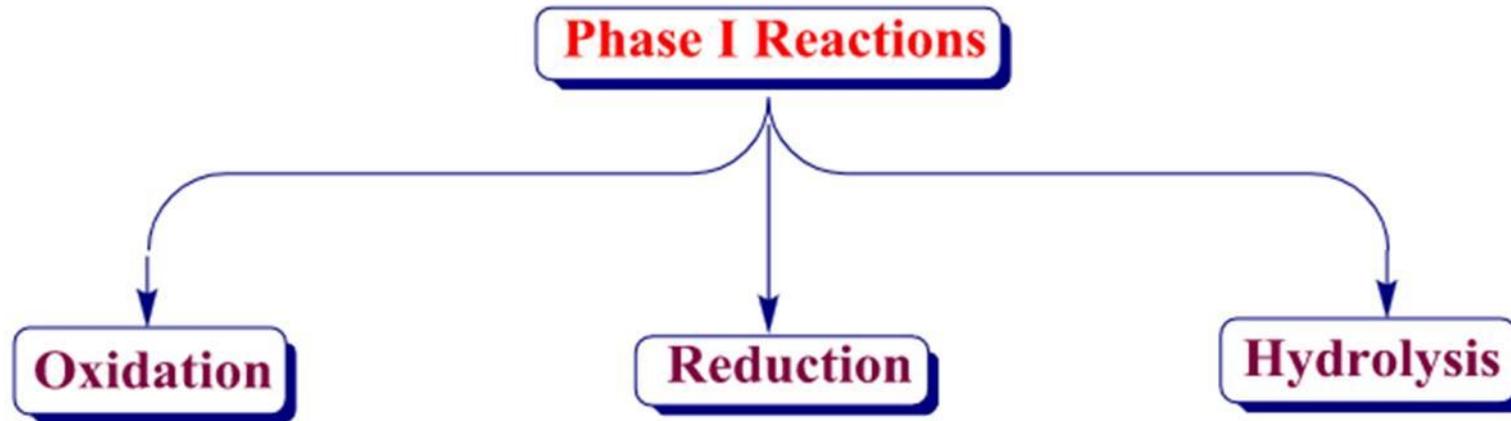


**Phase I reactions involve hydrolysis, reduction, and oxidation. These reactions expose or introduce a functional group ( $-OH$ ,  $-NH_2$ ,  $-SH$  or  $-COOH$ ), and usually result in only a small increase in hydrophilicity.**



## General Pathways of Xenobiotic Biotransformation and Their Major Subcellular Location

REACTION	ENZYME	LOCALIZATION
<i>Phase I</i>		
<i>Hydrolysis</i>	Esterase	Microsomes, cytosol, lysosomes, blood
	Peptidase	Blood, lysosomes
	Epoxide hydrolase	Microsomes, cytosol
<i>Reduction</i>	Azo- and nitro-reduction	Microflora, microsomes, cytosol
	Carbonyl reduction	Cytosol, blood, microsomes
	Disulfide reduction	Cytosol
	Sulfoxide reduction	Cytosol
	Quinone reduction	Cytosol, microsomes
<i>Oxidation</i>	Reductive dehalogenation	Microsomes
	Alcohol dehydrogenase	Cytosol
	Aldehyde dehydrogenase	Mitochondria, cytosol
	Aldehyde oxidase	Cytosol
	Xanthine oxidase	Cytosol
	Monoamine oxidase	Mitochondria
	Diamine oxidase	Cytosol
	Prostaglandin H synthase	Microsomes
	Flavin-monooxygenases	Microsomes
	Cytochrome P450	Microsomes

## 1.Oxidation

- Addition of oxygen OR removal of hydrogen.
- Oxidation by cytochrome P<sub>450</sub> enzymes (microsomal mixed-function oxidases).
  
- Oxidation by enzymes other than cytochrome P<sub>450</sub> is—most of these
  - (a) oxidation of alcohol by alcohol dehydrogenase,
  - (b) oxidation of aldehyde by aldehyde dehydrogenase,
  - (c) N-dealkylation by monoamineoxidase.
  
- Eg. phenytoin, barbiturates, propranolol, imipramine etc.

