

# CHIMIE **du** et **pour** le VIVANT : OBJECTIF SANTE

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*Centre d'Alembert  
Seminaire Chimie  
8/12/2016*

**1 – Pourquoi la CHIMIE du et pour le VIVANT va-t-elle connaître un développement tout particulièrement important au cours des 20 années à venir ?**

**2 – Parce que le quart de siècle passé a vu un développement spectaculaire et sans précédent des SCIENCES de la VIE, avec, en particulier, un accès à toutes les bases moléculaires du Vivant.**



30-40% de gènes « orphelins »



### Schémas métaboliques



nouveaux médiateurs (**NO, CO, SH<sub>2</sub>..**)

nouvelles réactions

nouveaux catalyseurs

nouveaux schémas de biosynthèse



**CHIMIE du VIVANT**

## **2 – Pourquoi les chimistes doivent-ils prendre ce créneau de la biochimie moléculaire ?**

- ◆ **A cause du choix de la plupart des biologistes biochimistes d'aller de plus en plus vers l'étude des systèmes intégrés → vide progressif dans les domaines les plus moléculaires de la biochimie (enzymologie, biochimie analytique...)**

# CHIMIE pour le VIVANT



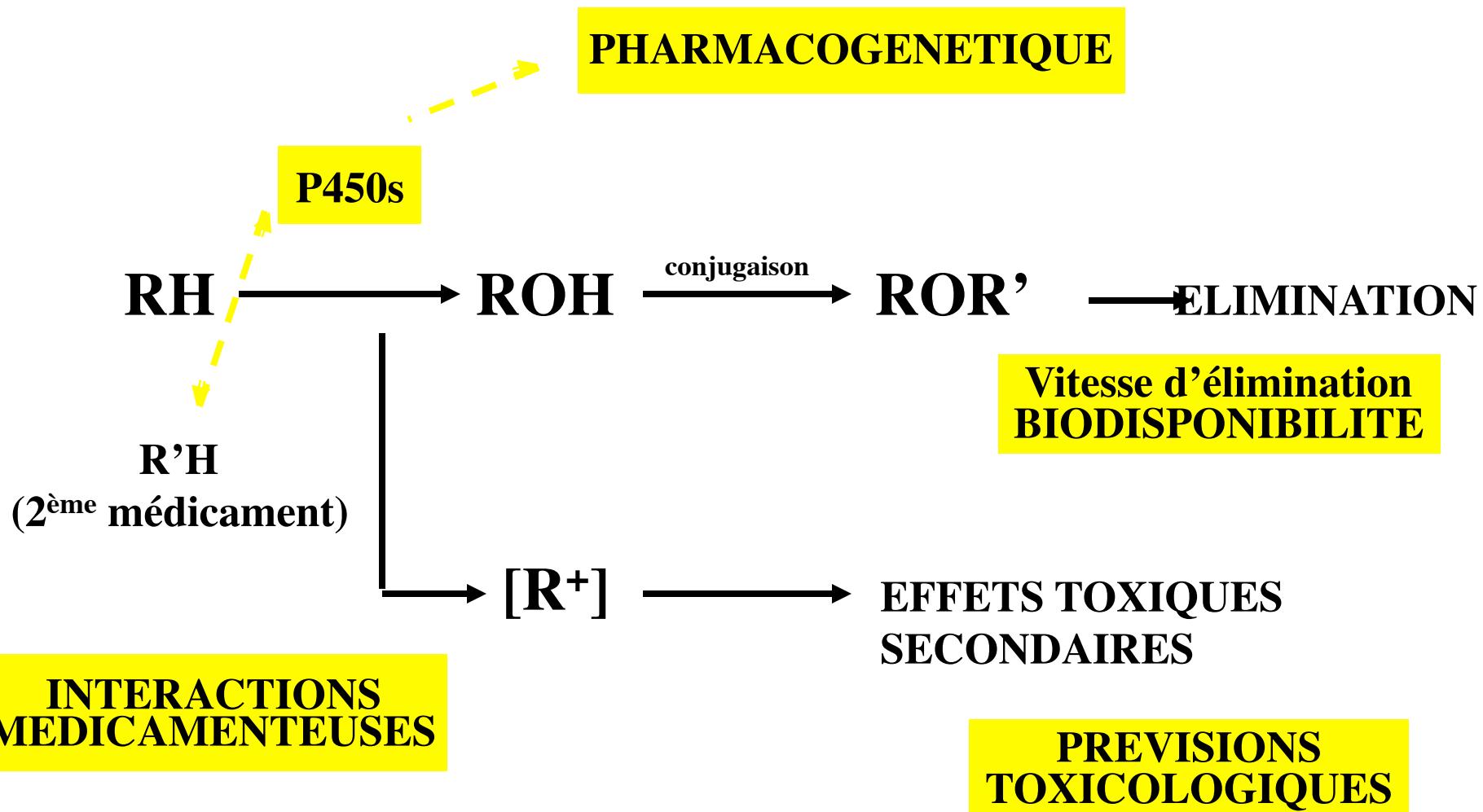
Médicaments, diagnostic, biomatériaux,  
secteur agro-alimentaire...



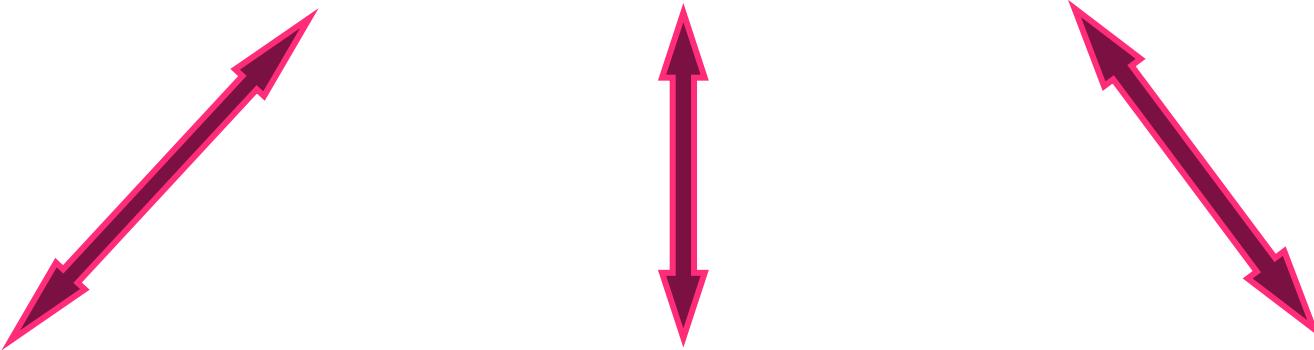
**OUTILS (molécules, matériaux) d'ETUDE et de CONTRÔLE du VIVANT**



# IMPORTANCE de la CONNAISSANCE du METABOLISME des MEDICAMENTS chez l'HOMME dans la RECHERCHE de NOUVELLES MOLECULES ACTIVES

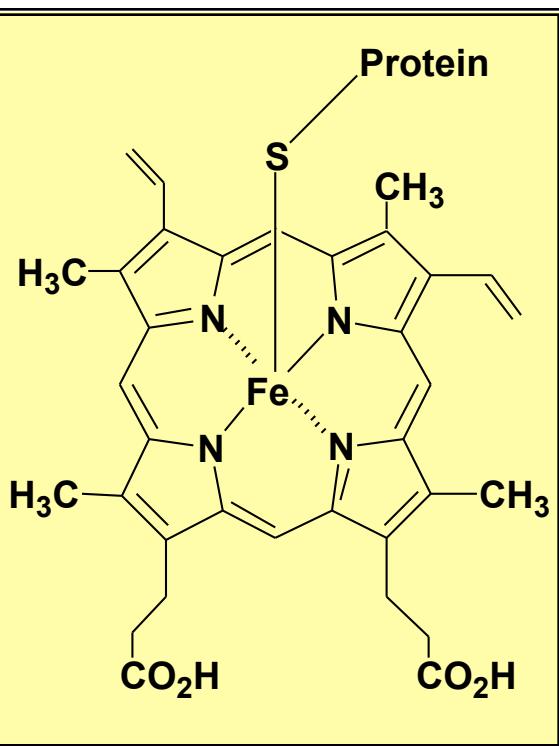


## ADVERSE DRUG REACTIONS (ADR)



- **COST for the US society : 100 billions US\$ (2001)**
- **100,000 DEATHS annually in the USA**
- **up to 7% of all hospital admissions**

