A simple question...

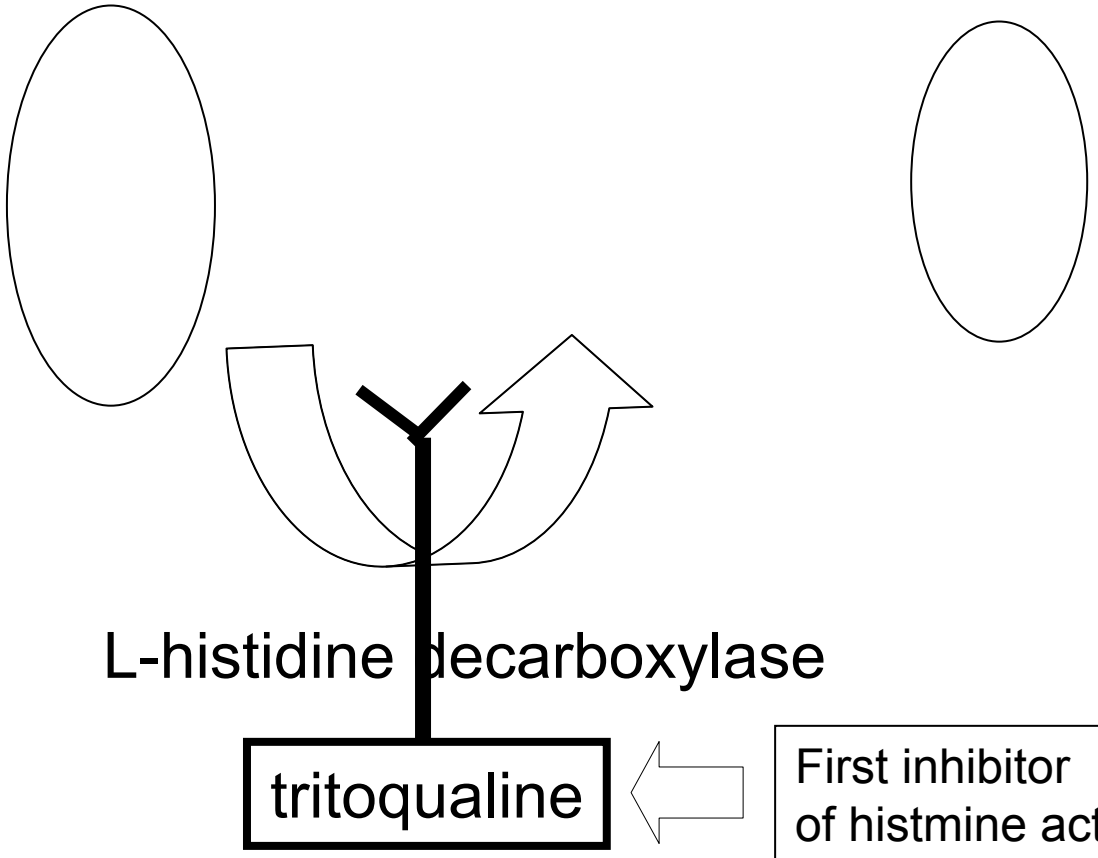
How was histamine discovered ?

- **by chemical synthesis …**
- **from the analysis of plant extracts (ergot fungus *Claviceps purpurea*)**
- **from the analysis of animal tissues extracts**
- **through none of these approaches**

Histamine ...

- ➔ obtained by synthetic chemist in 1907 …as a chemical curiosity …
  - ➢ detection of an identical compound in an extract from ergot fungus … and shown to cause a marked vasodilatation
    - ➢ a similar effect is seen with tissues extracts
      - ➢ produces a similar picture as a very severe allergic reaction
        - ➔ recognized as a "biological" molecule (and not a product from putrefaction in 1927 ...

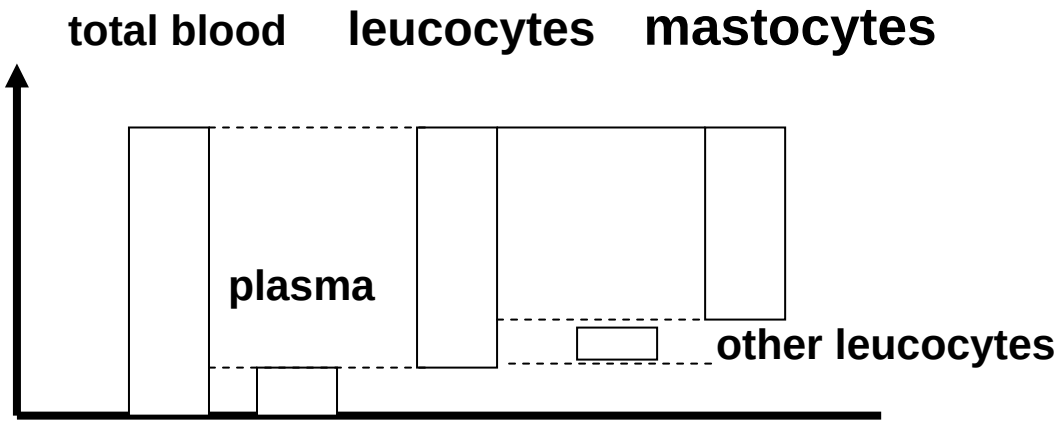
From histidine to histamine ...



First inhibitor
of histmine action …
commercialized in France
(HYPOSTAMINE ®)

Localization of histamine

1. blood



2. tissues ... the word comes from ιστος ("*histos*" = tissue !!)

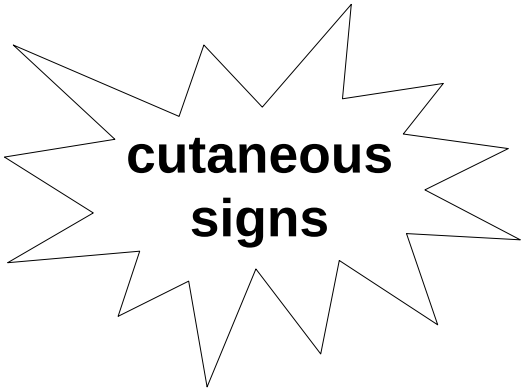
- **skin**
- **lung**
- **gastrointestinal tract**
- **central nervous system**

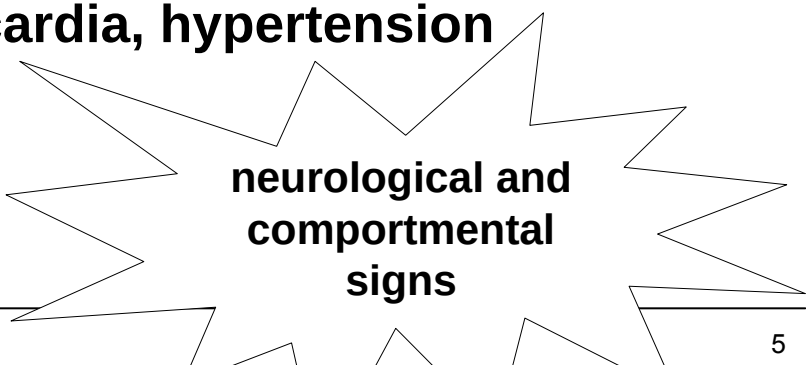
Actions of histamine

- **↑ of capillary permability and vasodilatation**
  - ➔ rednesses
  - ➔ inflammation
- bronchoconstriction

  important with the guinea-pig but under H_2 retrocontol in man
- **↑ of HCl secretion**

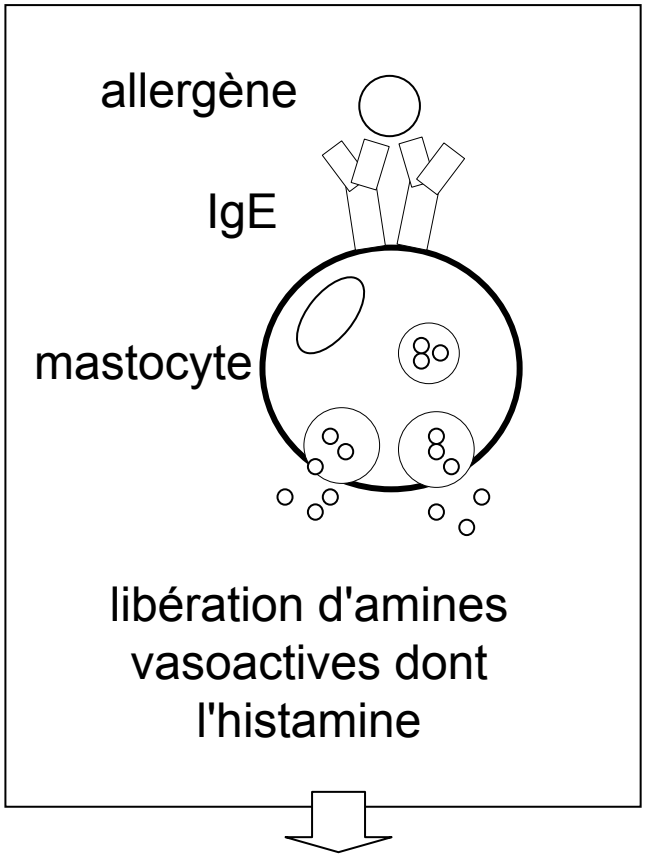
  (pariteal cells of the stomach)
- **neurotransmission**
  - ➔ **awakening reactions, tachycardia, hypertension**
  - ➔ **nauseas, vomitting**
  - ➔ **migraines**





Rappel: les 4 types de réactions d'hypersensibilité

Réaction de type I anaphylactique



- rhinite, conjonctivite, urticaire, asthme aigu, (bronchospasme), oedème
- délai: endéans les 30 min

Réaction de type II: cytotoxique

- médiée par les IgG et/ou les IgM
- action directe sur une cellule cible
- implique le complément
- lyse, phagoytose (anémie hémolytique, agranulocytose, thrombopénie)
- délai: 5-12h

Réaction de type III: formation de complexes immuns

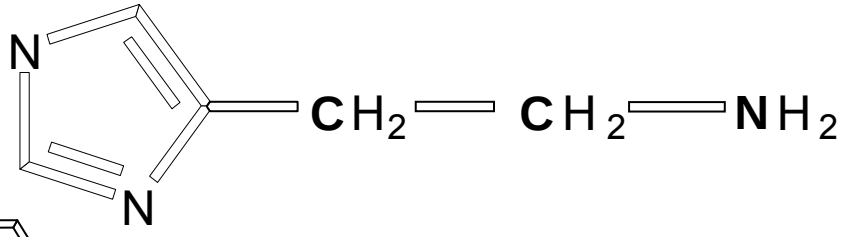
- dépôts dans les tissus avec réaction inflammatoire disséminée
- activation du complément et libération de toxines des leucocytes
- agrégation plaquettaire, microthrombonses…
- délai: 3-8h

Réaction de type IV : cellulaire

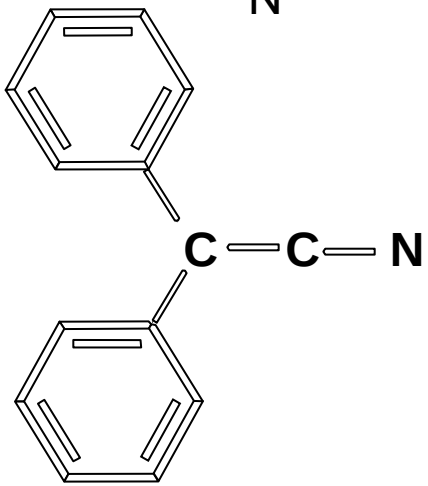
- activation directe des cellules T
- libération de cytokines et de TNFα
- induit typiquement des manifestations cutanées (dermatite de contact, exanthèmes, eczema, …)
- délai: 24 à 48h

From histamine to anti-histamines ...

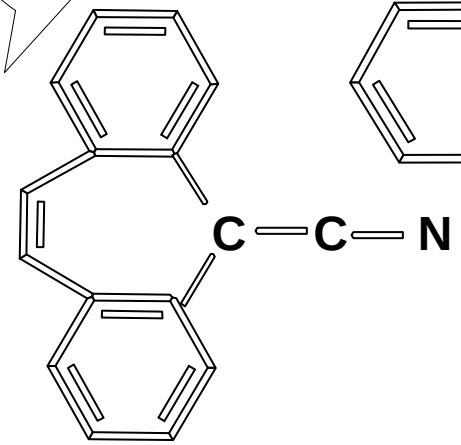
Seen last year !



starting in the 40s ...



