of anchimeric assistance …

example for carbapenems (very unstable)



Carbapenem

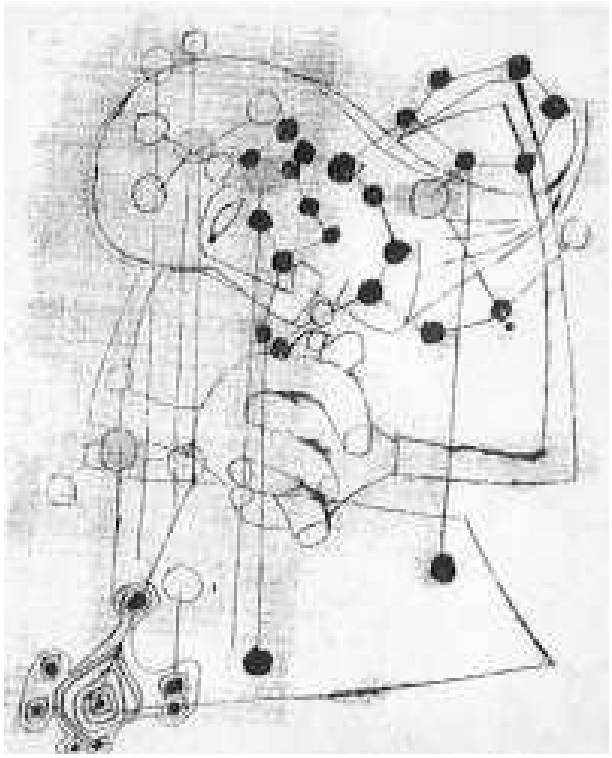
greater intrinsic activity due to larger instability of the β-lactam ring because of C1-C2 double bond and **electrocapturing effect of the basic group**



meropenem

1β-methyl, C2-pyrrolidylthio-dimethylcarbamoyl

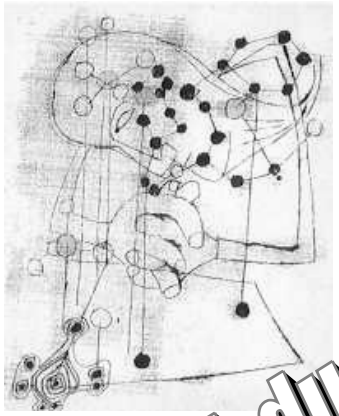
Le médicament …



"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 …