# CYTOCHROME P450-DEPENDENT MONOOXYGENASES

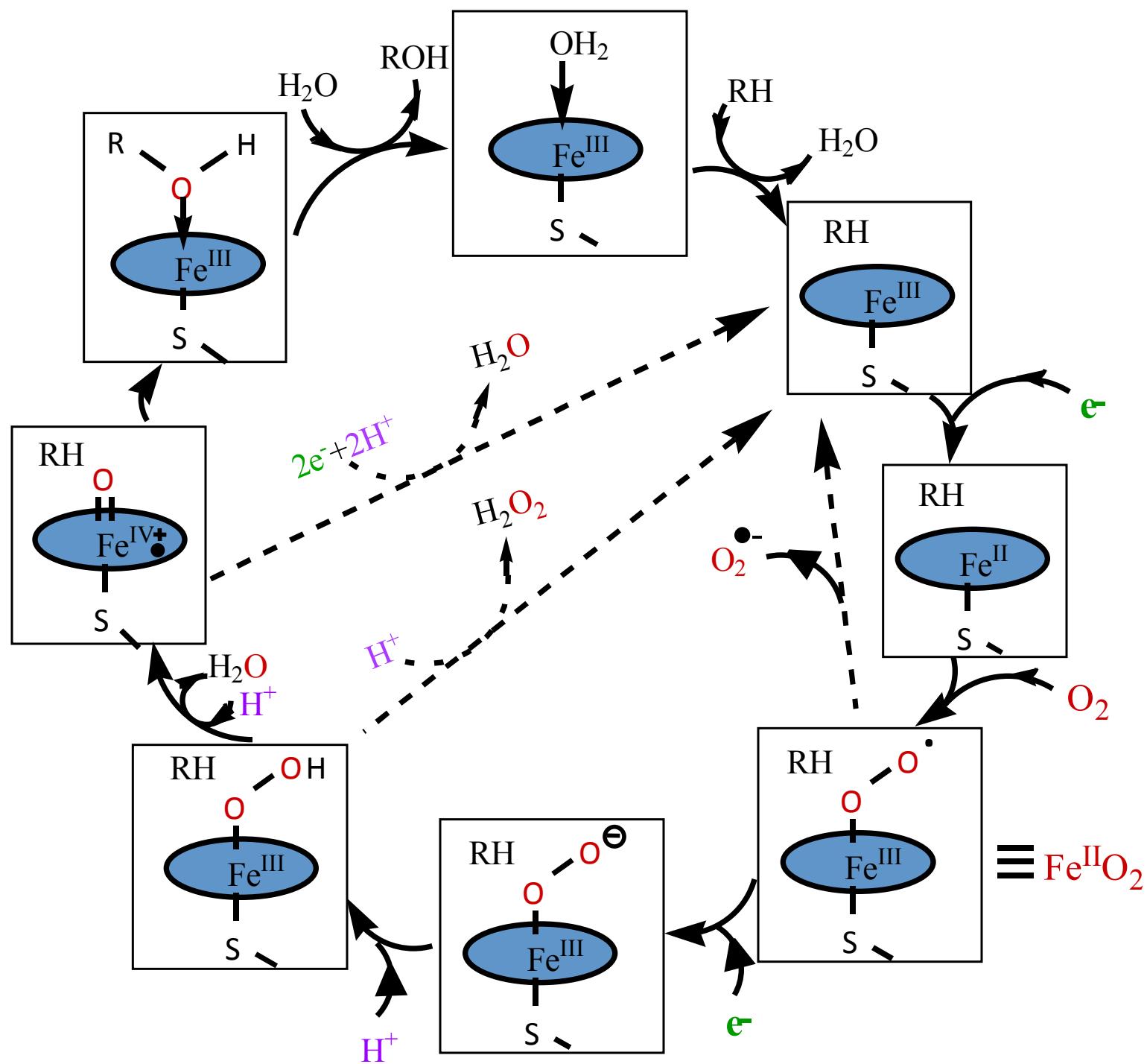


OXIDATION  
CATALYSIS

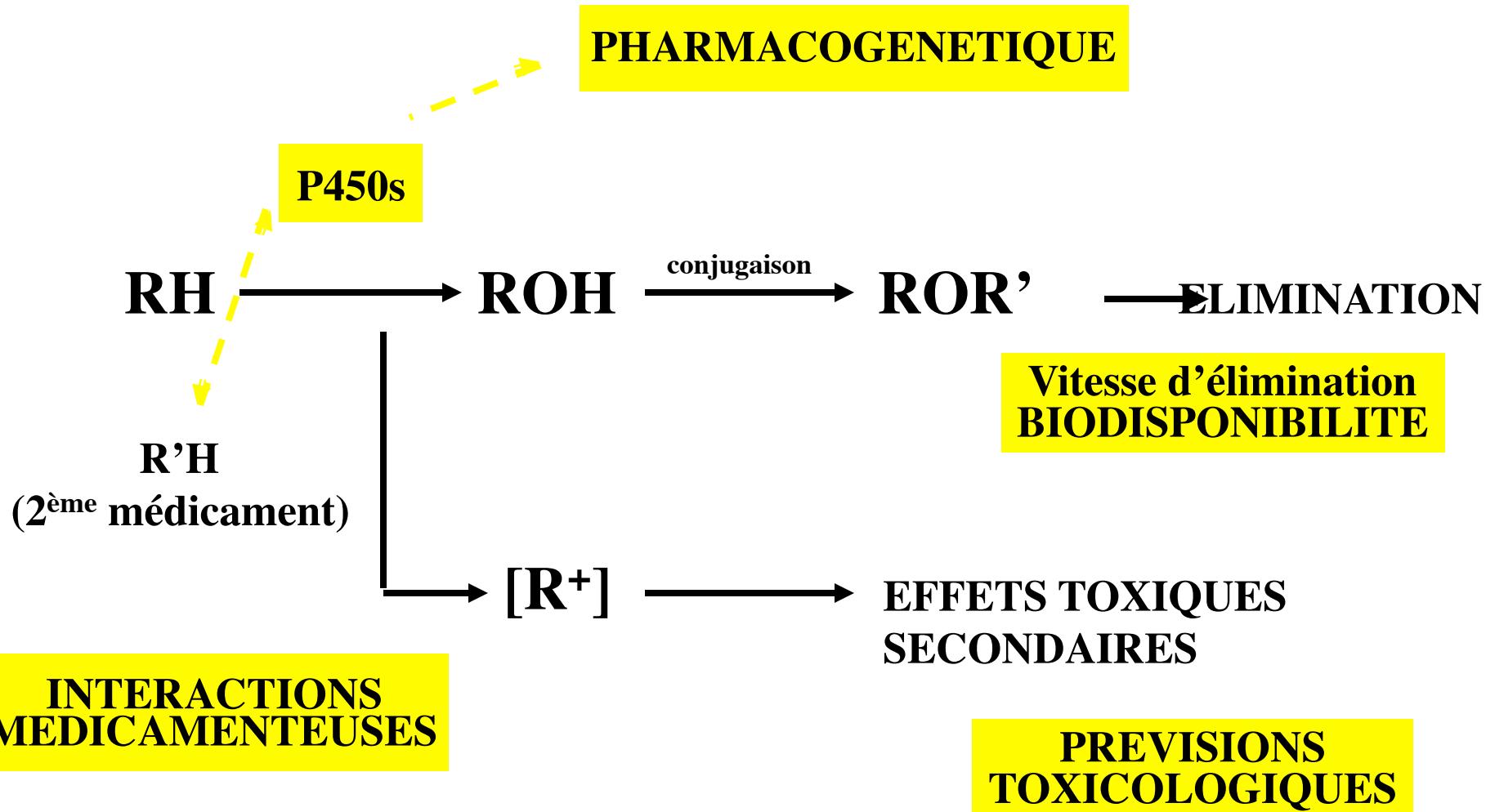
TRANSFER of one O from O<sub>2</sub>

MONOOXYGENASES involved in the BIOSYNTHESIS of ENDOBIOTICS (steroids, fatty acid mediators, terpenes, alkaloids...) and the METABOLISM of XENOBIOTICS (Drugs, pollutants...) in all organisms

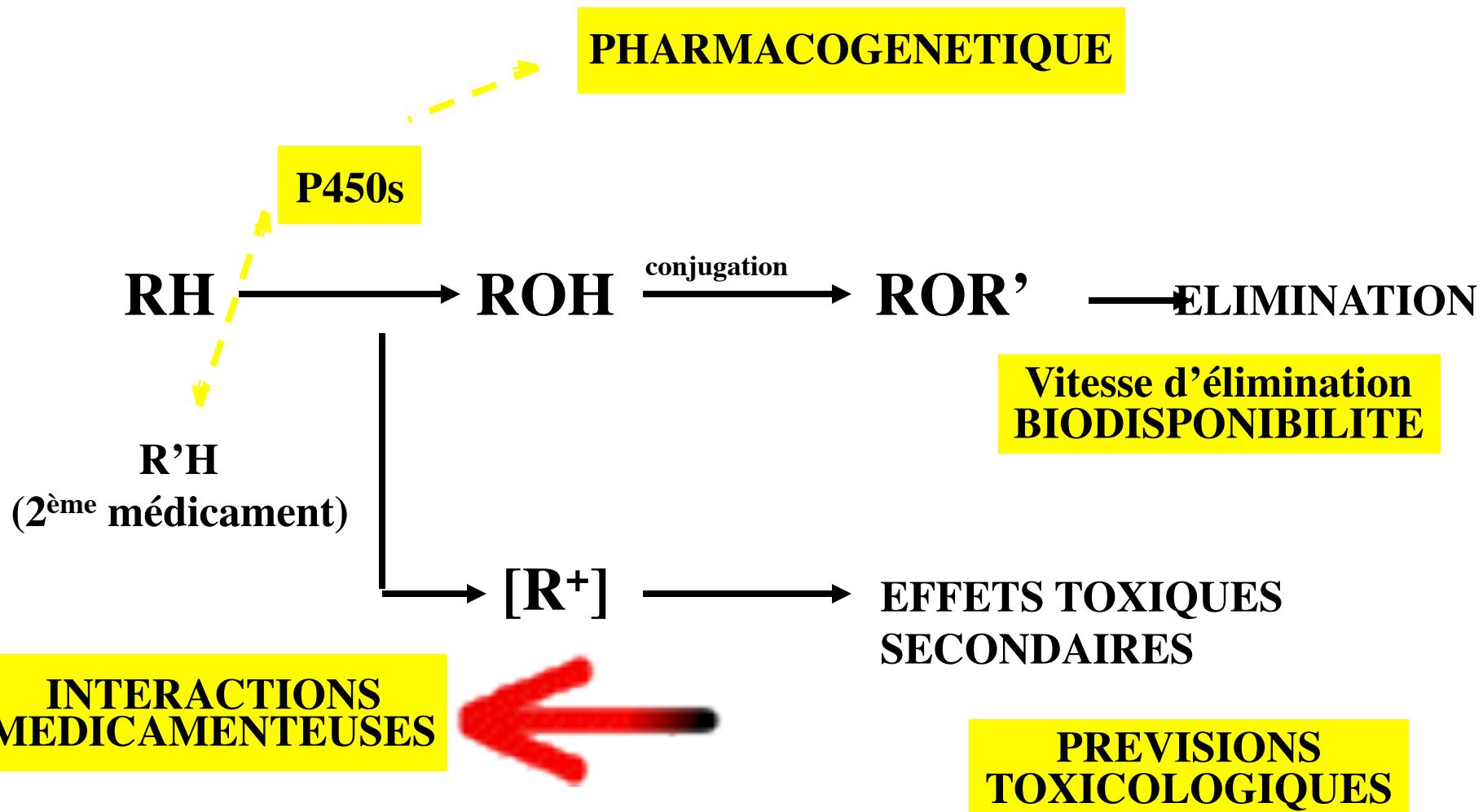
VERY WIDE SUBSTRATE DIVERSITY



# IMPORTANCE de la CONNAISSANCE du METABOLISME des MEDICAMENTS chez l'HOMME dans la RECHERCHE de NOUVELLES MOLECULES ACTIVES