Building two aromatic rings

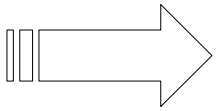


or get a rigidified structure with the same shape (tricyclic)

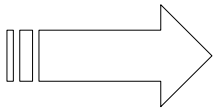
➔ ALL H_1 antihistaminics

Rationalization through a deep understanding of the receptor

- H_1 receptor
  - **CNS**
  - **périphery**
- H_2 receptor
  - **stomach**
  - lung
  - CNS
- H_3 receptor
  - CNS

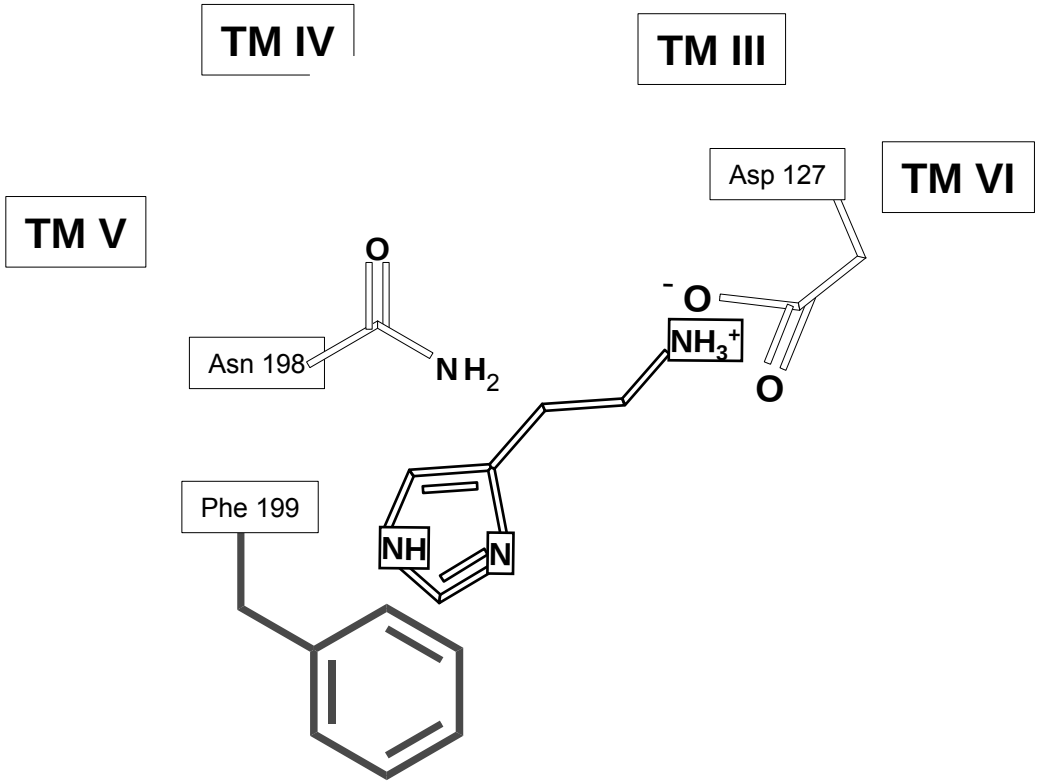


action mediated by the phosphoinositides

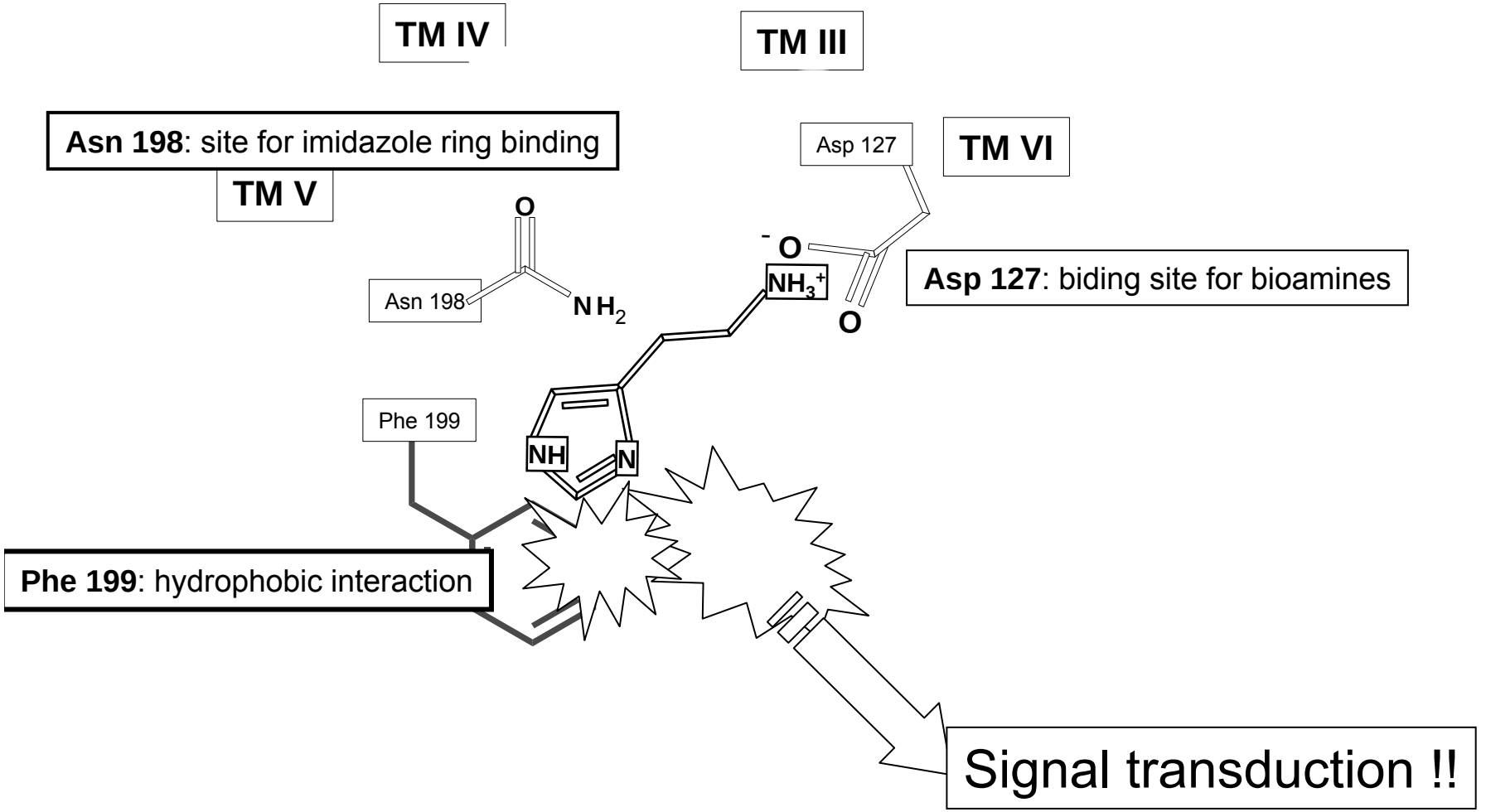


action mediated by cyclic AMP

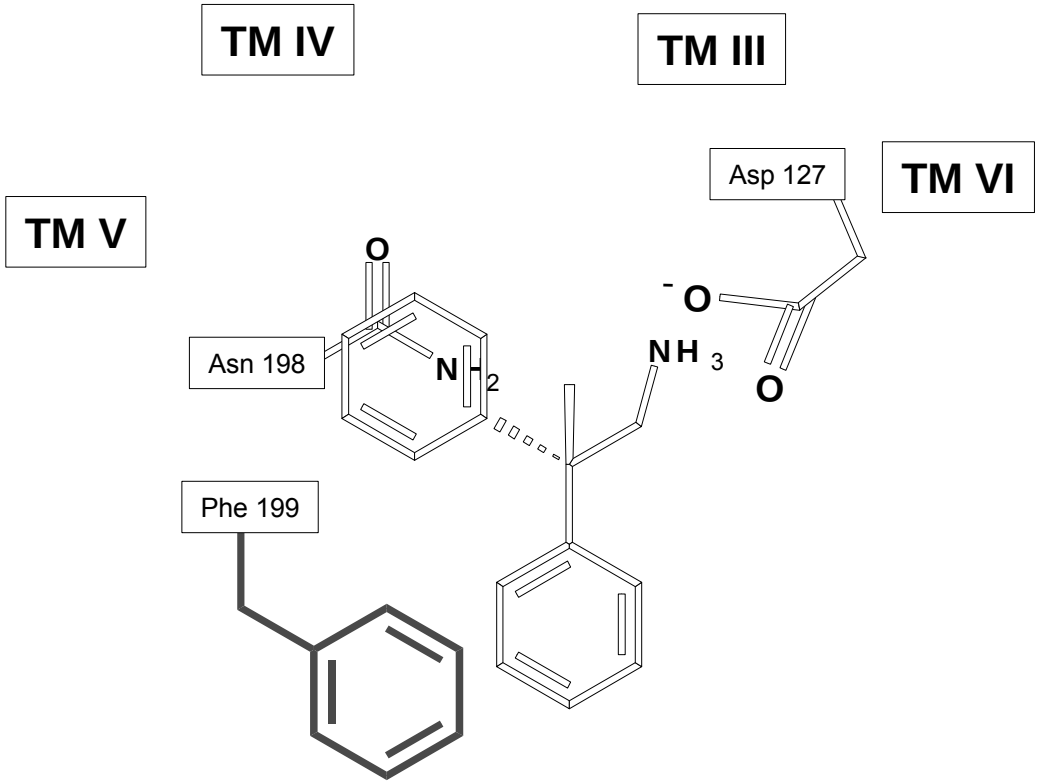
Binding of histamine to H1 receptor



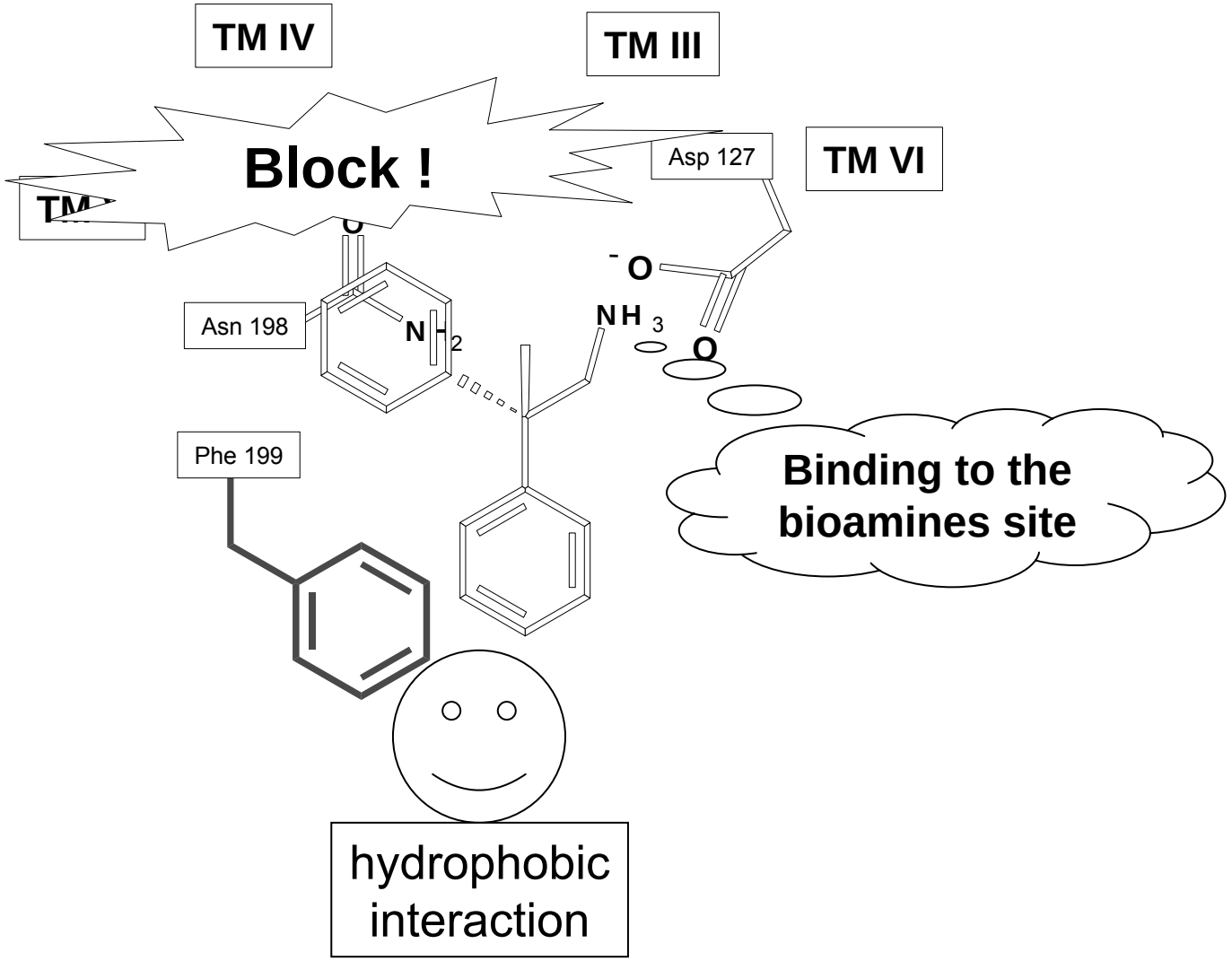
Binding of histamine to H1 receptor



Binding of an antagonist ...



