



## Prodrugs and Soft Drugs

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## Prodrugs, Soft Drugs and Targeted Drugs

**Prodrugs** are inactive (less active) drug analogs with better pharmacokinetic properties (e.g. oral bioavailability, BBB penetration).

**Soft drugs (antedrugs)** are drugs that are readily degraded to inactive analogs, e.g. to prevent or reduce systemic activity.

**Targeted drugs** are drugs or prodrugs which exert their biological action only in certain cells or organs (e.g. omeprazole, aciclovir).

## Why Prodrugs ?

**Drug is not (sufficiently) bioavailable**  
(most prodrug concepts)

**Drug does not permeate the blood-brain barrier**  
(dopamine, GABA)

**Drug has poor properties (solubility, taste)**

**Drug has no (sufficient) chemical stability**  
(active principles of acetylsalicylic acid,  
isoniazid, omeprazole, clopidogrel)

**Drug has no (sufficient) organ or cell specificity**  
(sulfamethoxazole, capecitabine, aciclovir)

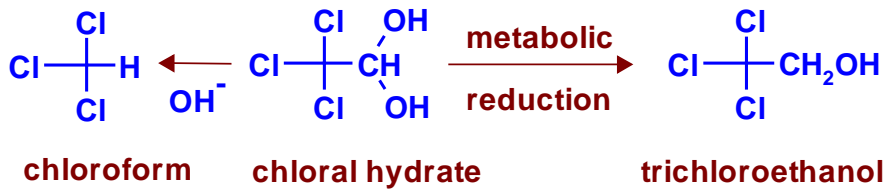
## Introduction

<b>L</b>	<b>Liberation</b>
<b>A</b>	<b>Absorption</b>
<b>D</b>	<b>Distribution</b>
<b>M</b>	<b>Metabolism</b>
<b>E</b>	<b>Elimination</b>
<b>T</b>	<b>Toxicity</b>

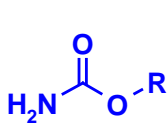
## Reasons for Clinical Failure



## Chloral Hydrate, a Prodrug of Chloroform ?

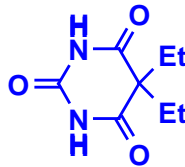


## Urethane, a Prodrug of Ethanol ?



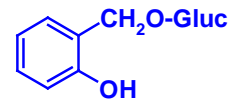
urethane, R = -CH<sub>2</sub>CH<sub>3</sub>

isopentylcarbamate,  
R = -CH<sub>2</sub>CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>



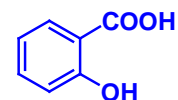
barbitone

## The Doctrine of Signatures: „Nature helps Mankind“



salicin ,  
a pro-drug

↓ hydrolysis,  
oxidation

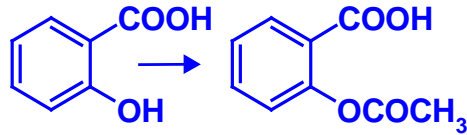


salicylic acid

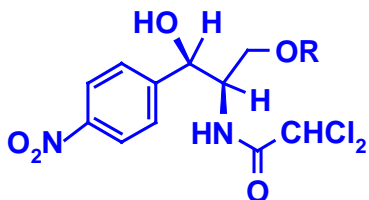
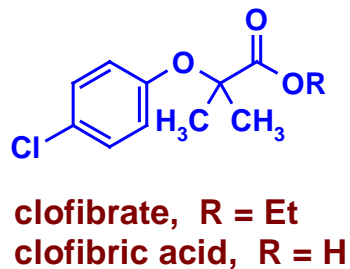
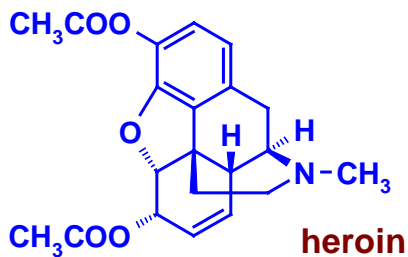
Willow tree – Roots in Water – Feet in Water - Common Cold



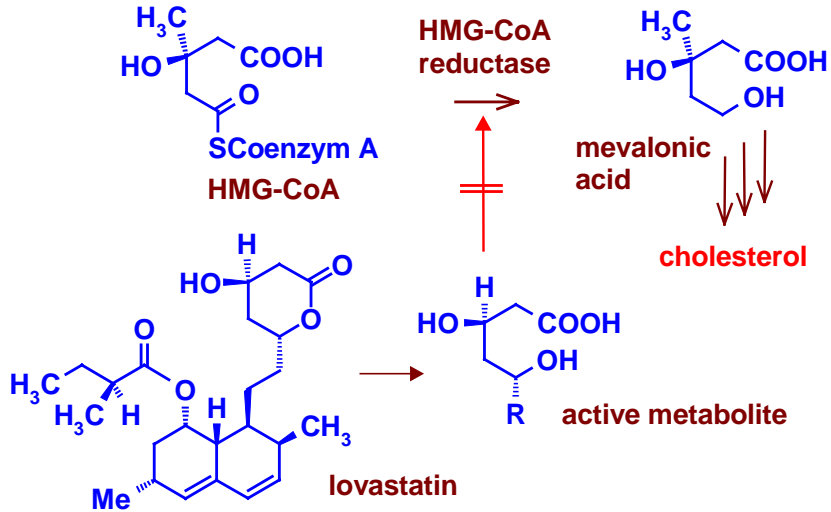
## Aspirin<sup>®</sup>, a Prodrug? (Felix Hoffmann, 1897)