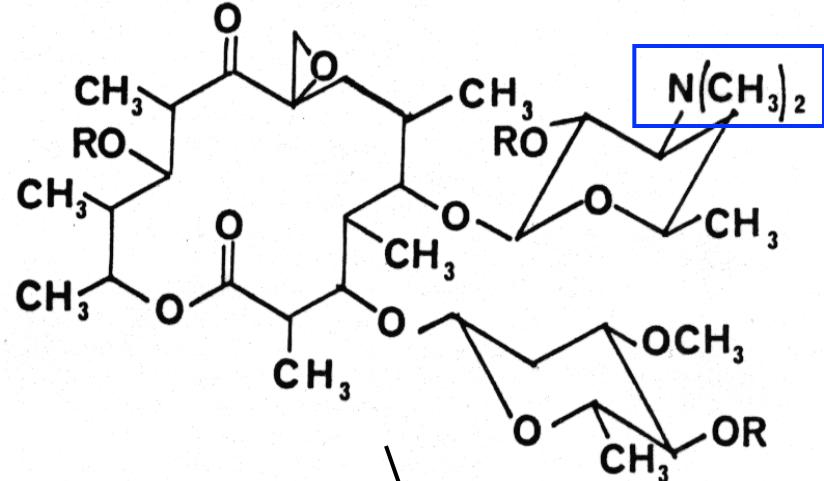


# IMPORTANCE de la CONNAISSANCE du METABOLISME des MEDICAMENTS chez l'HOMME dans la RECHERCHE de NOUVELLES MOLECULES ACTIVES



## DRUG INTERACTIONS INVOLVING TAO

DRUG	EFFECT	Pharmacological Consequence
TAO + CARBAMAZEPINE + THEOPHYLLINE + DIHYDROERGOTAMINE + Me - PREDNISOLONE	→ ELIMINATION RATE OF THE DRUG → " " " → " " → ELIMINATION RATE OF THE DRUG	- + - - +

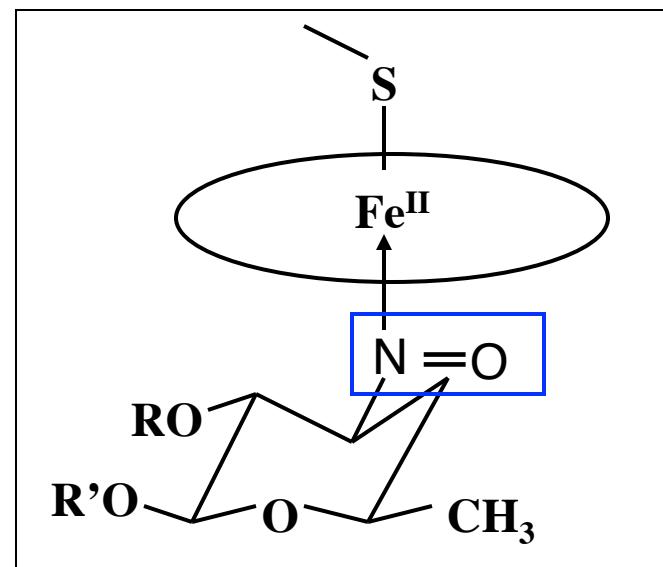


TAO

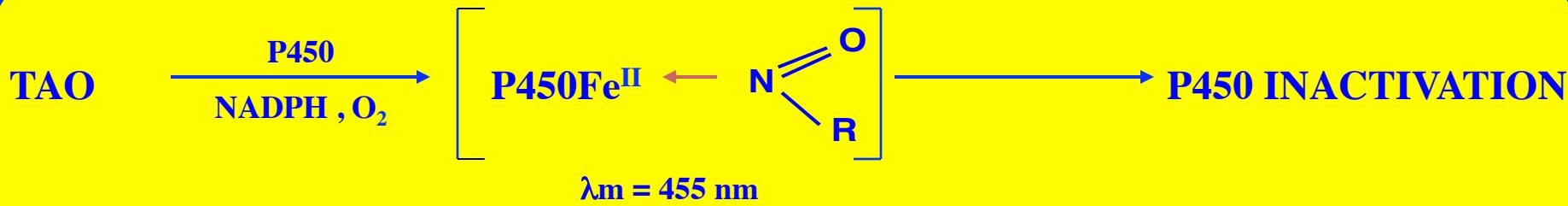
P450 inactivation

P450

(4 oxidation turnovers)



$$\lambda_m = 455 \text{ nm}$$



### PREDICTIVE TEST

Treatment of rats with macrolide antibiotics

Preparation of liver microsomes

Measurement of 455 nm - absorbing complex  
by difference visible spectroscopy

TAO

++

Erythromycin

+ -

Roxythromycin

-

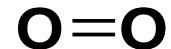
Josamycin

-

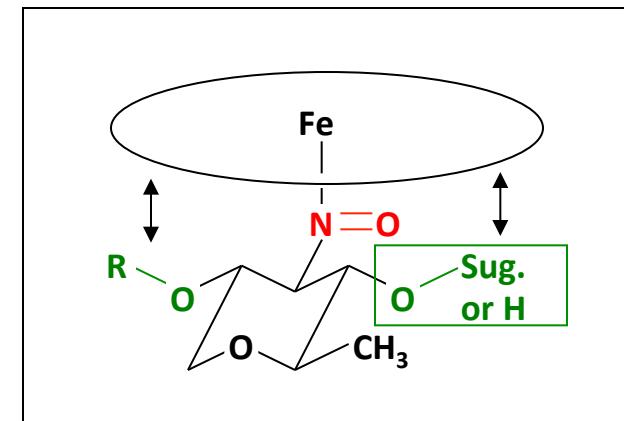
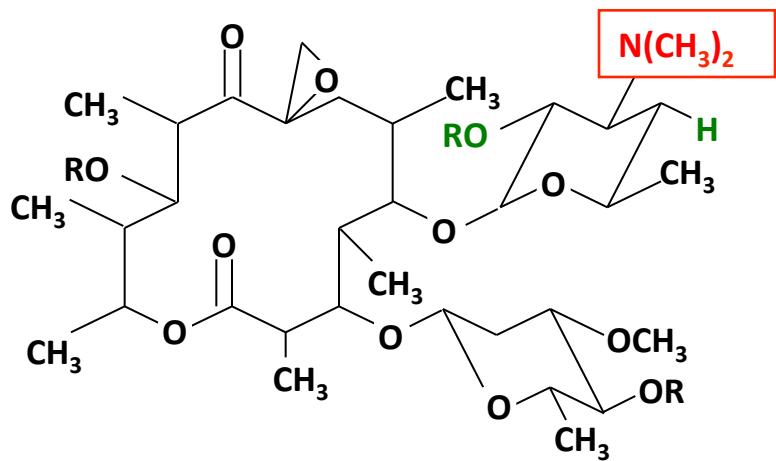
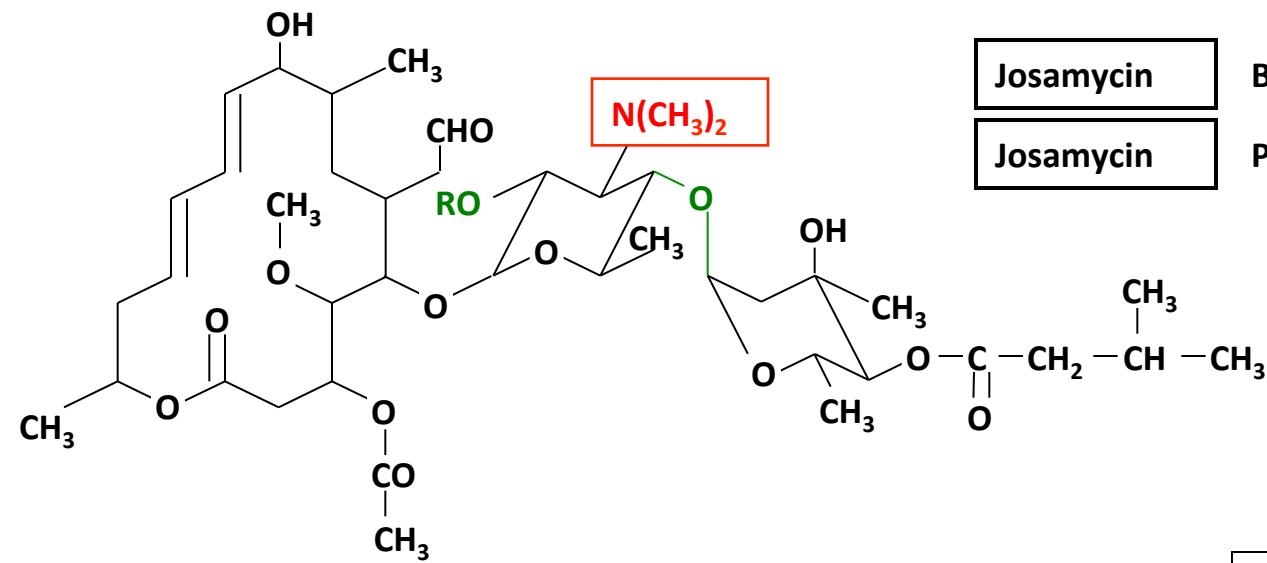
### COORDINATION CHEMISTRY