Binding of an antagonist ...



Une famille d'antagonistes H1….

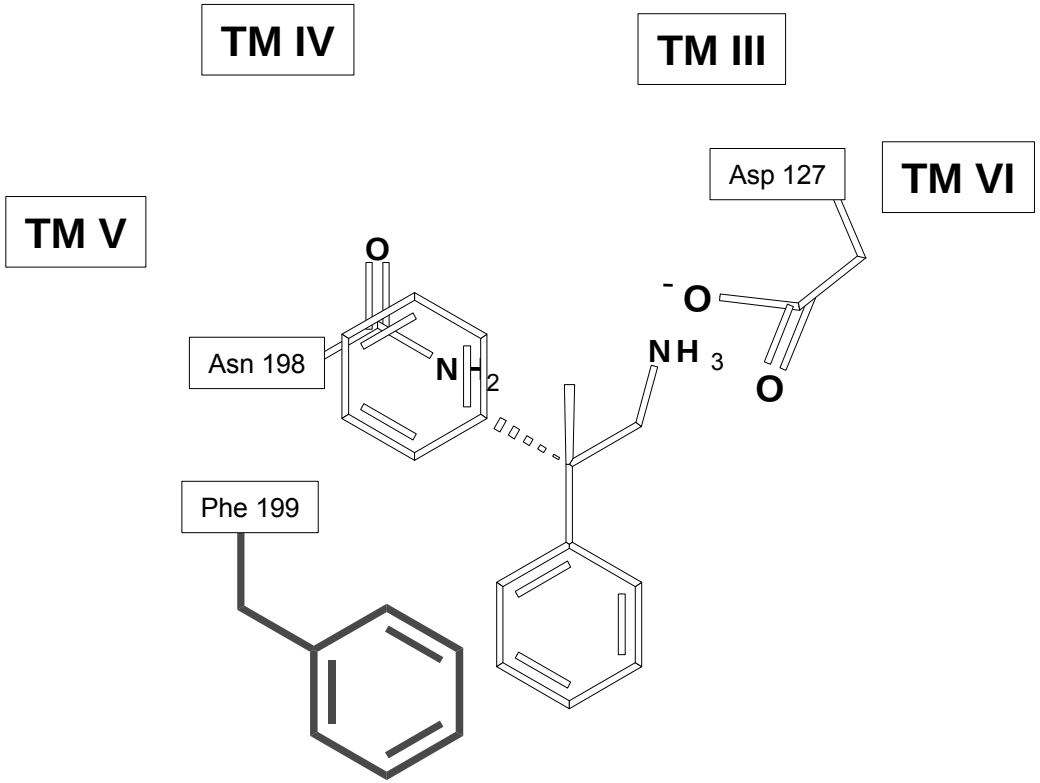
Nom DCI	nom commercial en Belgique *
• alimémazine	THERALENE
• prométhazine	PHENERGAN
• dimenhydrinate	PARANAUSINE / VAGOMIN
• diphenhydramine	BENYLIN
• dexchlrorphéniramine	POLARAMINE
• ciproheptadine	PERIACTIN
• dimétindène	FENISTIL
• méclozine	AGYRAX / POSTAFENE
• cetirizine	ZYRTEC / REACTINE / ….
• loratadine	CLARITINE / SANELOR
• fexofenadine	TELFAST

et plus récemment

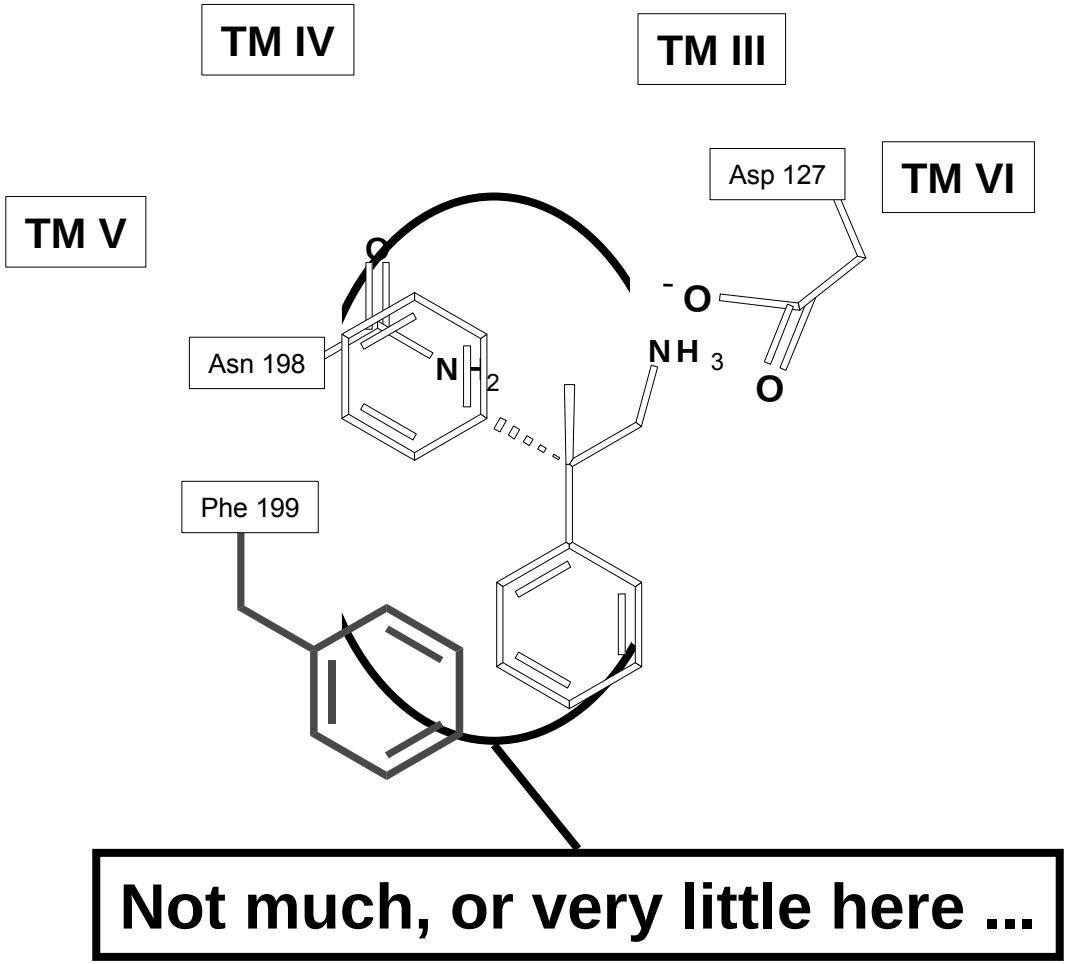
• lévocetirizine	XYZAL
• desloratadine	AERIUS

* liste non limitative…

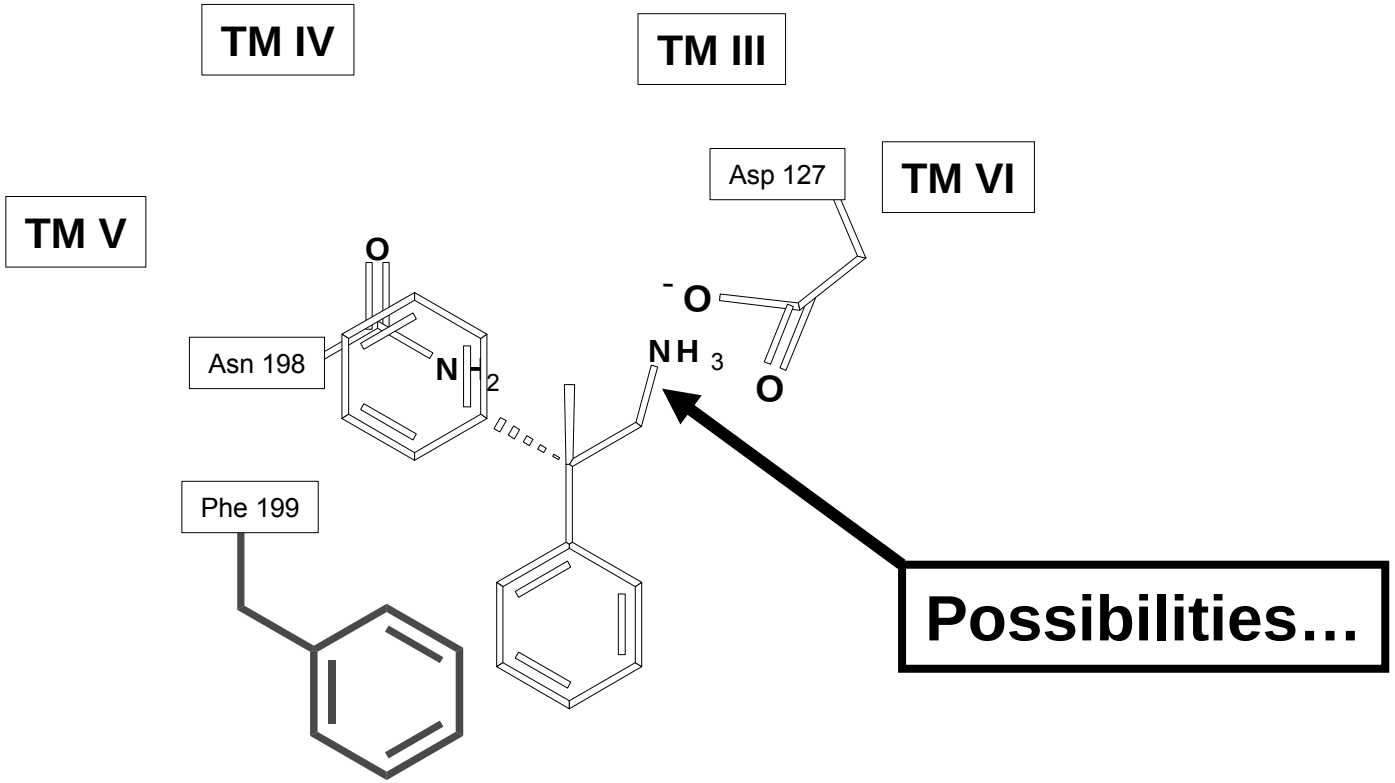
Binding of an antagonist: what can you modify ?