# **Cytochrome P450**

**Cytochrome P450 is**

- a superfamily of heme containing enzymes**
- molecular weights of 45-60 kDa.**
- isoforms**
- several families, CYP1, CYP2**
- one or more subfamily, CYP1A, CYP2A, CYP3A4**

## □ Role of Cytochrome P-450 monooxygenases in oxidative biotransformation



Cytochrome P450 catalyzes several types of oxidation reactions, including:

1. Hydroxylation of an aliphatic or aromatic carbon
2. Epoxidation of a double bond
3. Heteroatom (S-, N-) oxygenation and N-hydroxylation
4. Heteroatom (O-, N- ) dealkylation
5. Oxidative deamination
6. Cleavage of esters
7. Dehydrogenation

# Mechanism of Cytochrome-P450

## Mechanism of reaction

In the overall reaction:

- the drug is oxidized
- oxygen is reduced to water.

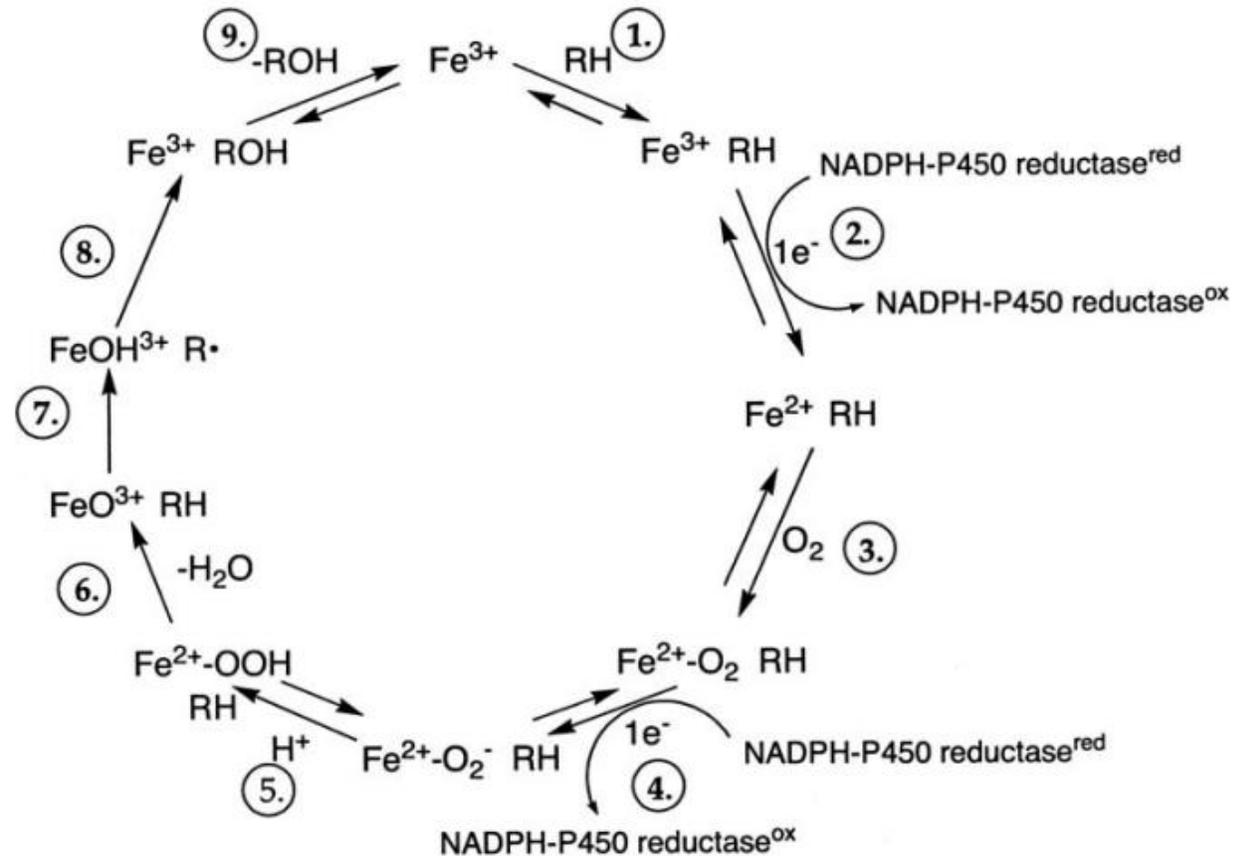
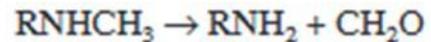