NITROSOALKANES as new strong  
LIGANDS of HEMEPROTEINS

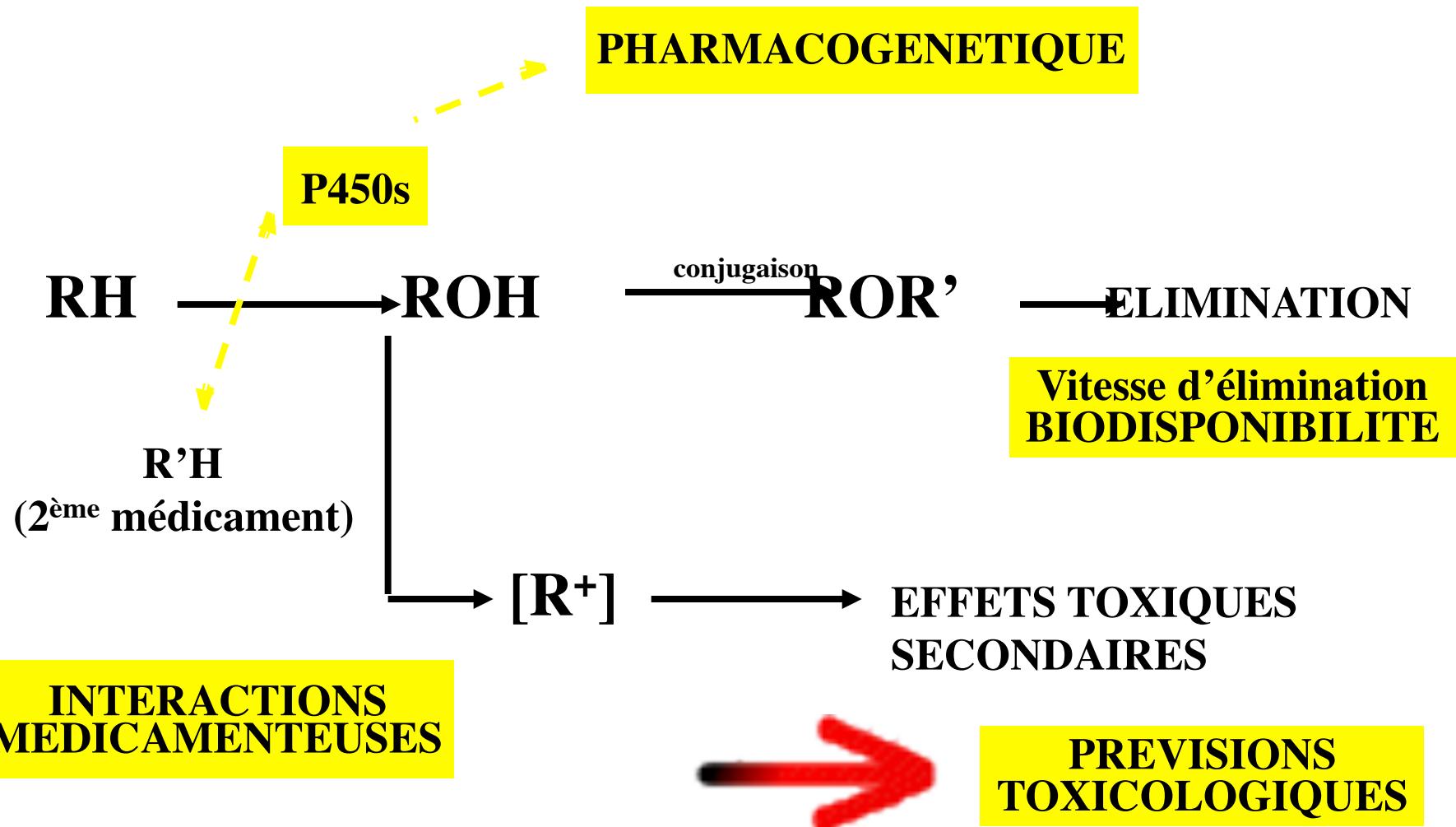
(Hb, Mb, NO - synthases, Prostaglandin  
Synthase, Cytochromes P450...)

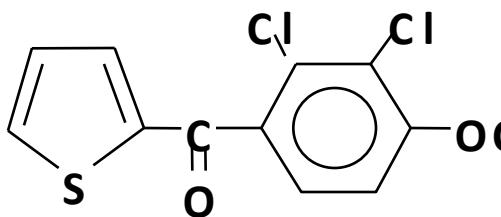


Isoelectronic



# IMPORTANCE de la CONNAISSANCE du METABOLISME des MEDICAMENTS chez l'HOMME dans la RECHERCHE de NOUVELLES MOLECULES ACTIVES



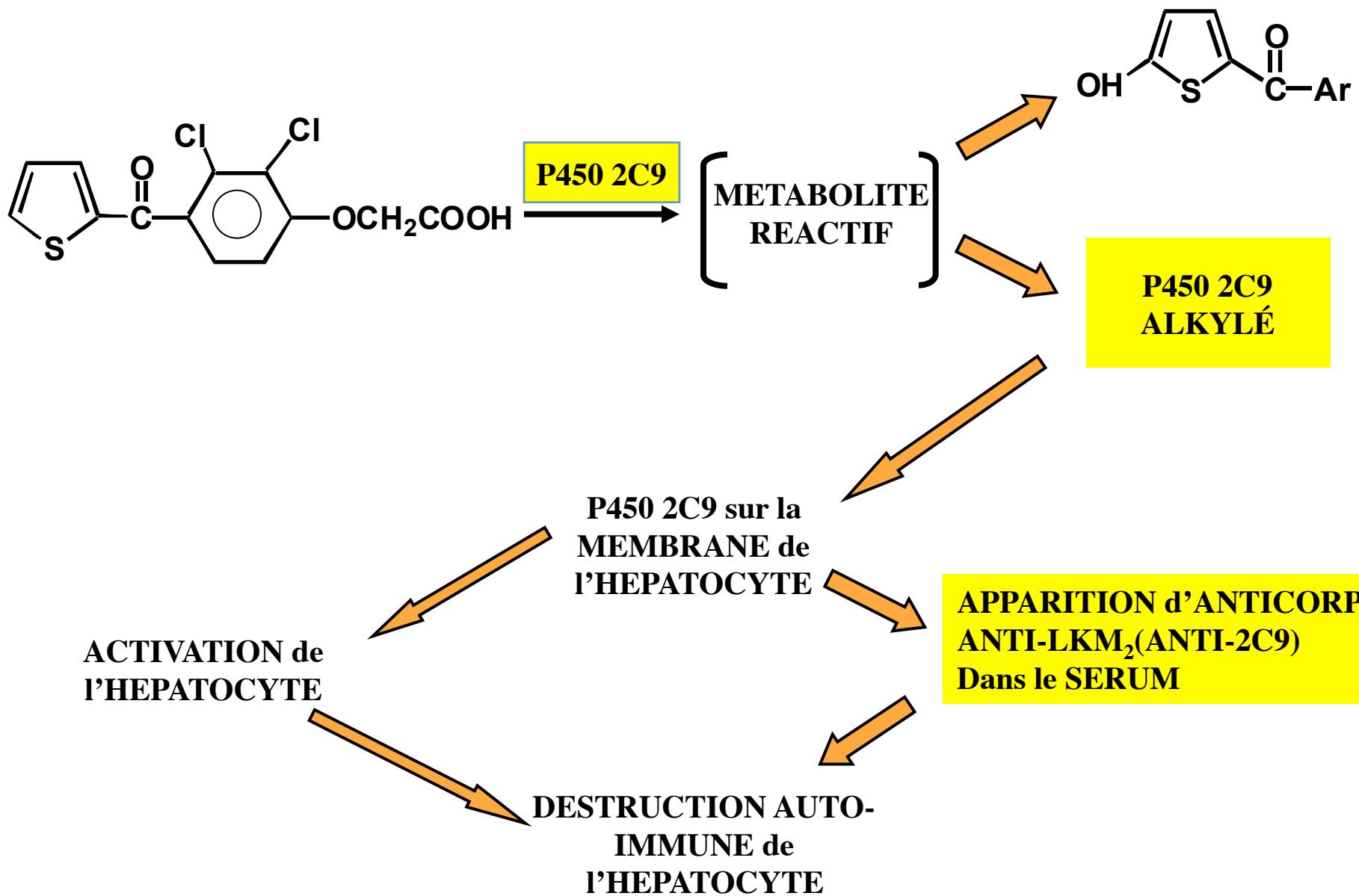


ACIDE TIENILIQUE

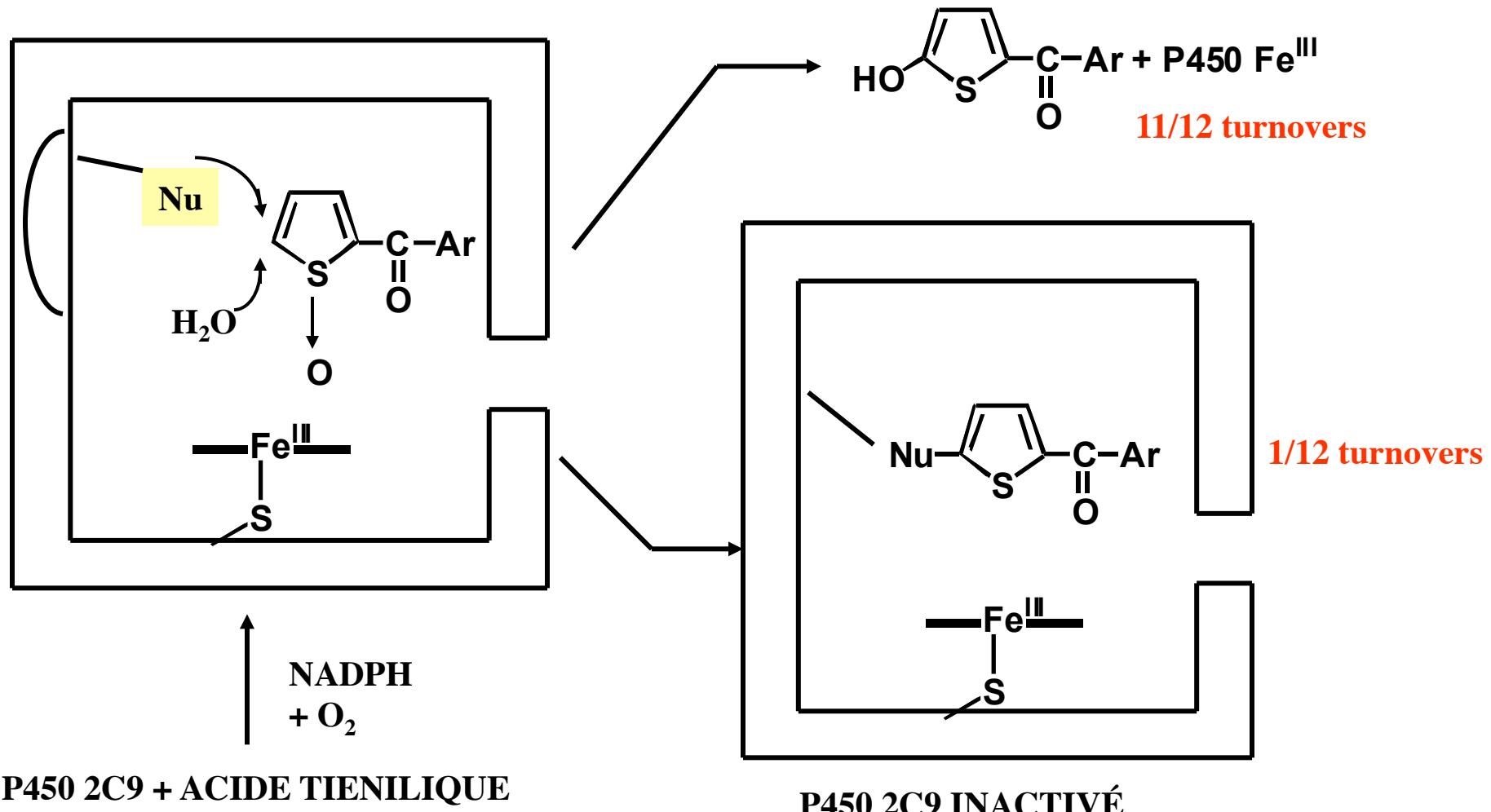
PAS de  
TOXICITE DIRECTE

HEPATITES de type  
IMMUNOALLERGIQUE  
(1 cas sur 10 000)