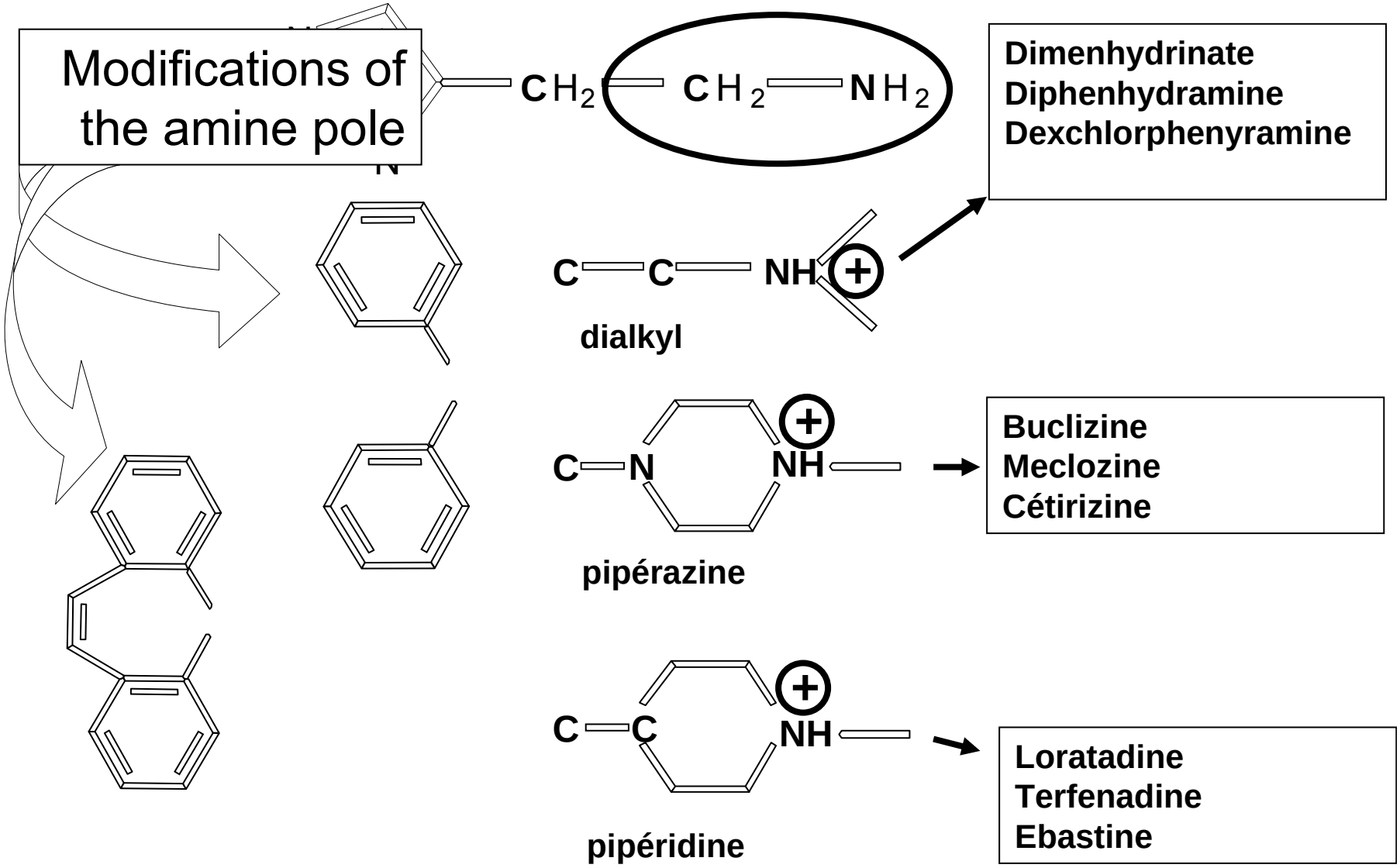
Binding of an antagonist: what can you modify ?



Binding of an antagonist: what can you modify ?



Variations among antihistamines....



The ideal antihistaminic drug for the treatment of allergy

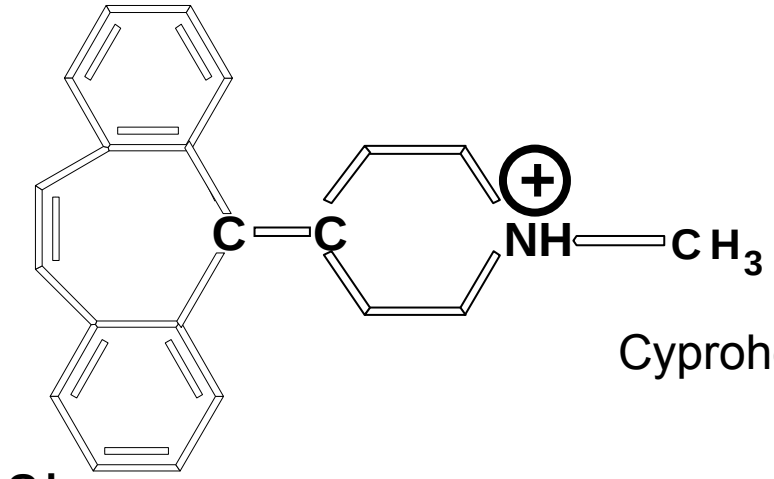
What is your "wish list" ?

- Low sedation activity *
- No or little anticholinergic effects **
- Getting a rapid and prolonged action ***

* most "old" antihistamines make you to fall asleep…
** because their structure is reminiscent of atropine
*** I want a fast relief, and not needing taking pills every hour…

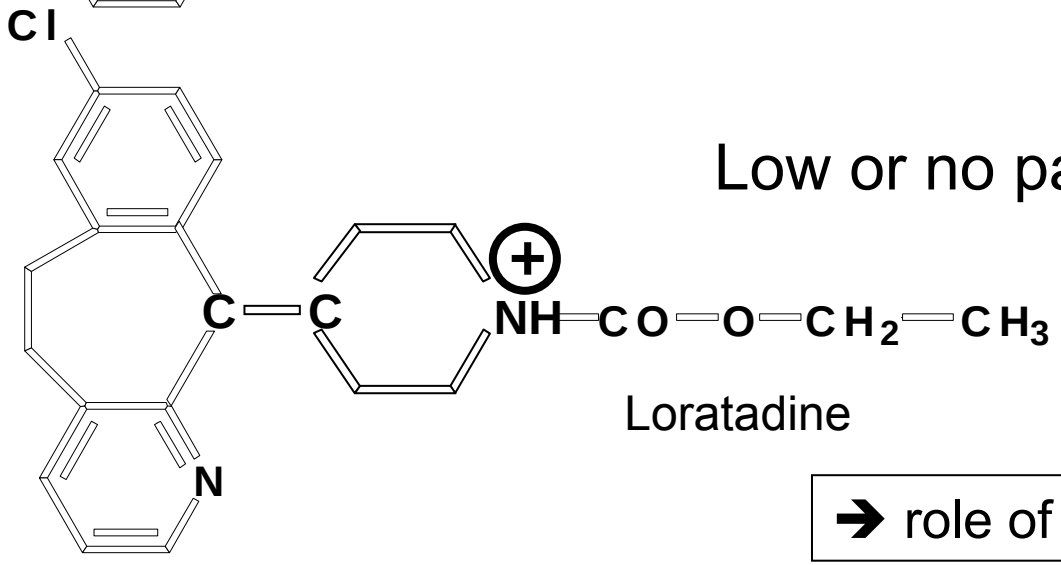
Low sedation activity ...

➔ **Modulation of the hematoencephalic barrier passage...**



Cyproheptadine

Fast and important passage



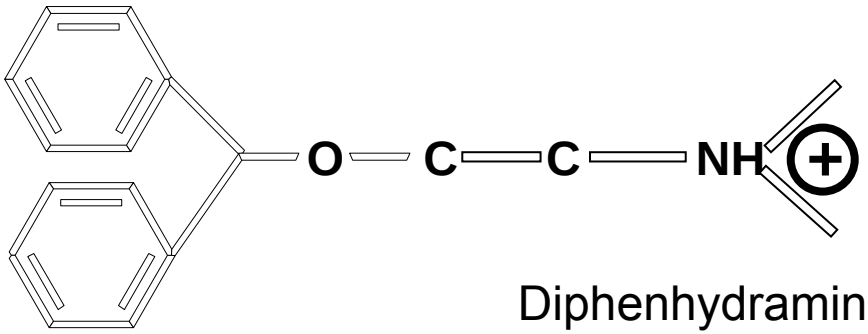
Loratadine

Low or no passage

➔ role of the side-chain...

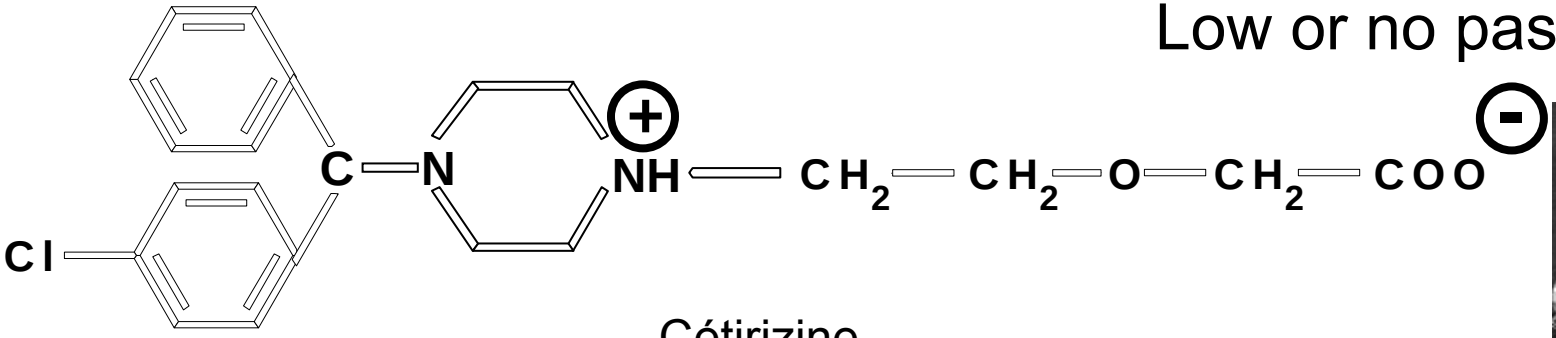
Low sedation activity ...

Another example…



Diphenhydramine

Important passage



Cétirizine

Low or no pasage

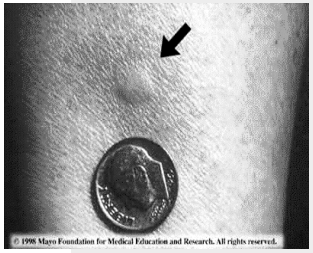
➔ role of the length and of the polarity of the side-chain

Molécules à passage hémato-méningé important et causant de la sédation ...

Nom DCI	sédation	OTC
alimémazine	+++	oui (partiel.)
prométhazine	+++	oui
dimenhydrinate	+++	oui
	+++	oui
diphenhydramine	+++	oui
oxomémazine	++	non
dexchlorphéniramine	++	oui
ciproheptadine	++	oui
dimétindène	+	oui
méclozine	+	oui
	+	oui

The antihistaminic and the sedative actions of the "old" antihistaminics go side by side