FIG. 6. **Generalized P450 catalytic cycle.** Only the heme iron of P450 is shown to represent the active site of the P450. the abbreviations are as follows: *Fe*, iron atom in P450 heme; *RH*, substrate; *ROH*, product; *ox* and *red*, the reduced and (1-electron) oxidized states of P450 reductase involved in electron transfers (under "Catalysis by P450s"). The figure was adapted from [1, 34].

# Oxidation by Cyt-P450

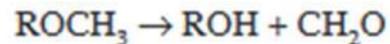
## I. Oxidative reactions

N-Dealkylation



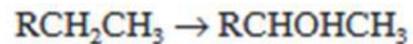
Imipramine, diazepam, codeine,  
erythromycin, morphine, tamoxifen,  
theophylline, caffeine

O-Dealkylation



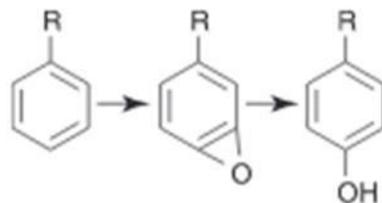
Codeine, indomethacin, dextromethorphan

Aliphatic  
hydroxylation



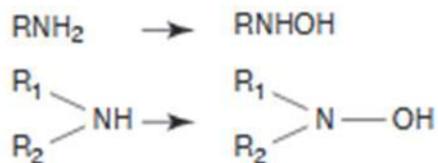
Tolbutamide, ibuprofen, phenobarbital,  
meprobamate, cyclosporine, midazolam

Aromatic  
hydroxylation



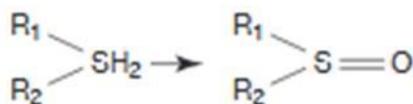
Phenytoin, phenobarbital, propranolol,  
ethinyl estradiol, amphetamine, war-  
farin

N-Oxidation



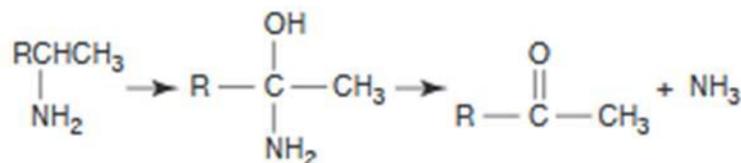
Chlorpheniramine, dapsone, meperidine

S-Oxidation



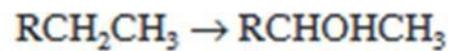
Cimetidine, chlorpromazine, thior-  
idazine, omeprazole