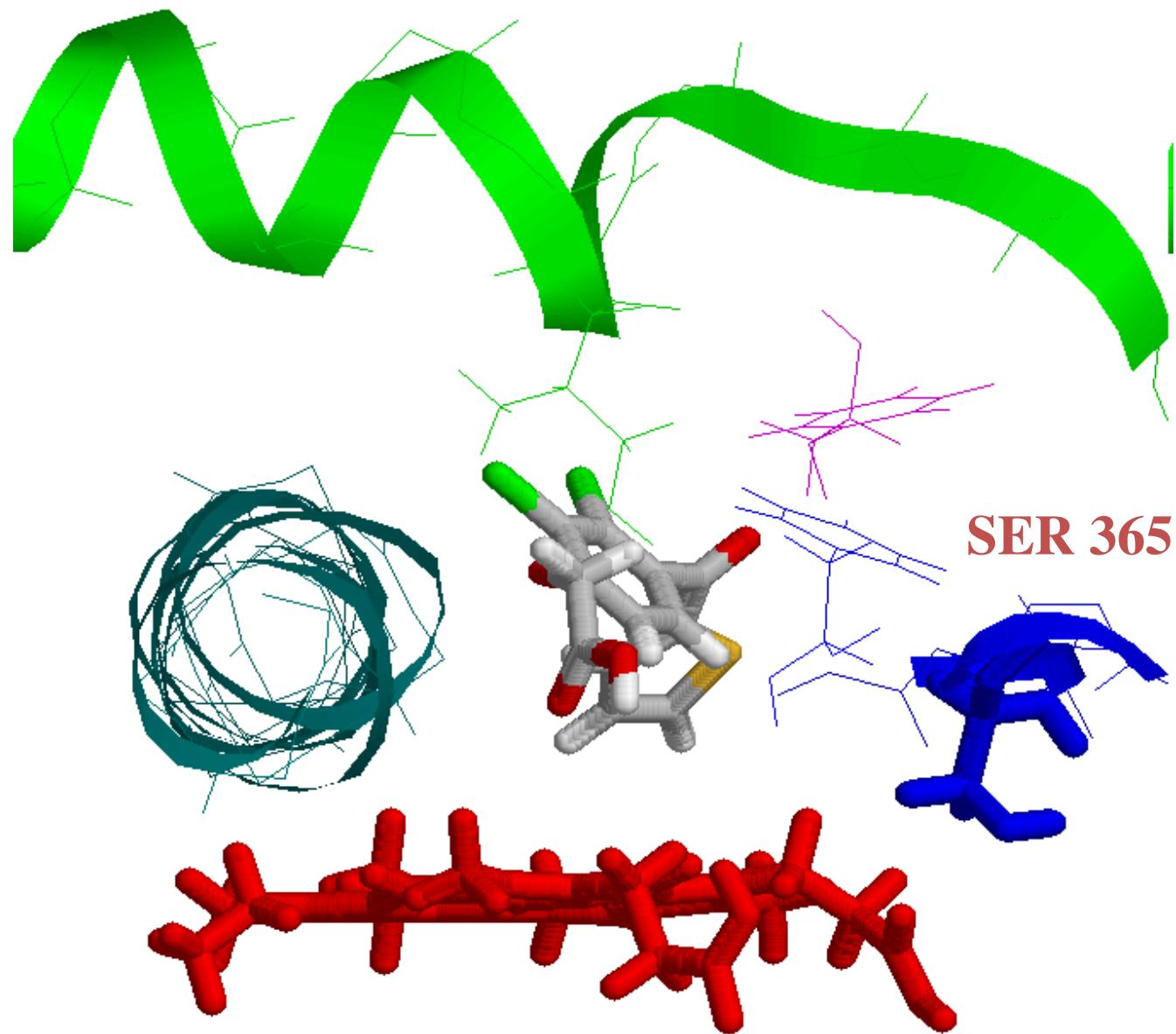
APPARITION  
d'ANTICORPS  
ANTI-RETICULUM  
(ANTI-LKM<sub>2</sub>) chez  
Les PATIENTS



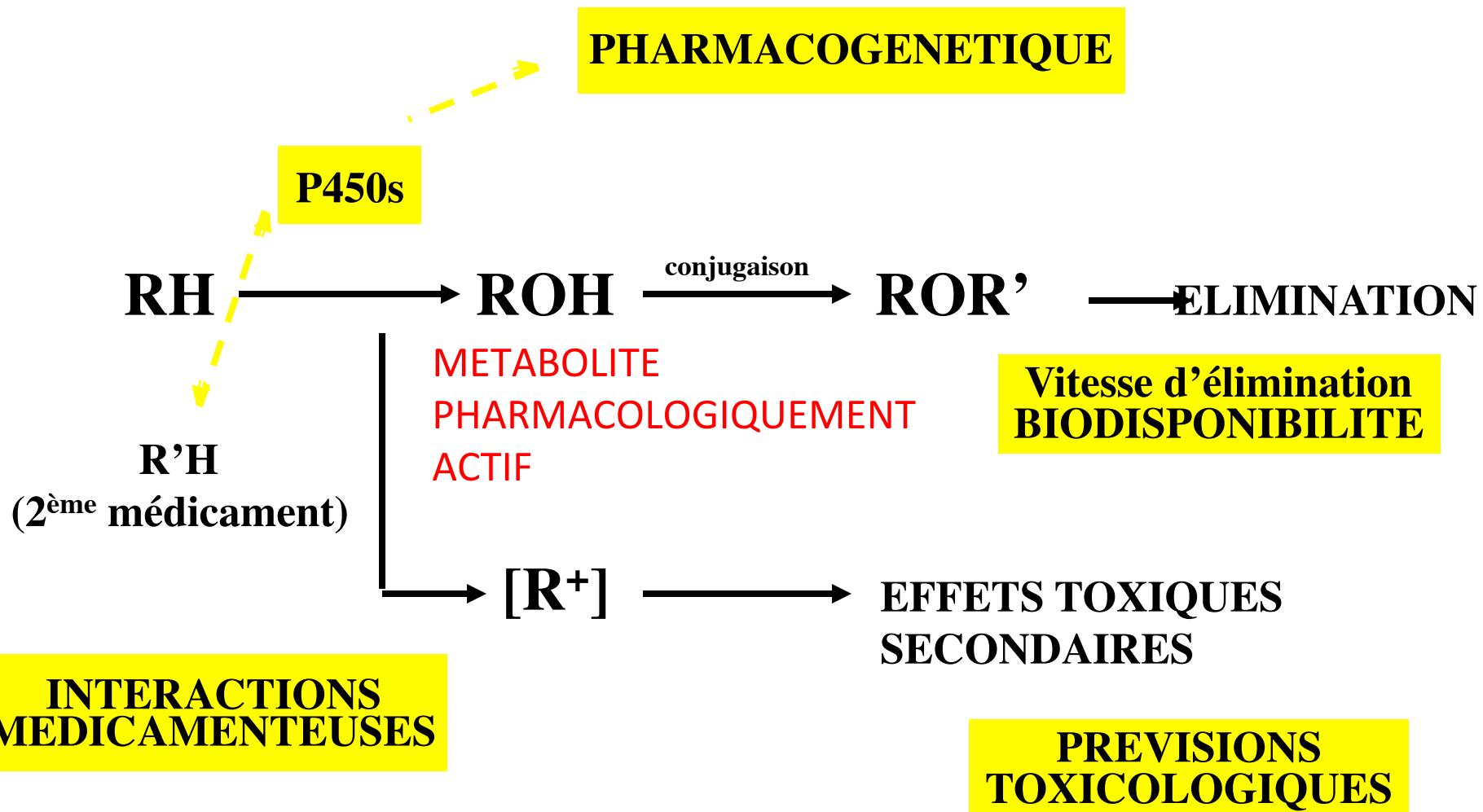
# INACTIVATION SUICIDE du CYTOCHROME P450 2C9 par l'ACIDE TIENILIQUE

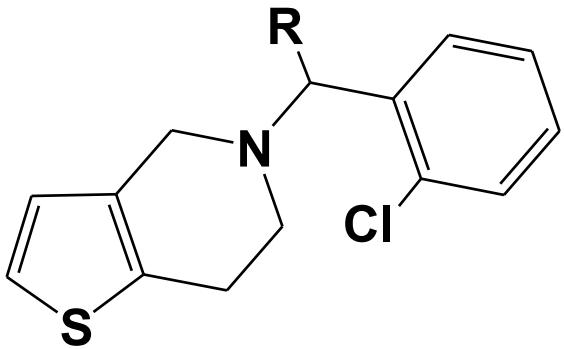


## CYP 2C9 + TIENILIC ACID



# IMPORTANCE de la CONNAISSANCE du METABOLISME des MEDICAMENTS chez l'HOMME dans la RECHERCHE de NOUVELLES MOLECULES ACTIVES