Promethazine (PHENERGAN 30 mg)



placebo

Antihistaminic action

Sedative action

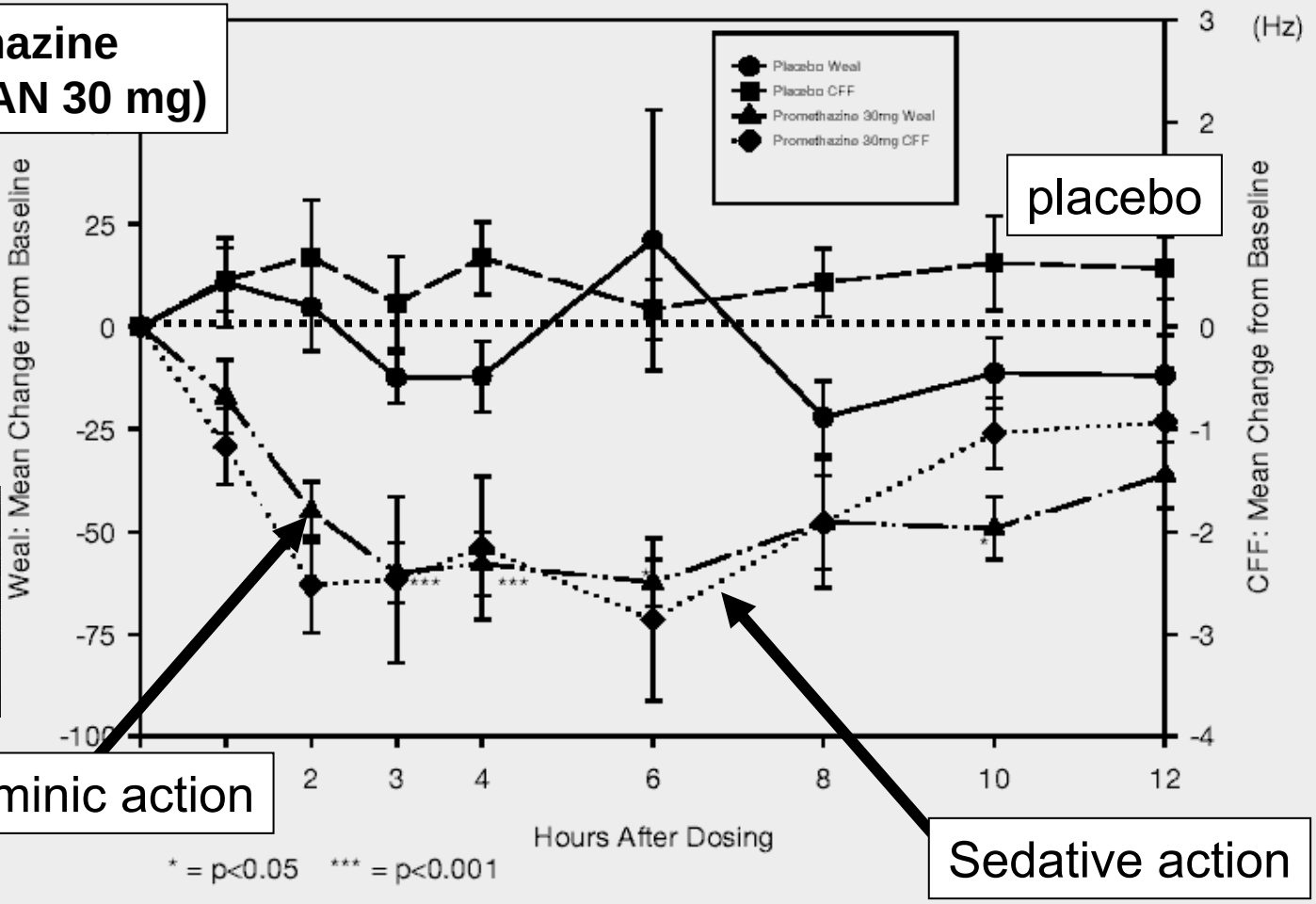


Figure 3. Change from baseline: peripheral antihistaminic suppression (weal) with respect to CFF threshold: acute dose promethazine 30 mg, day 1

Hindmarch et al., Curr. Med. Res. Opin., 17:241-255, 2001

First molecules with low level of passage through the hemato-encephalic barrier

- astémisole
- terfénadine

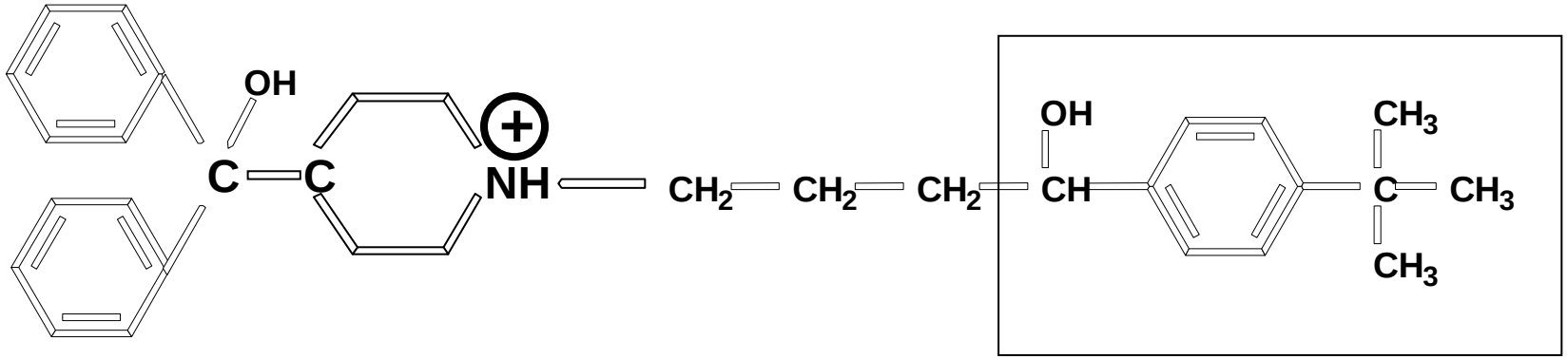
withdrawn because of cardiac toxicity
Torsades de pointe !!!

- fexofénadine

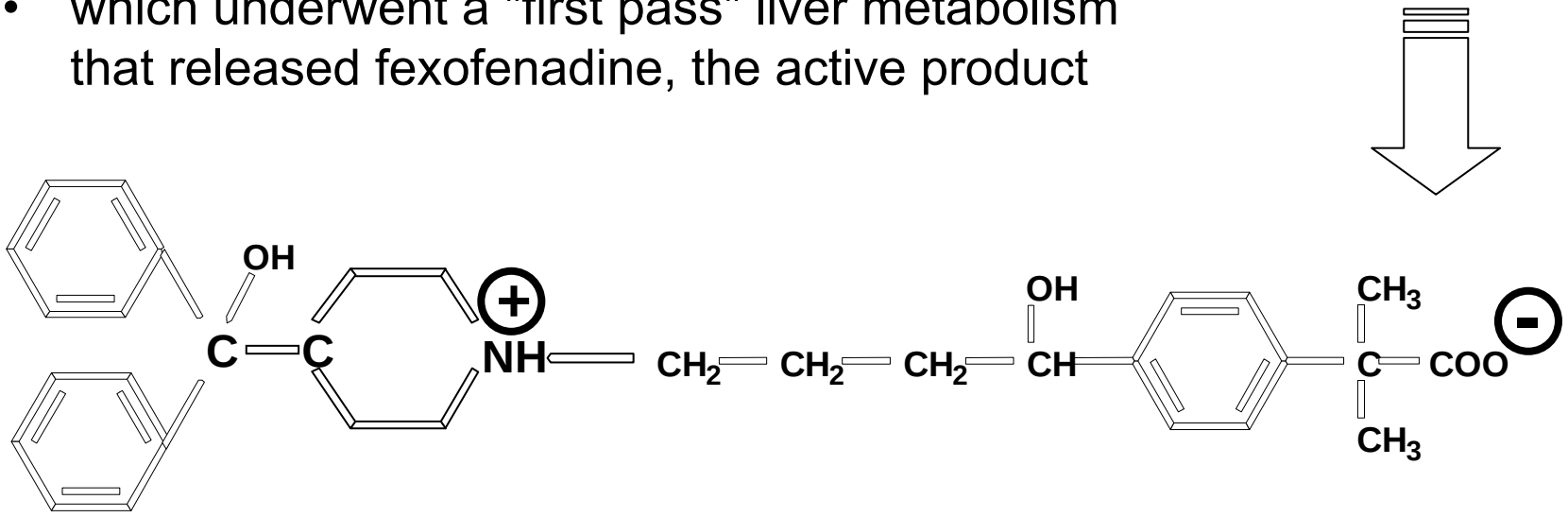
Active metabolite of terfenadine

The problem of terfanadine...

- **terfenadine was a pro-drug**

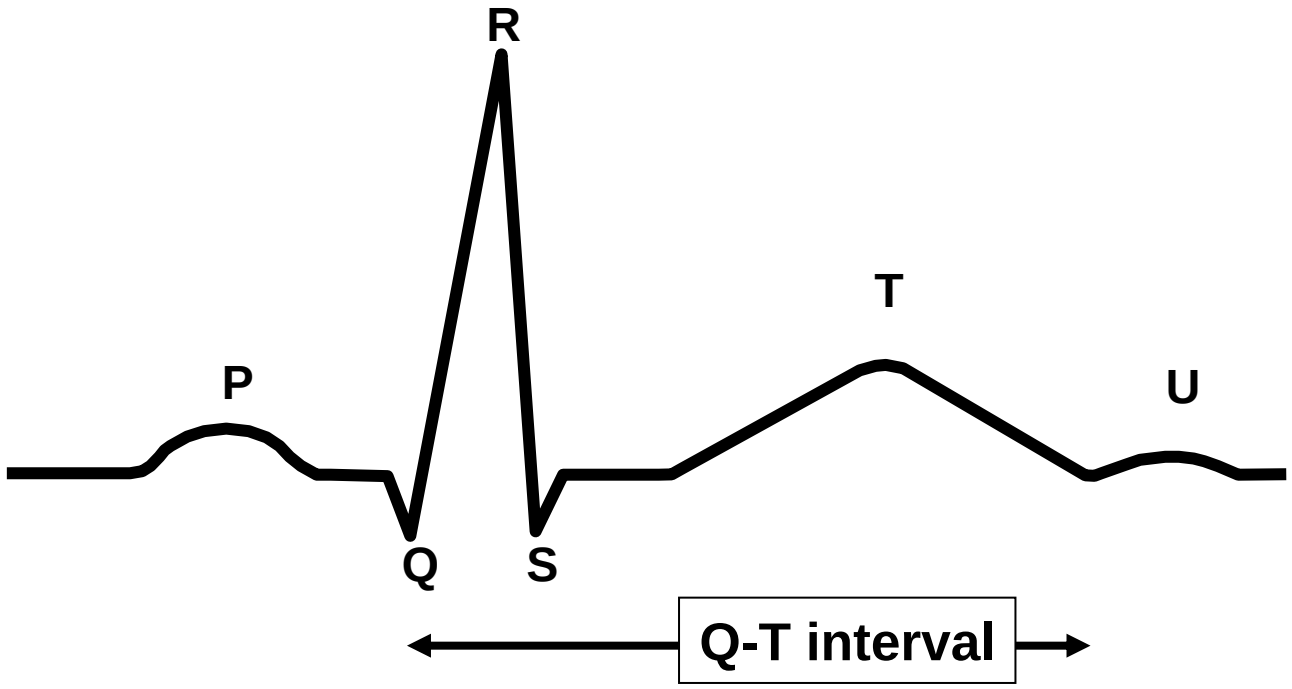


- which underwent a "first pass" liver metabolism that released fexofenadine, the active product

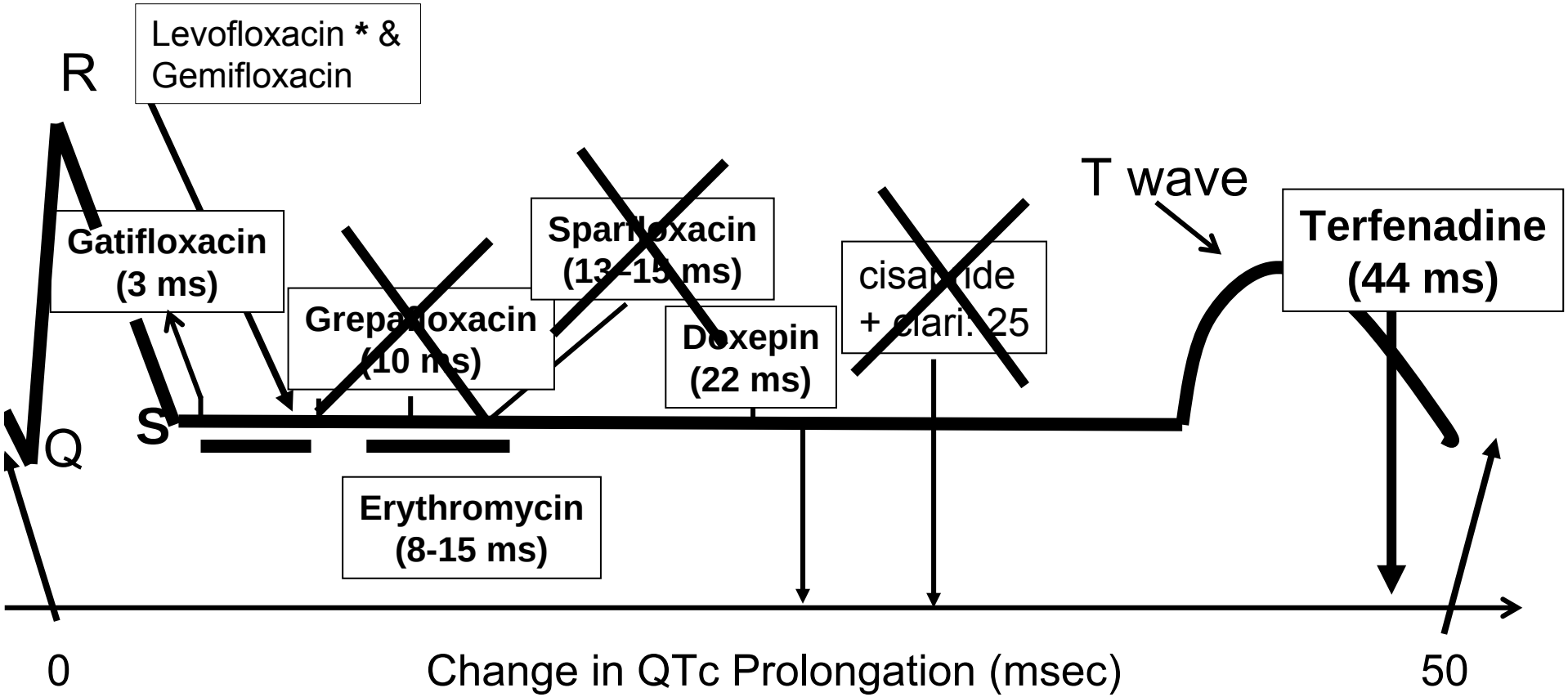


Le problème de la terfénadine ...