Deamination

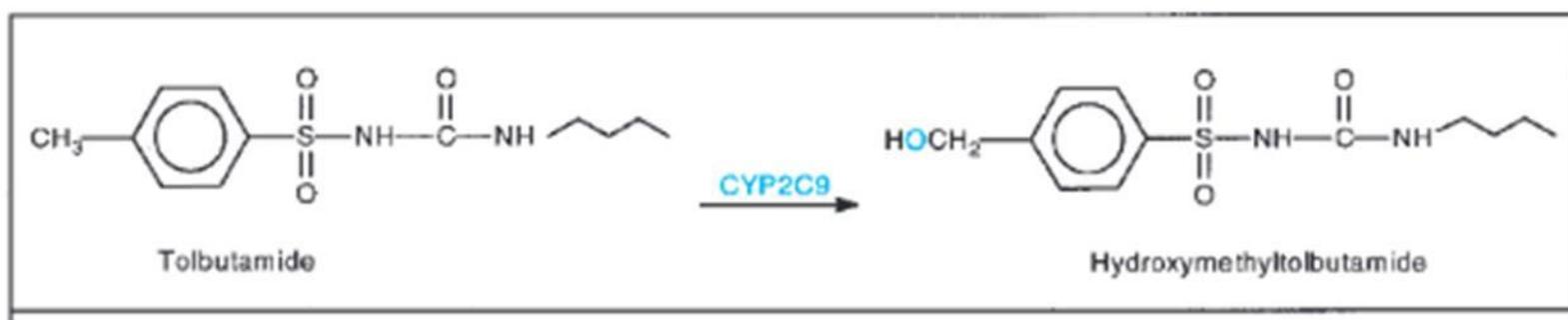


Diazepam, amphetamine

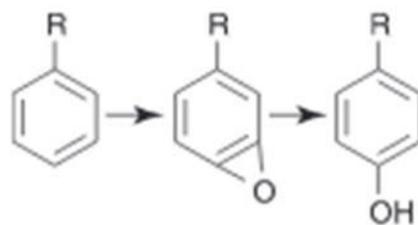
Aliphatic  
hydroxylation



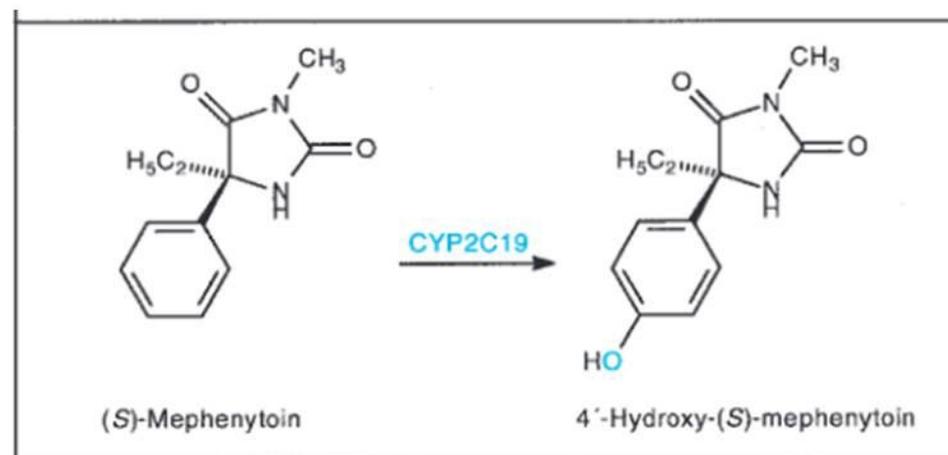
Tolbutamide, ibuprofen, phenobarbital,  
meprobamate, cyclosporine, midazolam



Aromatic  
hydroxylation



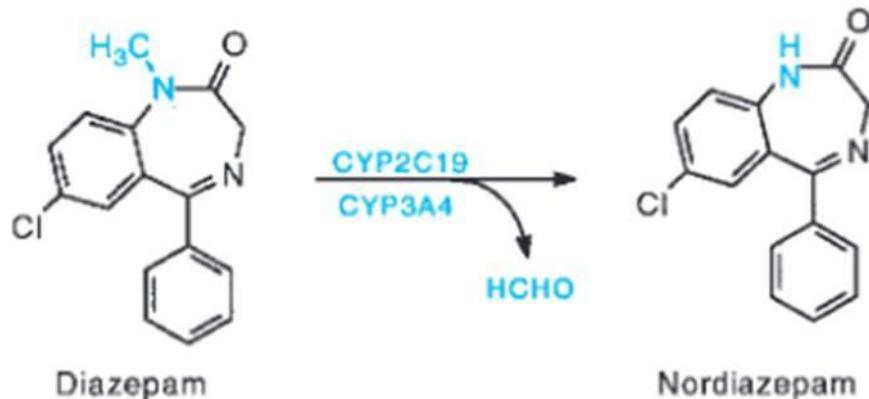
Phenytoin, phenobarbital, propranolol,  
ethinyl estradiol, amphetamine, war-  
farin