**R = H**  
**R = COOCH<sub>3</sub>**

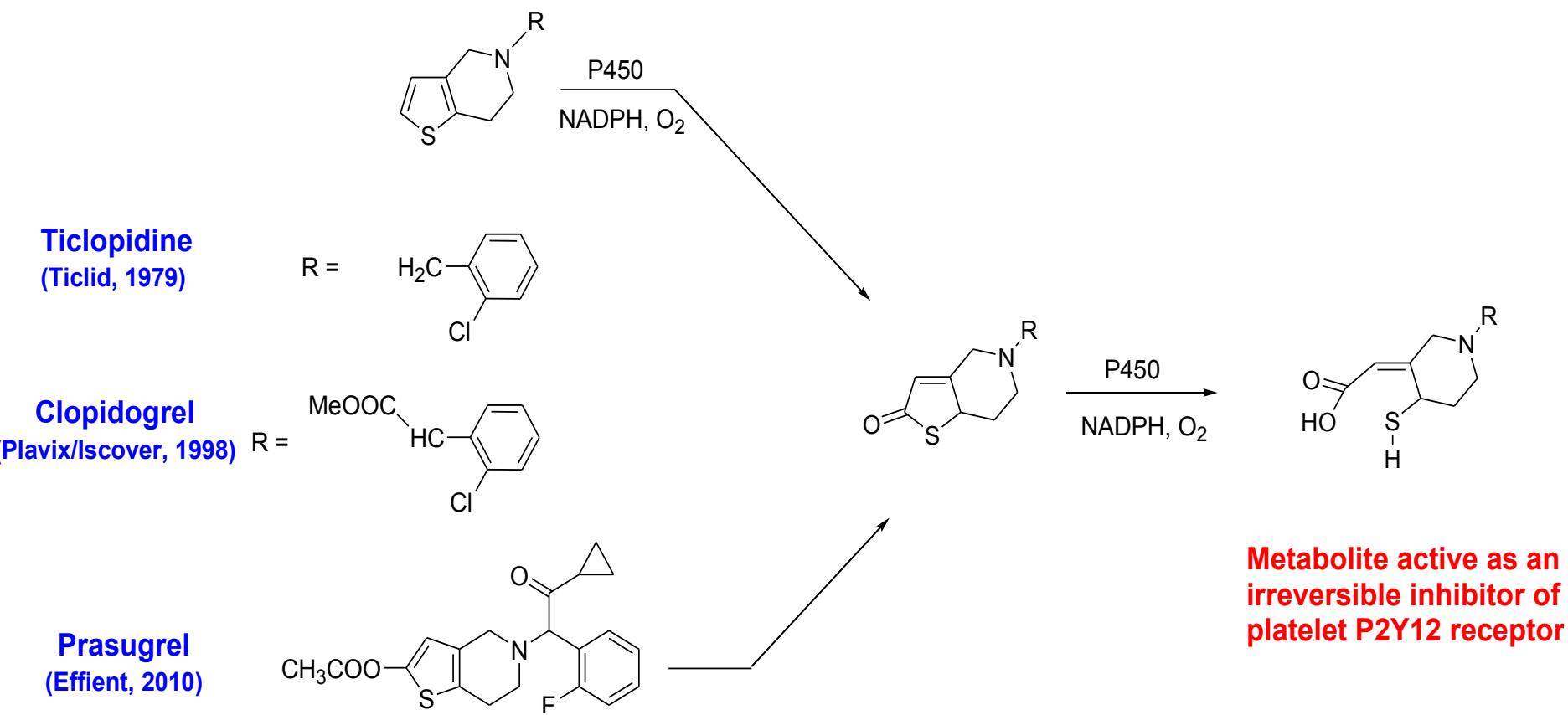
**Ticlopidine (Ticlid)**  
**Clopidogrel (Plavix)**

**(anti-thrombotic, Sanofi-Aventis)**

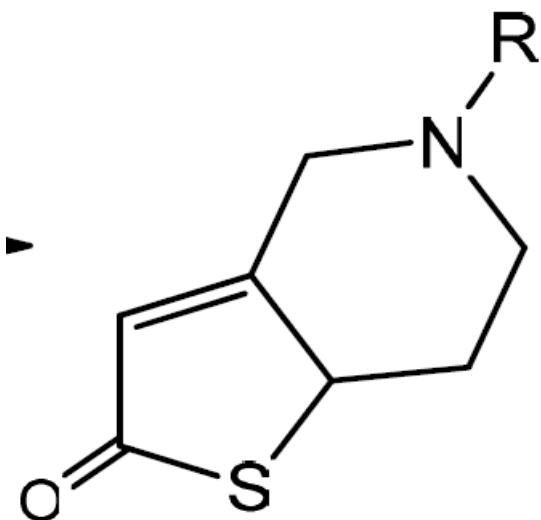
**Clopidogrel = 2<sup>nd</sup> most prescribed drug in the world with 9.4 billions \$ in global sales in 2010**

- Reduction of atherothrombotic events in patients with myocardial infarction or peripheral arterial disease
- Treatment of chest pain (heart attack, unstable angina), in association with aspirin
- To prevent blood clots after cardiac stent, coronary bypass graft, or balloon angioplasty

# THIENOPYRIDINE ANTITHROMBOTICS are PRODRUGS

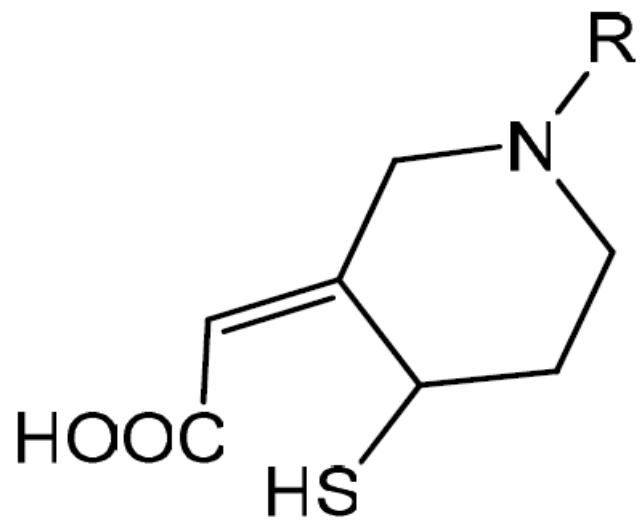


## BIOACTIVATION OF CLOPIDOGREL



2-OXO-CLOPIDOGREL

P450  
NADPH, O<sub>2</sub>

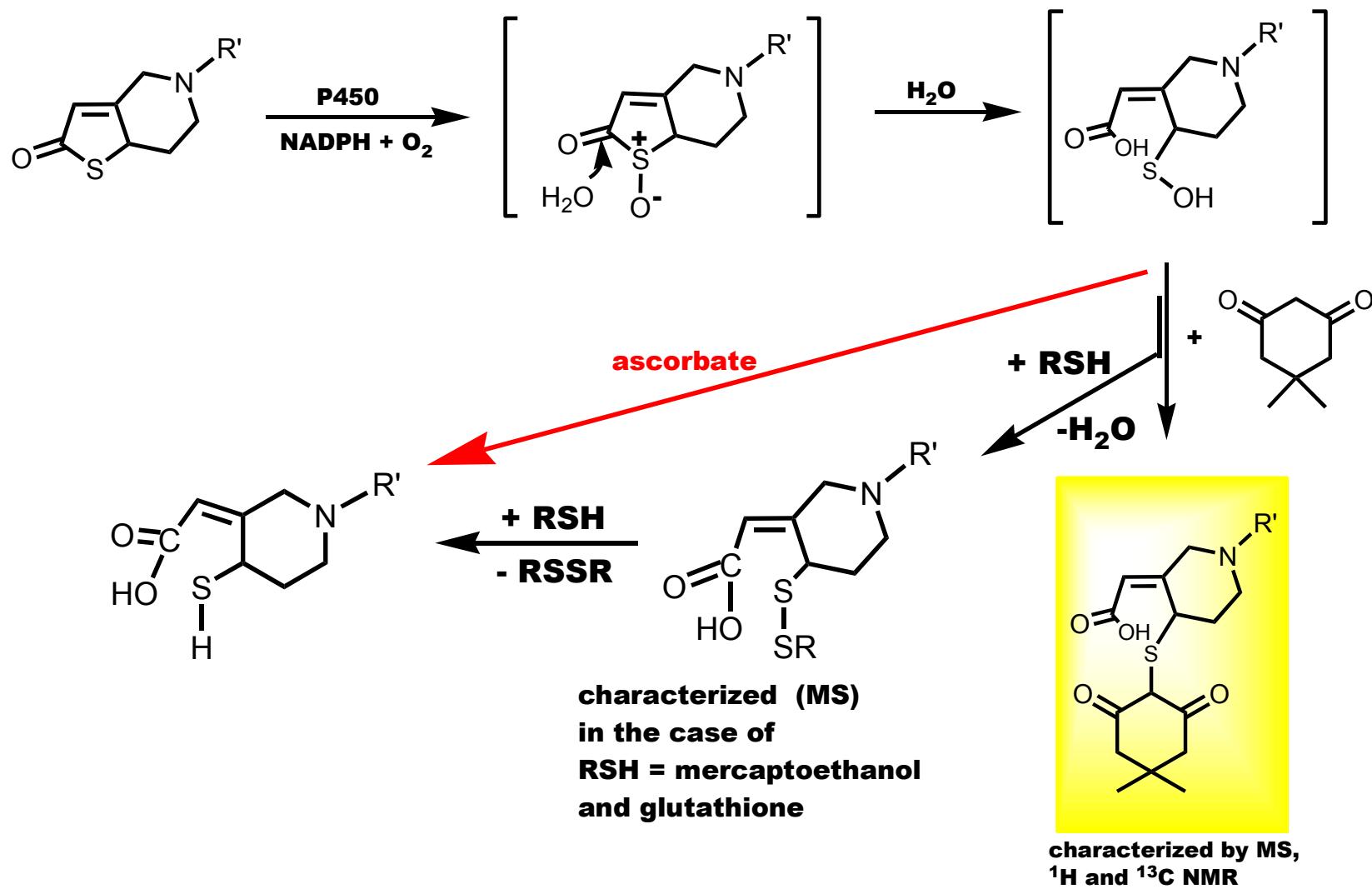


ACTIVE METABOLITE

1- WHY and HOW CYTOCHROME P450 ?