- si la terfénadine circule, elle provoque un allongement de l'intervalle Q-T de l'électrocardiogramme pouvant mener à des arythmies mortelles ...



Le problème de la terfénadine ...

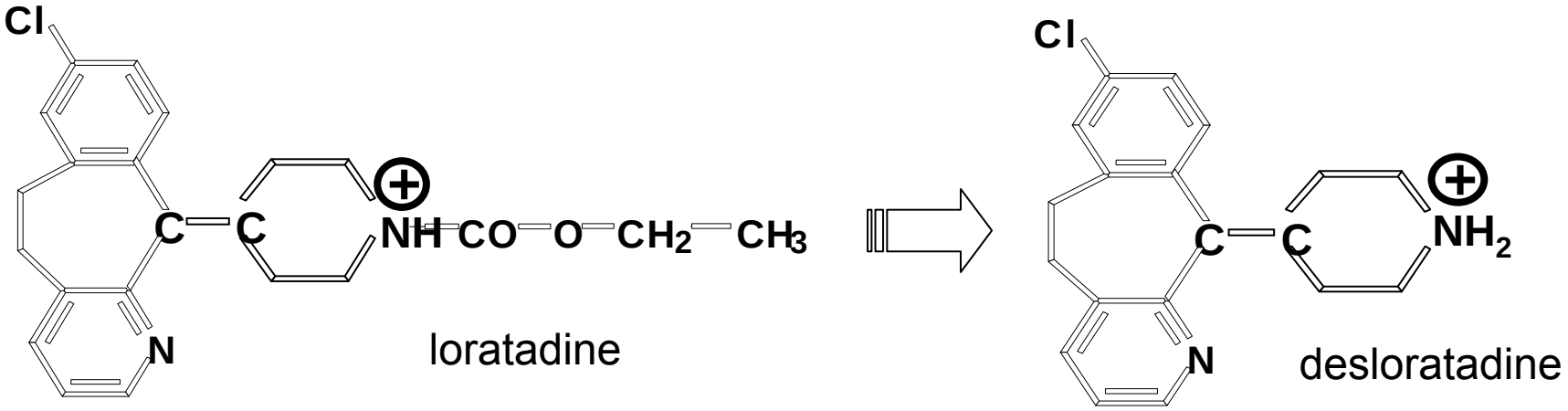


Adapted from Oberg and Bauman,1995; Baker et al,1997; van Haarst et al, 1998.

Molecules with a weak hemato-encephalic passage ...

- loratadine

must be metabolized into desloratadine



loratadine desloratadine

- ebastin
- cetirizine

not very sedative and acting as such

Dissociation of the antihistaminic and the sedative activities

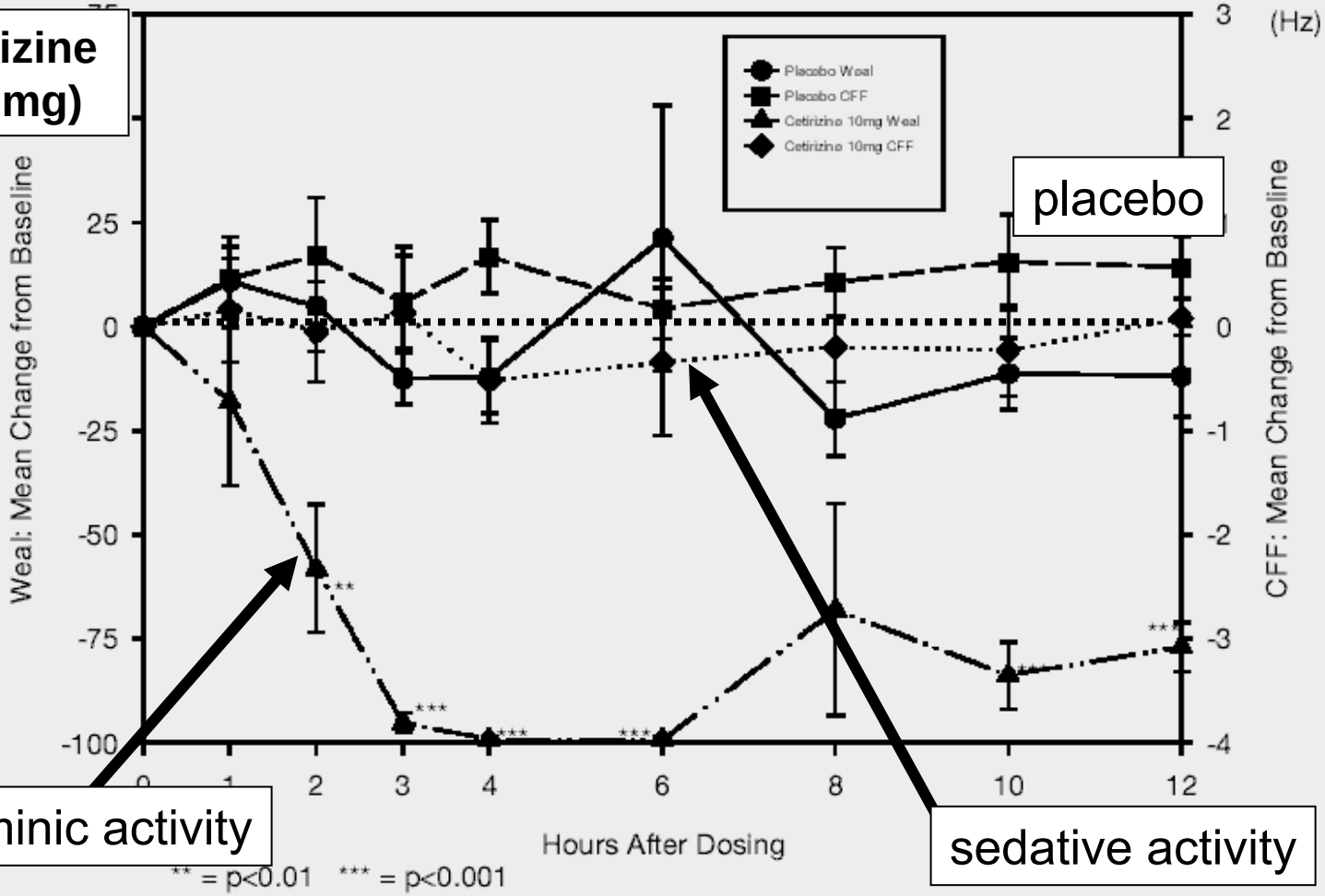


Figure 5. *Change from baseline: peripheral antihistaminic suppression (weal) with respect to CFF threshold: acute dose cetirizine 10 mg, day 1*

Hindmarch et al., Curr. Med. Res. Opin., 17:241-255, 2001

Dissociation des activités antihistaminique et sédative ...

Mais, attention:

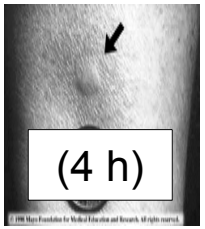
tout est une question de dose…

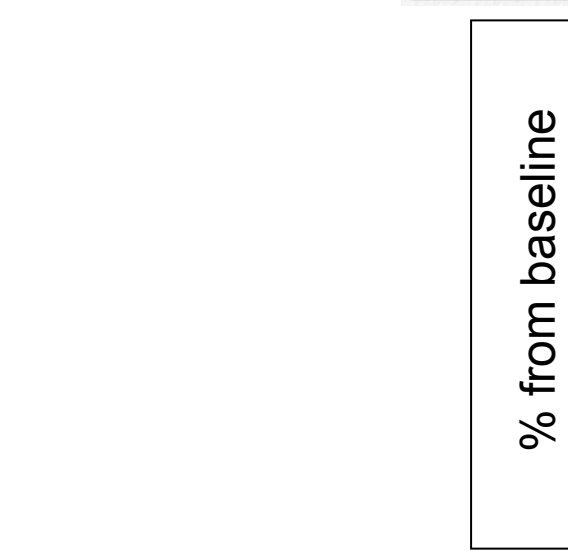
Dissociation des activités antihistaminique et sédative ...

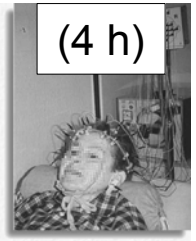
Mais, attention, tout est une question de dose…

Activité antihistaminique

placebo | cétirizine

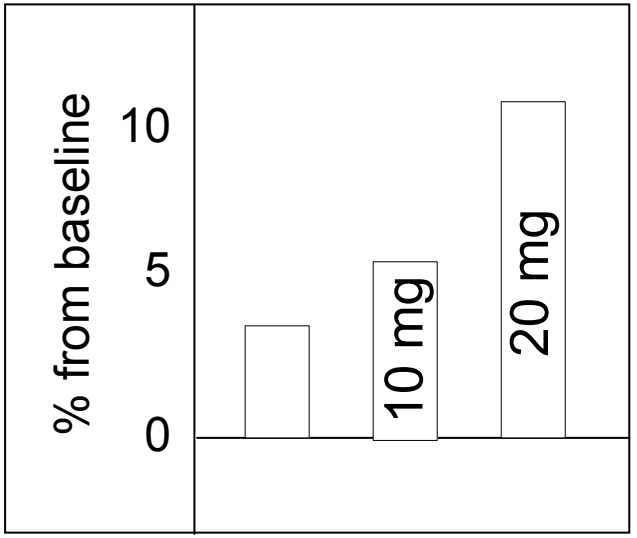






Activité sédative

placebo | cétirizine



Adapté de Sannita et al., Eur. J. Pharmacol. 300: 33-42, 1996

L' antihistaminique H1 idéal dans le traitement de l'allergie….

Cahier de charges

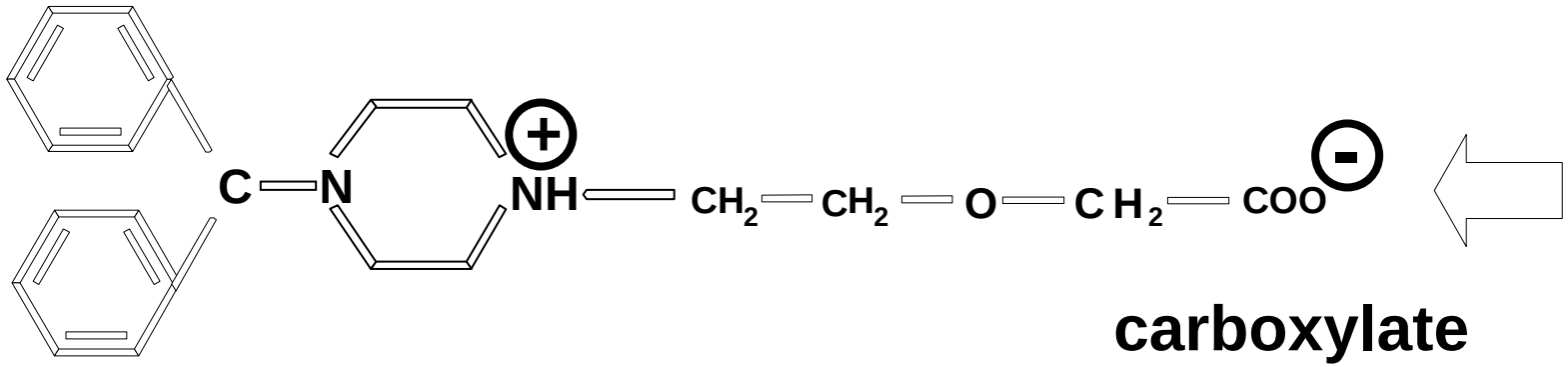
- Pouvoir de sédation faible
- **Eviter les effets anticholinergiques**
  - – élevé à moyen pour les anciennes molécules
    - ➔ troubles de la vue, rétention urinaire ...
  - – faible à nul pour les nouvelles molécules
    - (loratadine,fexofénadine, cétirizine)
- Obtenir une action rapide et prolongée

L' antihistaminique H1 idéal dans le traitement de l'allergie….