*N*-Dealkylation



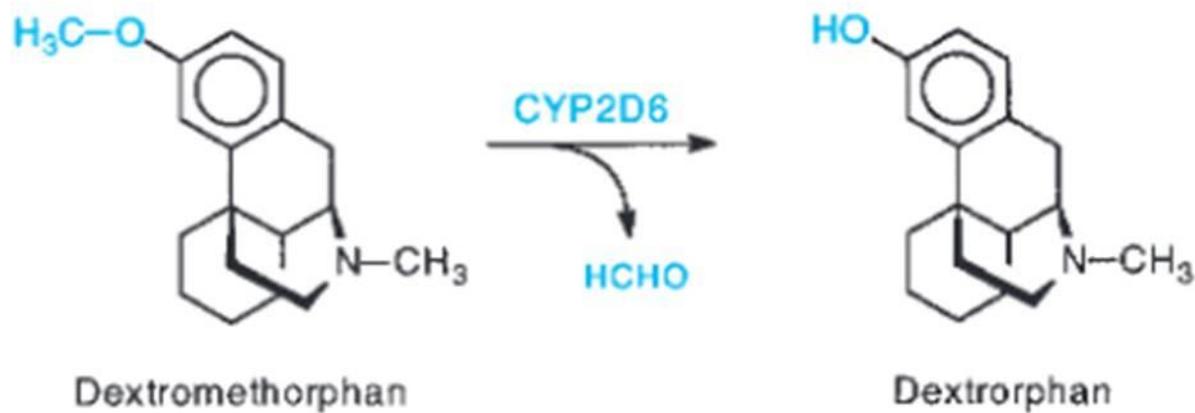
Imipramine, diazepam, codeine,  
erythromycin, morphine, tamoxifen,  
theophylline, caffeine