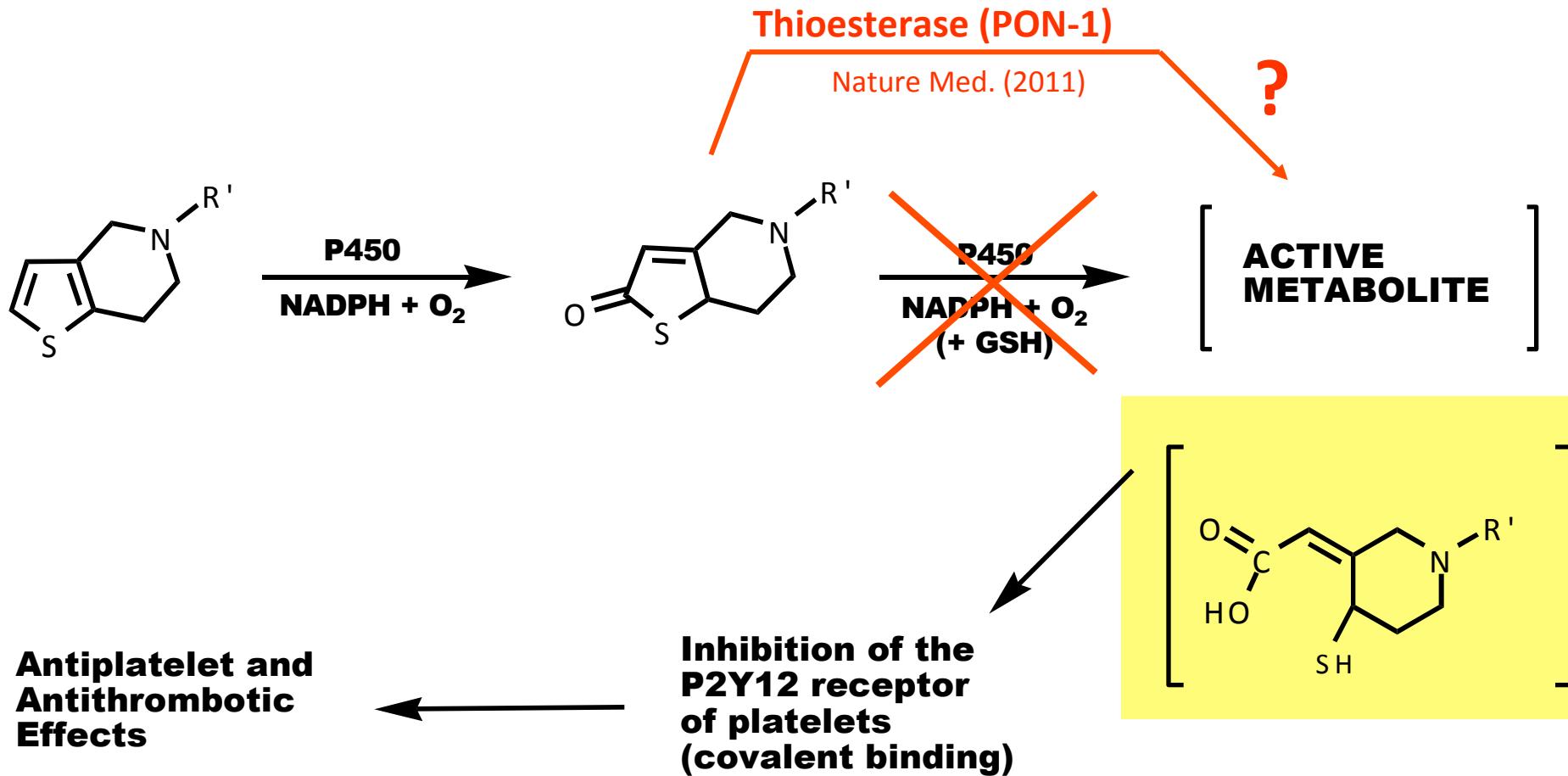
2- WHY NOT HYDROLASES (THIOESTERASES) ?

## MECHANISM of the P450-DEPENDENT ACTIVATION of CLOPIDOGREL (opening of its thiolactone metabolite)



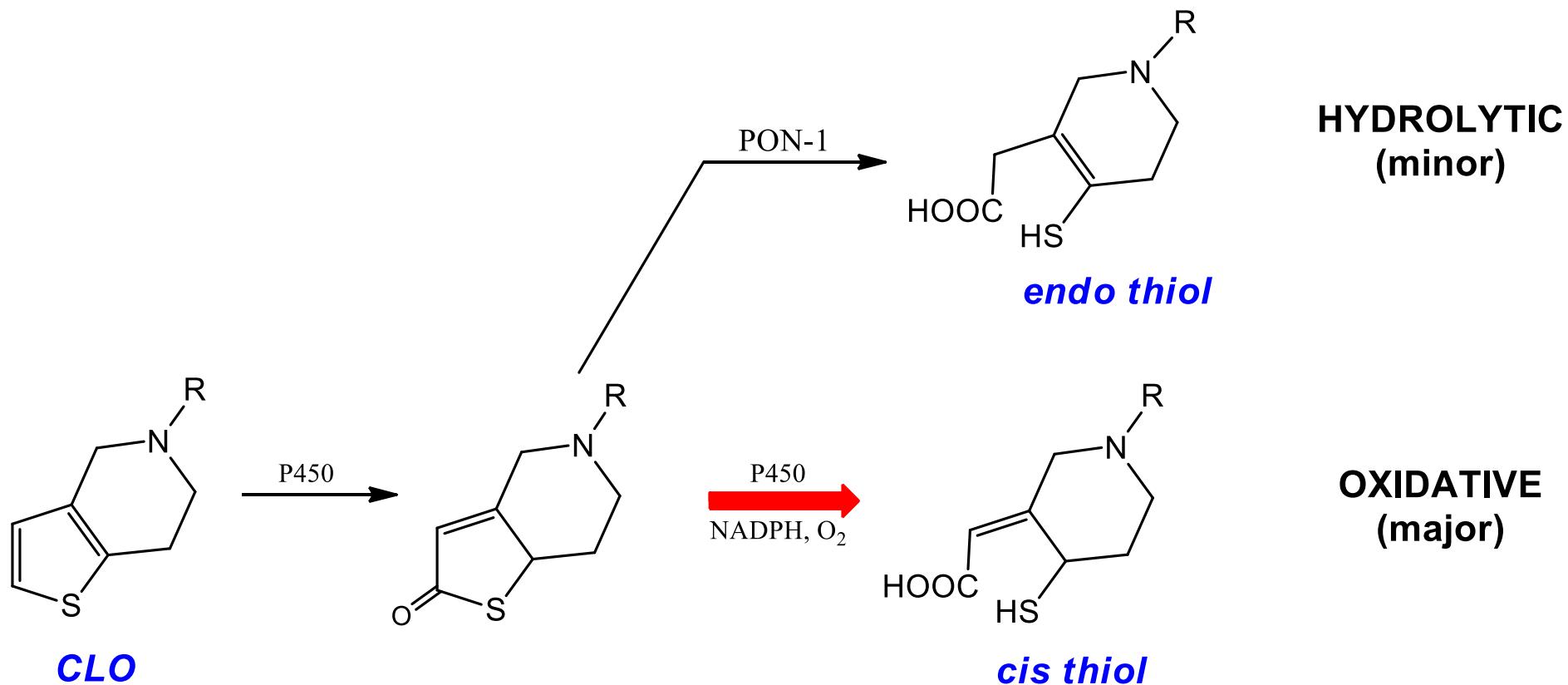
# Paraoxonase-1 is a Major Determinant of Clopidogrel Efficacy

Bouman et al., Nature Medicine, 110 (2011)

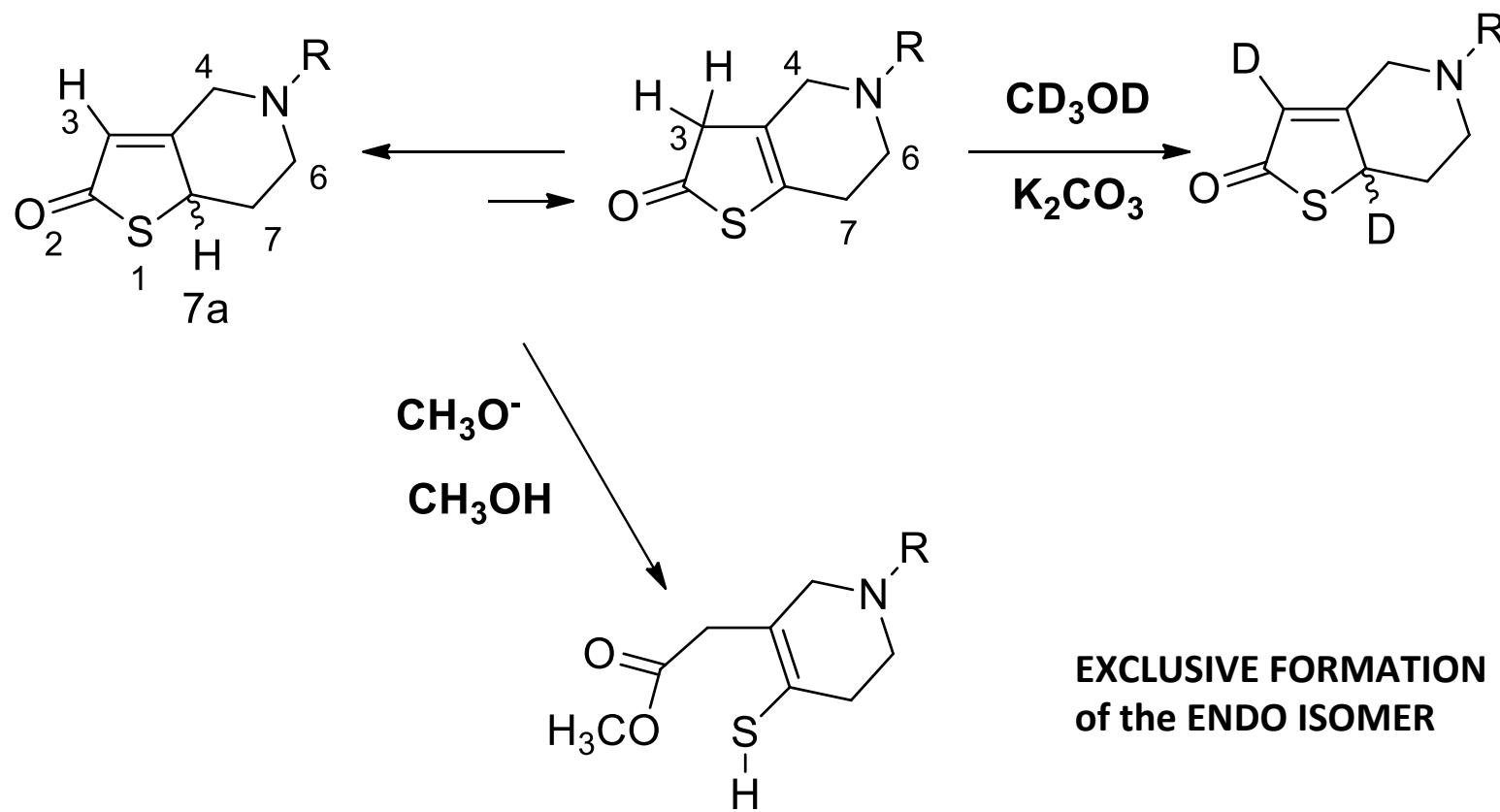


P450s not involved in the second step of CLO activation ?  
PON-1 determines the rate of active metabolite formation ?