Cahier de charges

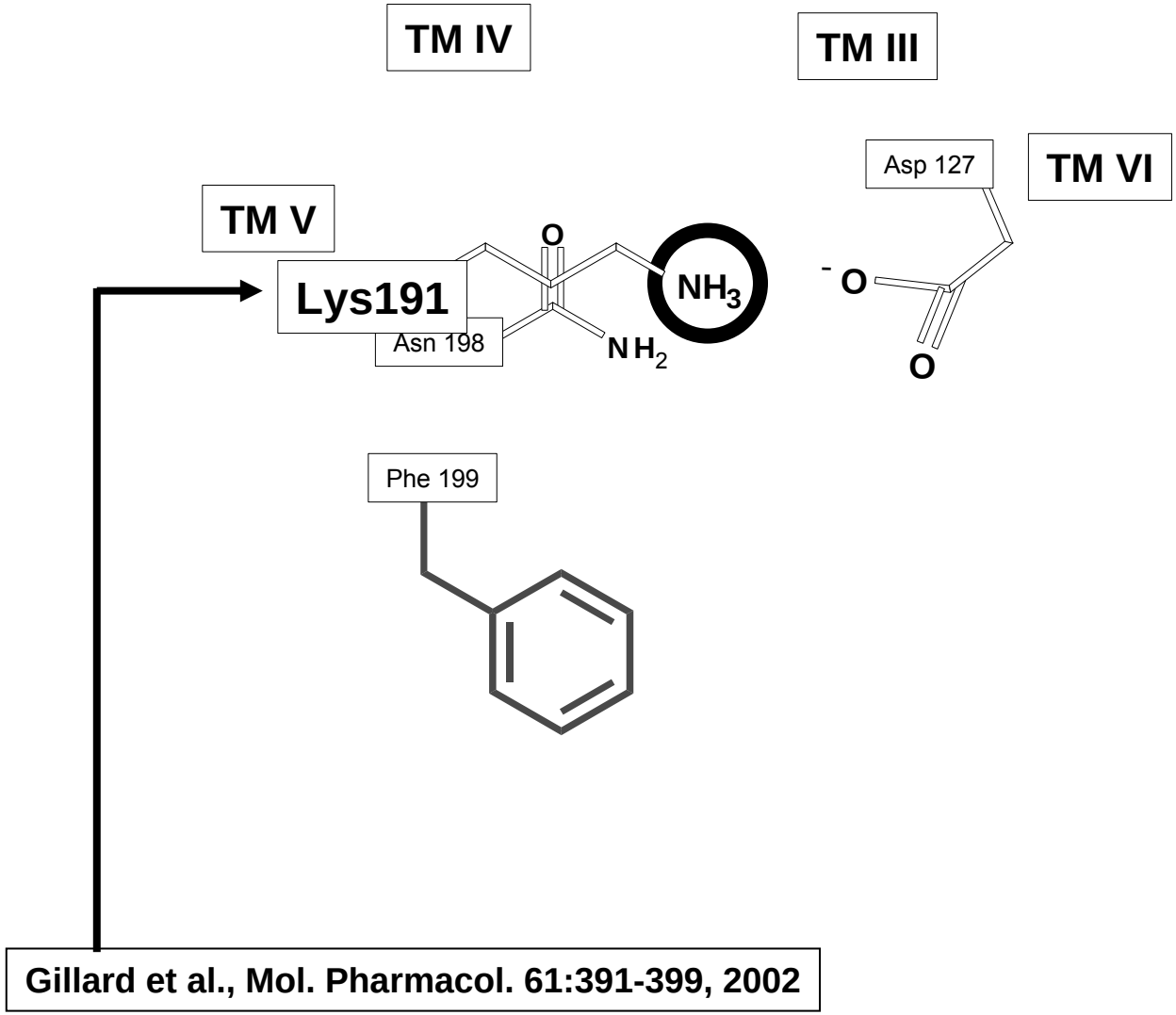
- Pouvoir de sédation faible
- Eviter les effets anticholinergiques
- **Obtenir une action rapide et prolongée**

Propriétés moléculaires de la cétirizine



- action directe car pas de nécessité de métabolisme activateur (>< terfénadine, loratadine…)
- pas ou peu de passage de la barrière hémato méningée
- **longue durée d'occupation du récepteur ....**

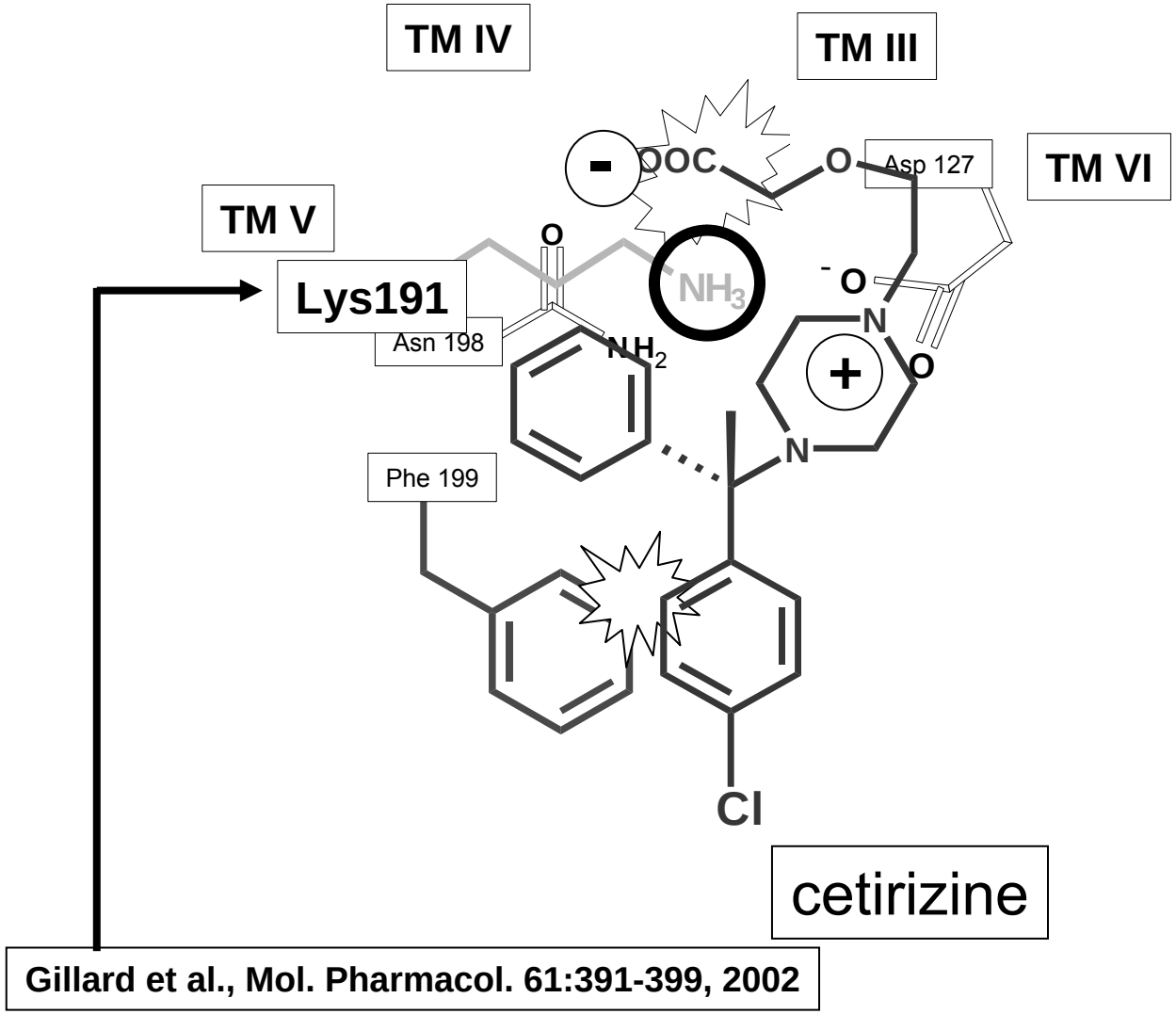
Binding of an H_1 antagonist to the receptor...



Presence
of a lysine
in position 191

Gillard et al., Mol. Pharmacol. 61:391-399, 2002

Slow release of an antagonist ...



Gillard et al., Mol. Pharmacol. 61:391-399, 2002

additional electrostatic bound

Slow dissociation and long-lasting action

Prolonged action ...