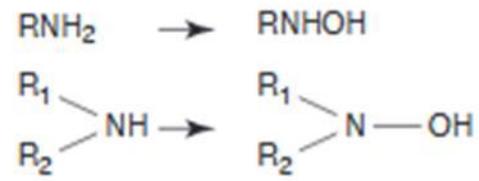
*O*-Dealkylation



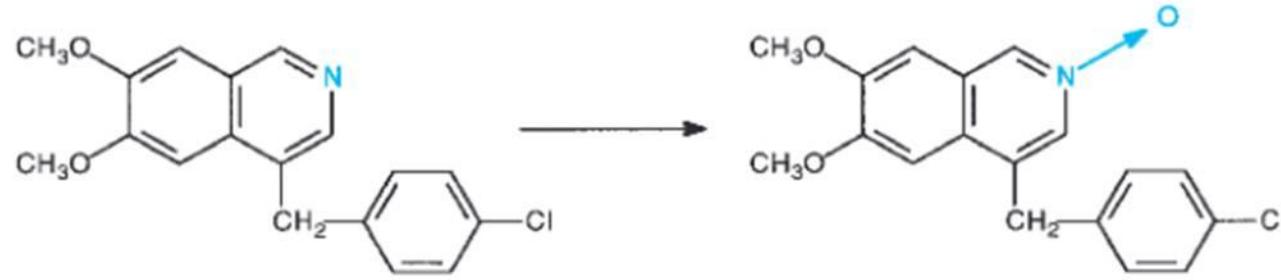
Codeine, indomethacin, dextromethorphan



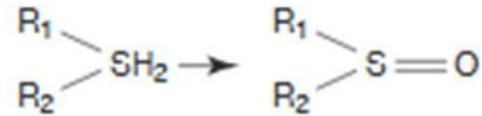
## N-Oxidation



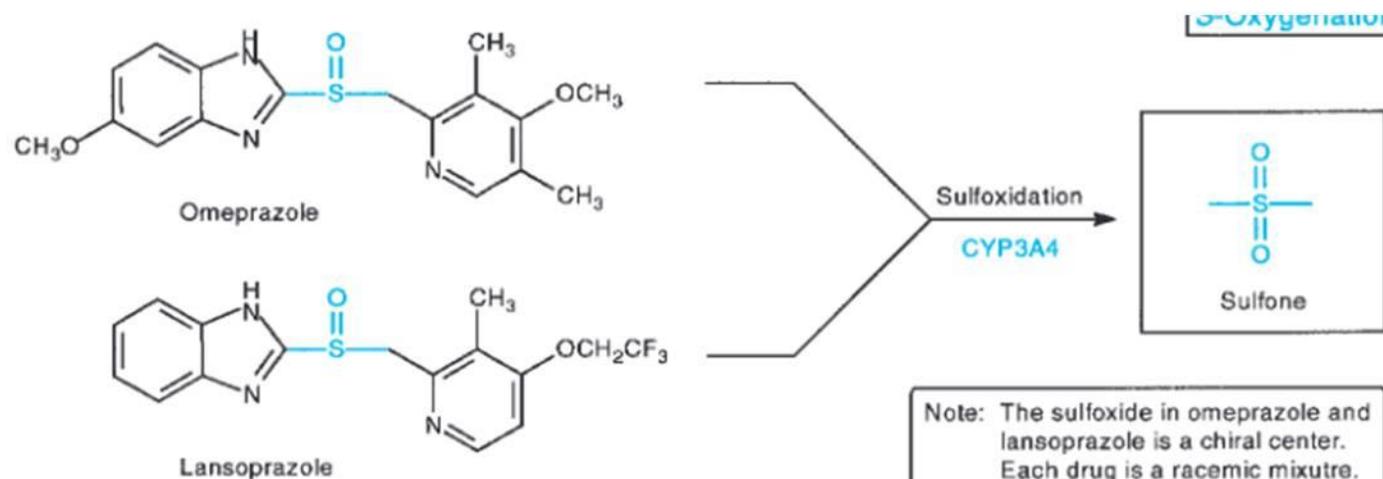
Chlorpheniramine, dapsone, meperidine  
isoquinoline group



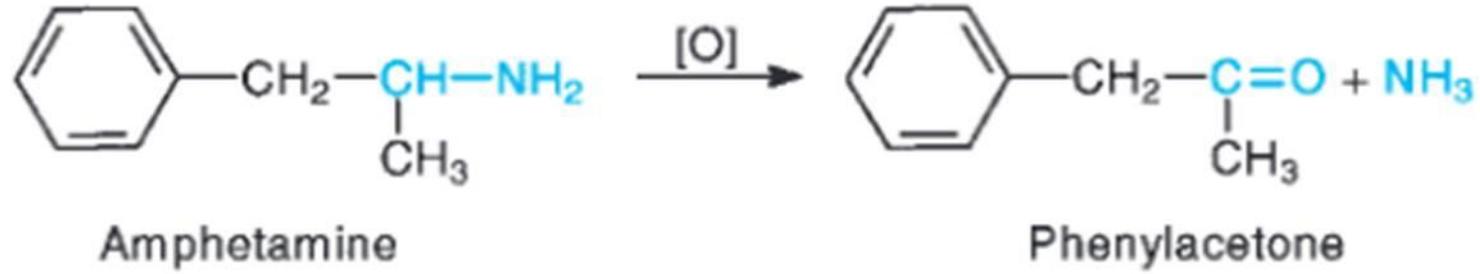
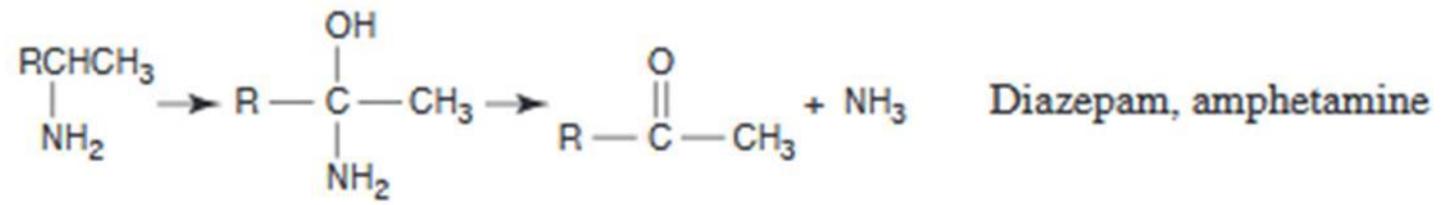
## S-Oxidation