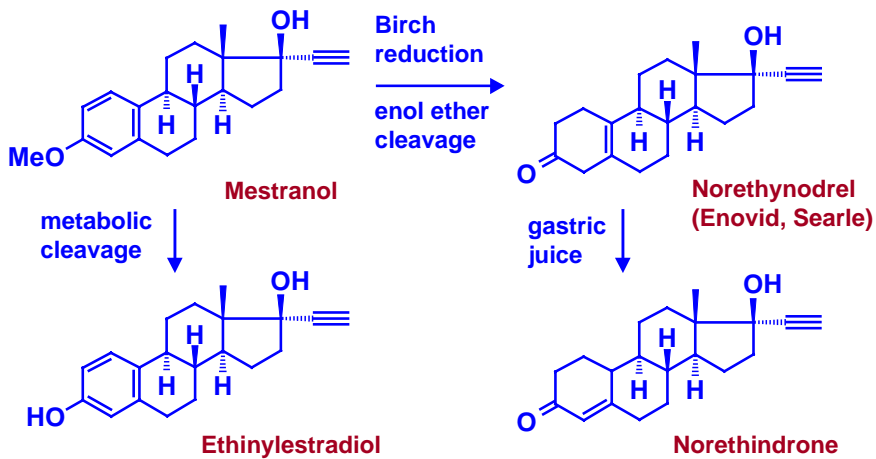
## Prodrugs: Esters



## Prodrugs: Lactones

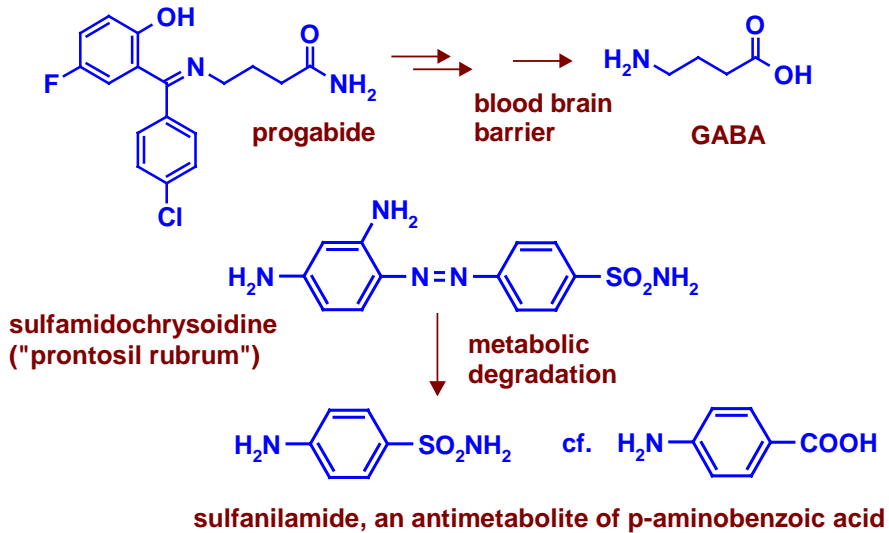


## The Serendipitous Discovery of the Pill



Source: J. Sutcliffe and N. Duin, *A History of Medicine*, Barnes & Noble Books, New York, 1992, p. 149; W. Sneader, *Drug Prototypes and their Expolitation*, Wiley, Chichester, 1996, p. 313 and 330-331

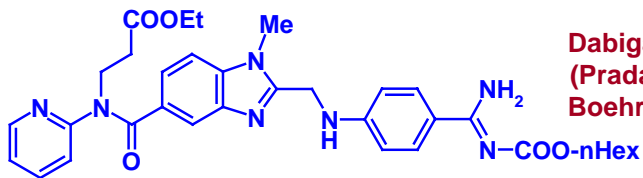
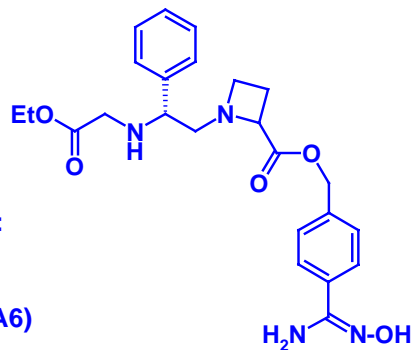
## Prodrugs: Amides and Azo Compounds