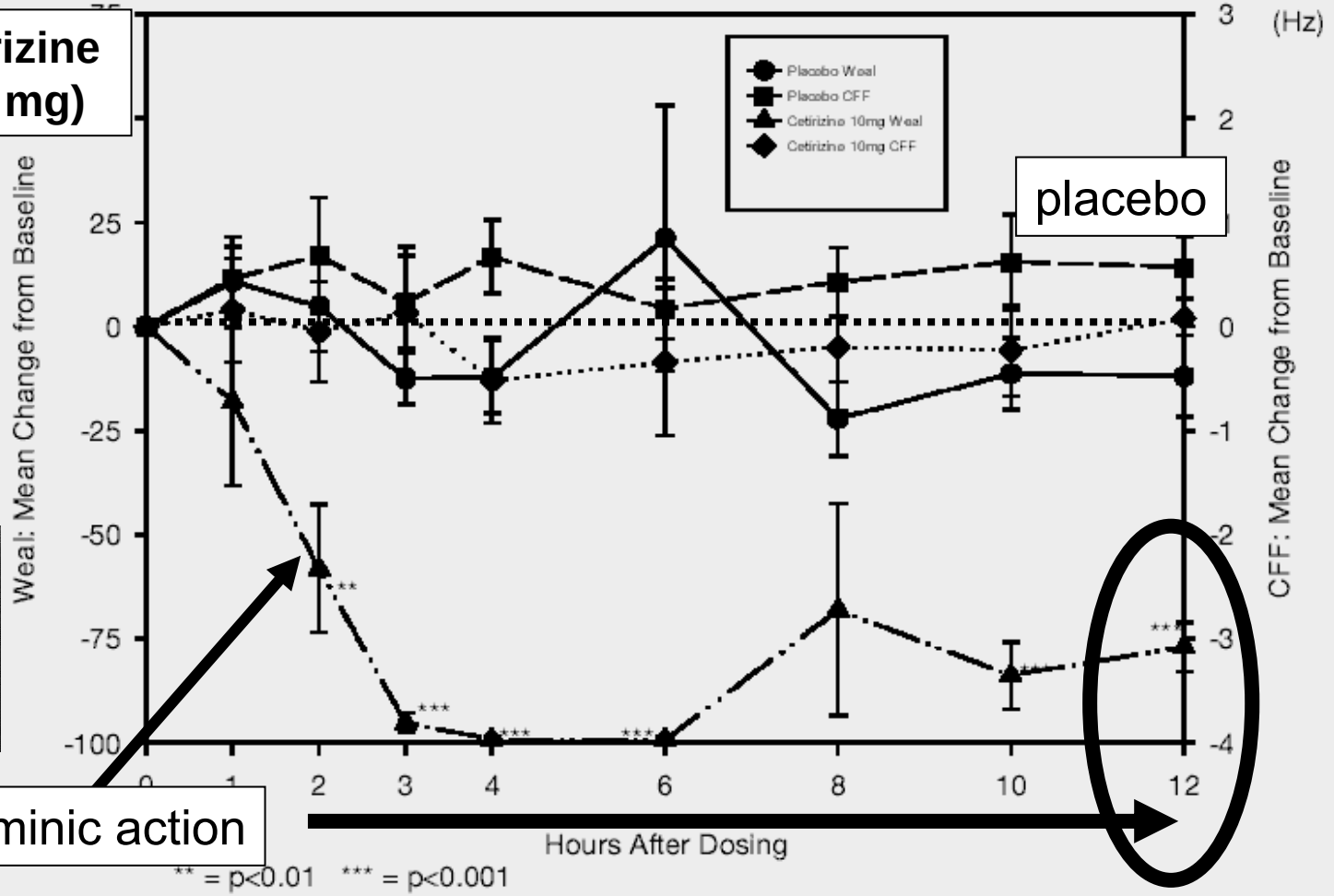
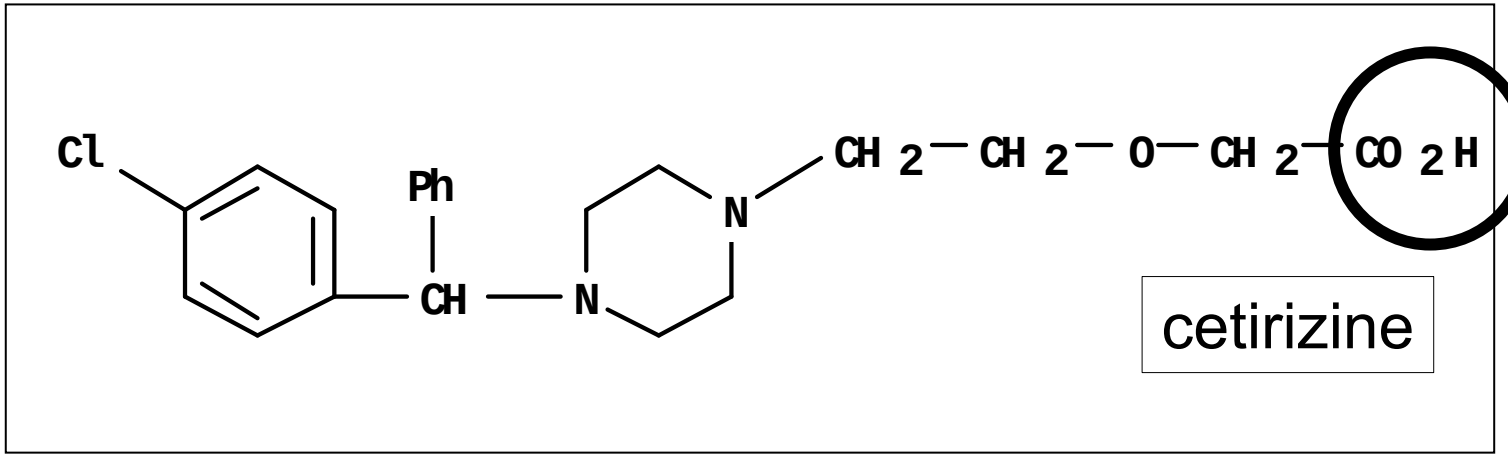
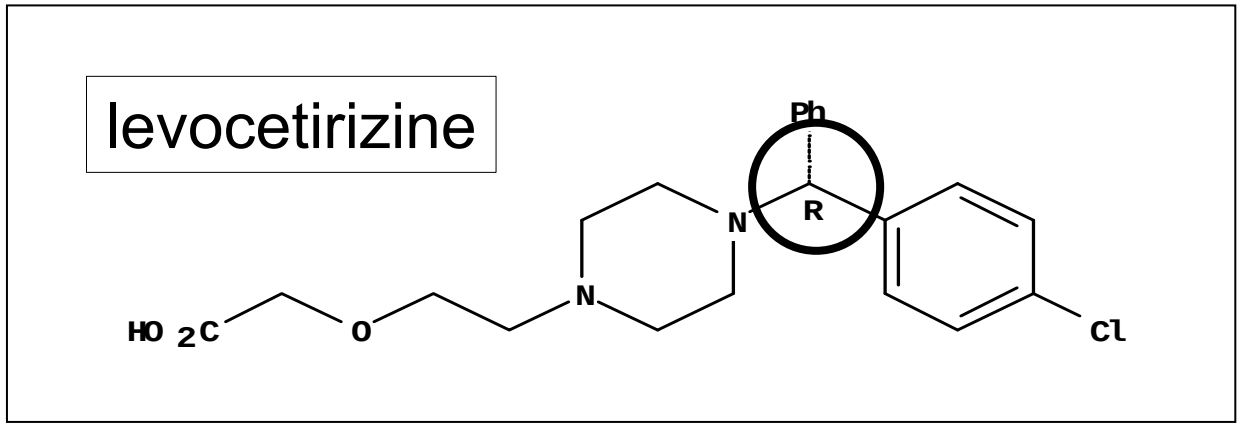


Figure 5. *Change from baseline: peripheral antihistaminic suppression (weal) with respect to CFF threshold: acute dose cetirizine 10 mg, day 1*

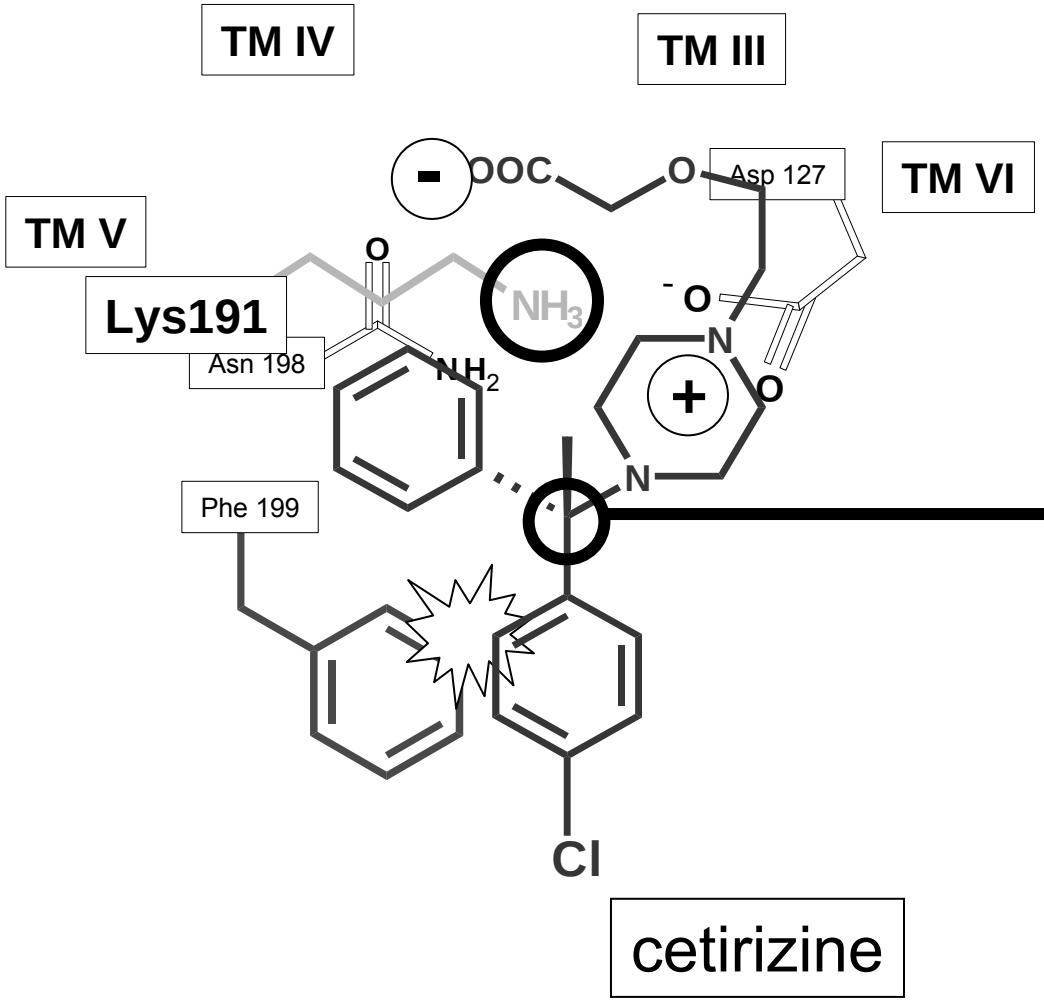
Hindmarch et al., Curr. Med. Res. Opin., 17:241-255, 2001

Cetirizine and levocetirizine....





Optic isomers and binding to the receptor …



La configuration correcte du C liant les 2 groupes hydrophobes et la pipérazine est essentielle

Do you speak English in Braine l'Alleud or Gosselies ?

0026-895X/02/6102-391–399$3.00
MOLECULAR PHARMACOLOGY
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Mol Pharmacol 61:391–399, 2002

Vol. 61, No. 2
1317/961623
Printed in U.S.A.

Binding Characteristics of Cetirizine and Levocetirizine to Human H_1 Histamine Receptors: Contribution of Lys^{191} and Thr^{194}

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Received August 28, 2001; accepted November 13, 2001

This paper is available online at http://molpharm.aspetjournals.org

Une longue histoire, mais ...

Sur base de ce que vous avez appris jusqu'ici, quel est, à votre avis, le conseil le plus essentiel à donner au patient lors de la délivrance d'un antihistaminique de type cétérizine, loratadine …

- **faire attention aux autres médicaments**
- **ne pas abuser du produit**
  (ne pas reprendre trop rapidement)
- **attention à l'alcool !**
- **respecter la posologie**
- **attention à la somnolence**

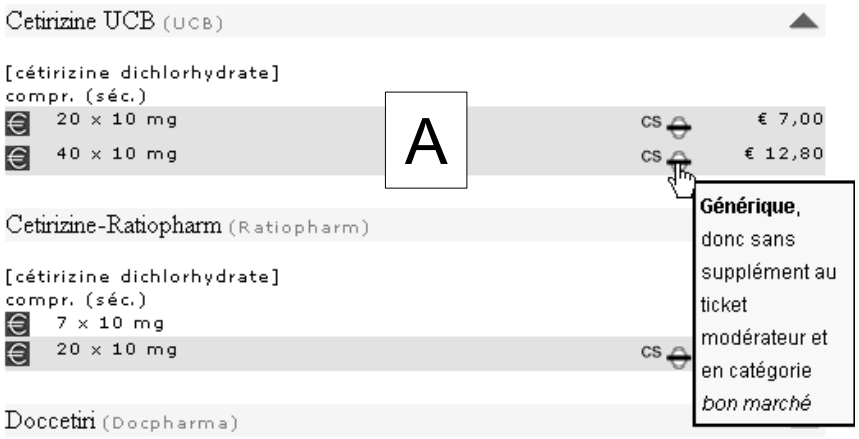
Et pour la suite ...

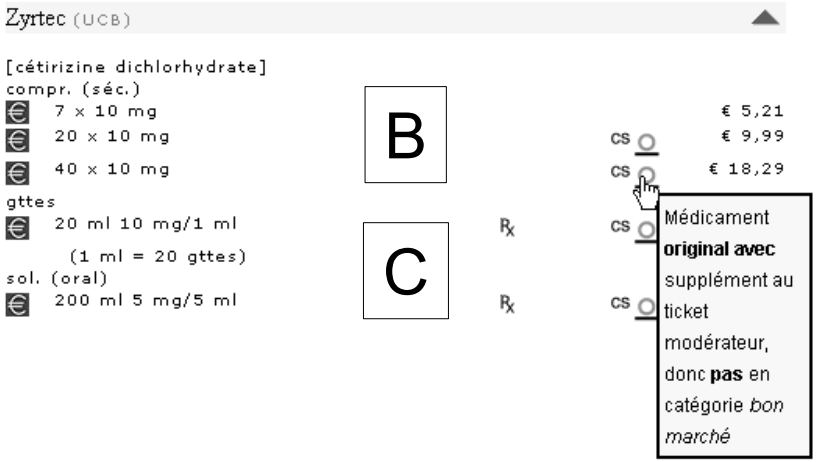
Sur quel point, selon vous, le pharmacien doit-il être particulièrement bien informé par la firme XXX à propos de YYY qui est en vente sans prescription ?

- les propriétés de base du produit
- les indications
- la posologie
- les effets indésirables
- les interactions médicamenteuses

Et pour la vraie suite ...

Quelle est la différence entre A et B … ?





Et pourquoi C est-il sous prescription ?

Et voyons les applications ...