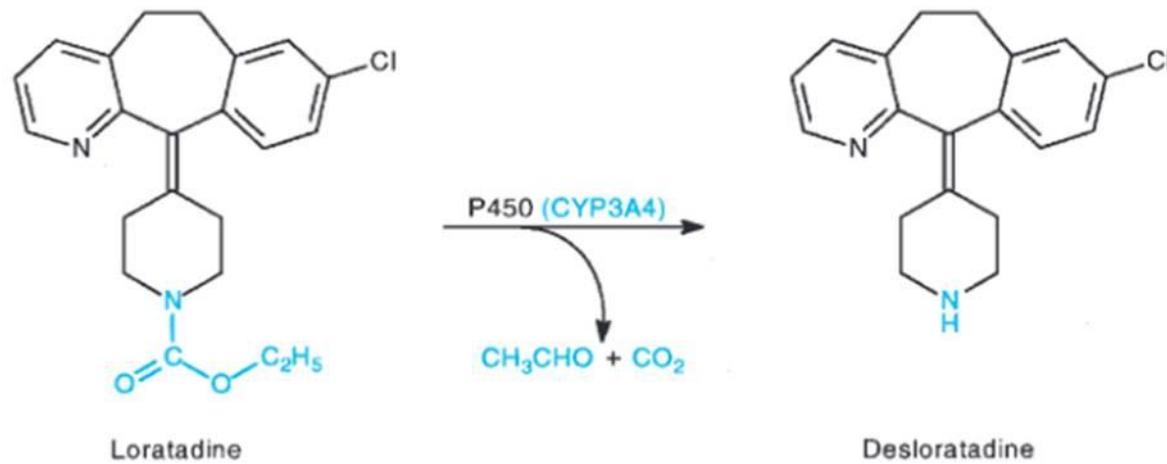
Cimetidine, chlorpromazine, thioridazine, omeprazole



Deamination



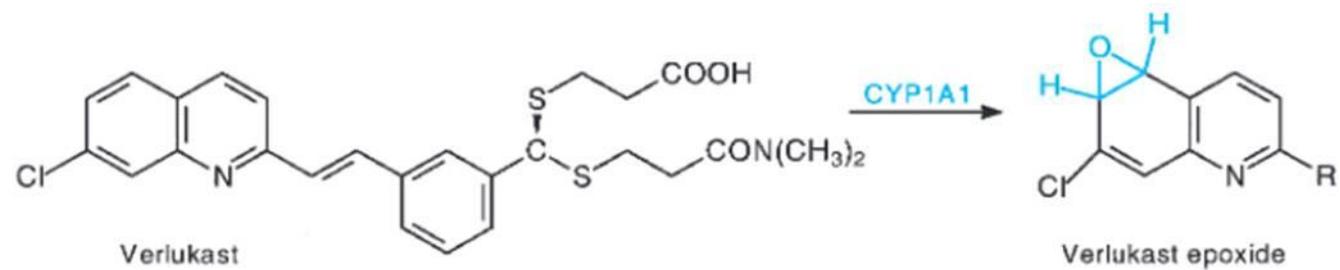
Cleavage of esters



## Dehydrogenation

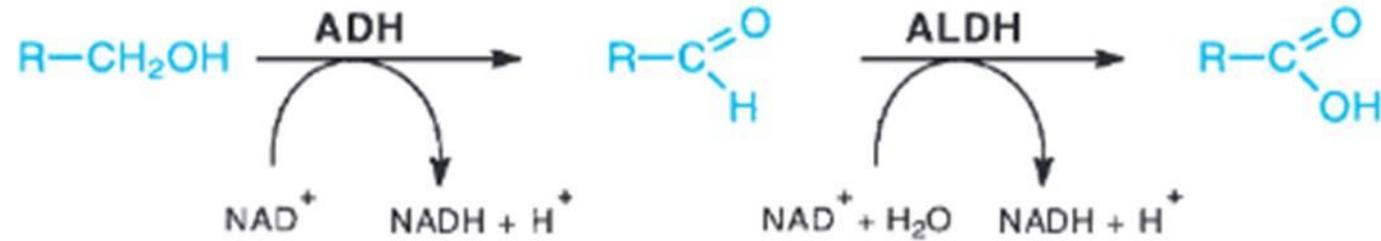


## Epoxidation



# Non microsomal enzymes

## Alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH)



## Xanthine oxidase and aldehyde oxidase