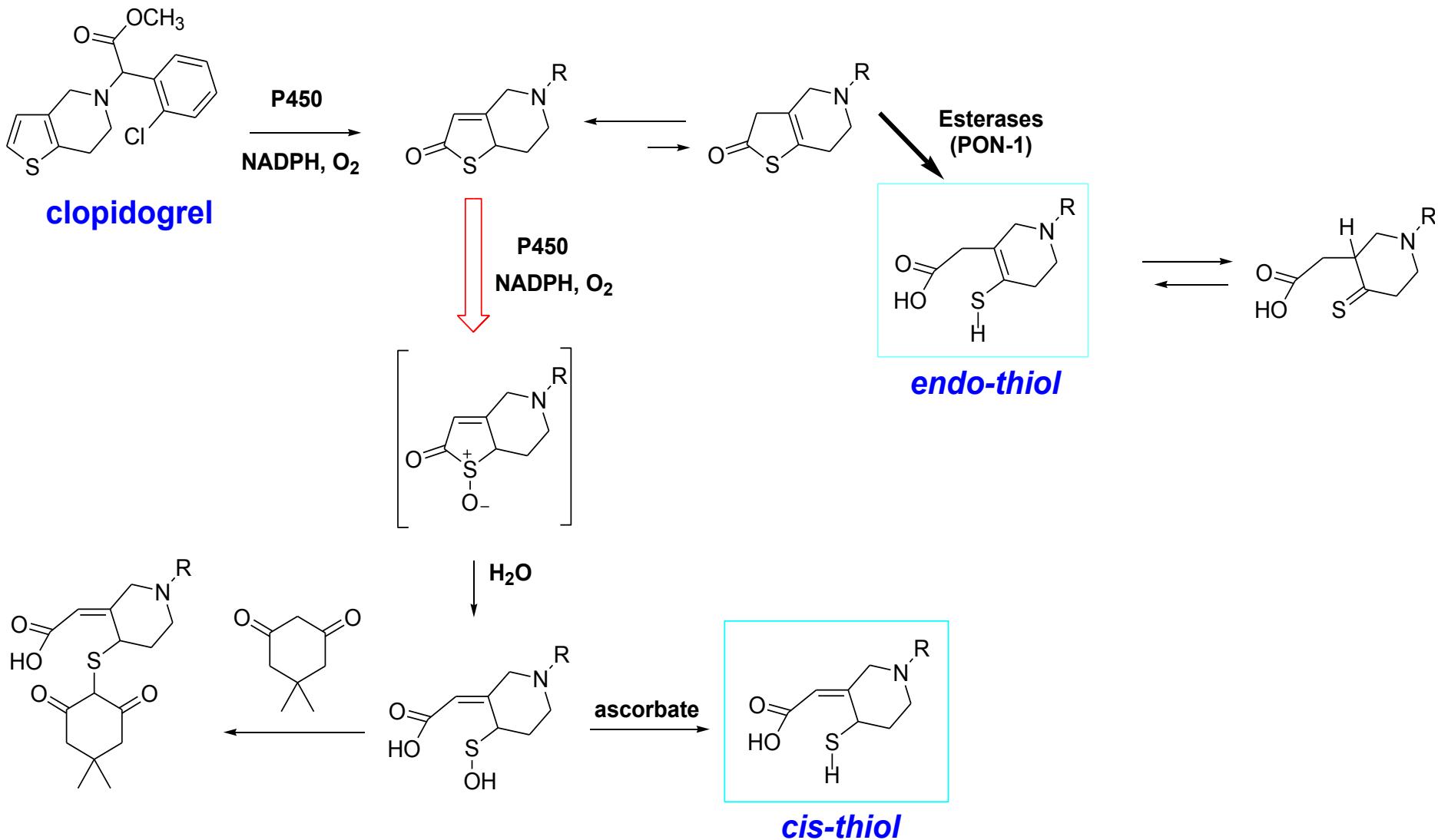
## THE TWO PATHWAYS INVOLVED IN THE OPENING OF THE CLOPIDOGREL THIOLACTONE RING BY HUMAN LIVER MICROSOMES

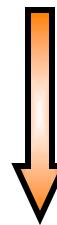


## CHEMICAL HYDROLYTIC OPENING of CLOPIDOGREL THIOLACTONE



# METABOLISM of CLOPIDOGREL by HUMAN LIVER MICROSOMES





**Schémas métaboliques**



**nouveaux médiateurs**

**nouvelles réactions**

**nouveaux catalyseurs**

**nouveaux schémas de biosynthèse**

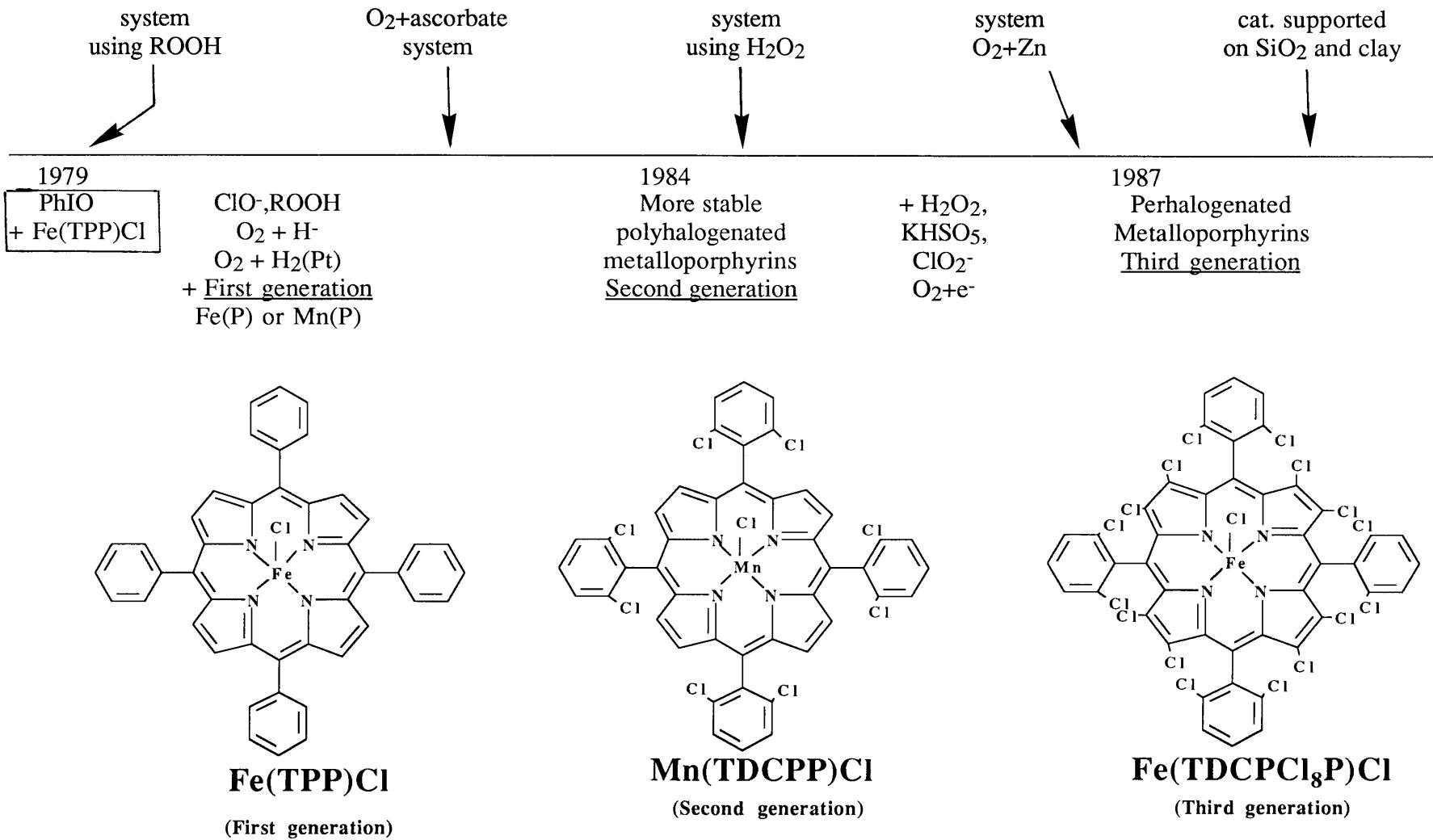


**CHIMIE d'après le VIVANT**



**CHIMIE du VIVANT**

## CYTOCHROME P450 MODELS STORY



- HepatoChem

*100 Cummings Center, Suite 424J Beverly, MA 01915*

The HepatoChem technology exploits an optimized panel of catalytic chemical reaction conditions in a multi-well parallel format, which by its diversity mimics the suite of cytochrome P450 enzymes (CYP) present in human hepatocytes. As such, this would be a chemical liver. This new approach to **biomimetic catalysis using metalloporphyrins as catalysts** has been elaborated in collaboration with Prof. John Groves at Princeton University.