## Prodrugs of Amidines

**Melagatran (AstraZeneca)**, one of the first thrombin inhibitors with some oral bioavailability,  $K_i = 2$  nM

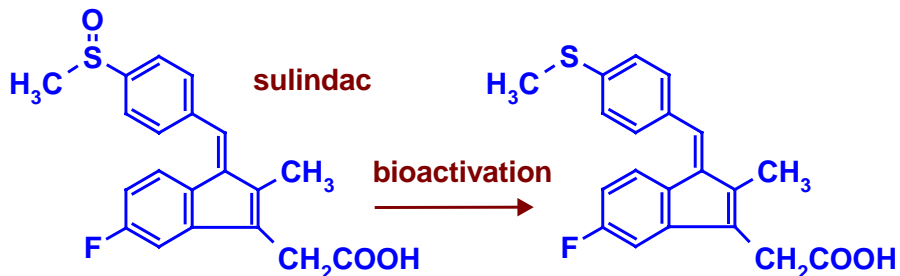
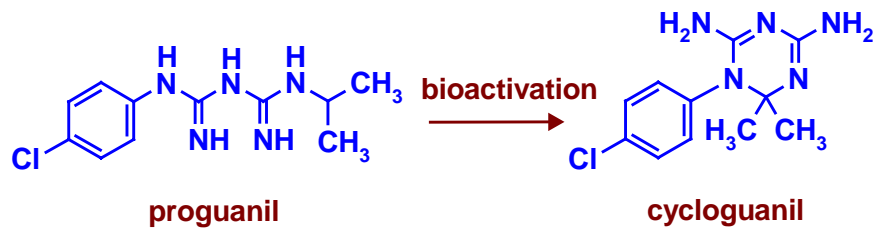
**Ximelagatran (H 376/95)** is a double prodrug (approved, later withdrawn):  
**ester group** (cleaved by esterases)  
**amidoxime** (reduced by NADH-cytochrome b5 reductase + CYP 2A6)



**Dabigatran etexilate**  
(Pradaxa<sup>®</sup>, Pradax<sup>®</sup>;  
Boehringer Ingelheim)

thrombin inhibitor for blood clot prevention; approved in Europe and Canada, FDA approval expected in 2010

## Other Prodrugs: Cyclization, Reduction

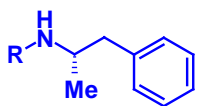


## Avoidance of Side Effects



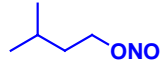
R = H, Castanospermine; antiviral agent, causes osmotic diarrhea by inhibition of intestinal sucrase  
R = CO(CH<sub>2</sub>)<sub>2</sub>CH<sub>3</sub>, Celgosivir prodrug without side effect

## Avoidance of Abuse

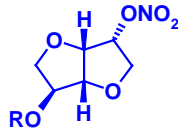


R = H, Dextroamphetamine, abuse by nasal or intravenous application  
R = Lys prodrug with oral activity; poor (<5%) nasal bioavailability, less than 10% dextroamphetamine released following i.v. application in rats.

## Nitrites, Nitrates and other NO Donors



Isoamyl nitrite  
1844, Balard

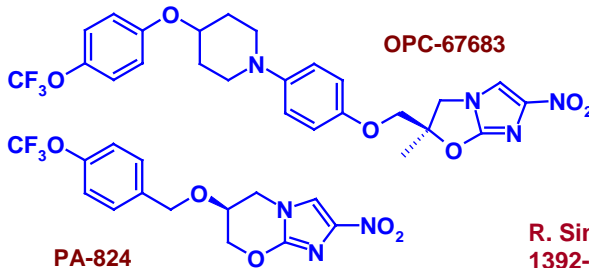


metabolic NO release  
enhances cGMP  
by stimulation of  
guanylate cyclase -  
acute application in  
coronary heart disease



Nitroglycerin  
Sobrero, 1847

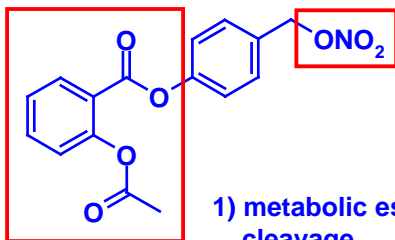
Isosorbide nitrates  
R = NO<sub>2</sub>, prodrug of  
R = H (2x more active)



selective NO release  
by bacterial enzyme  
kills replicating and  
non-replicating (!)  
*Mycobacterium  
tuberculosis* cells  
(clinical phase II)

R. Singh et al., *Science* **322**,  
1392-1395 (2008)

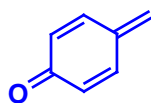
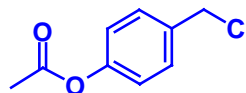
## A „Hybrid Drug“ is indeed a Prodrug



“NO-ASA”, strongly inhibits colon  
cancer growth *in vitro* and *in vivo*  
(J. L. Williams et al., *BBRC* **313**,  
784-788 (2004)); however, cGMP  
levels are not increased.

- 1) metabolic ester  
cleavage
- 2) 1,6-elimination  
of NO<sub>3</sub><sup>-</sup>

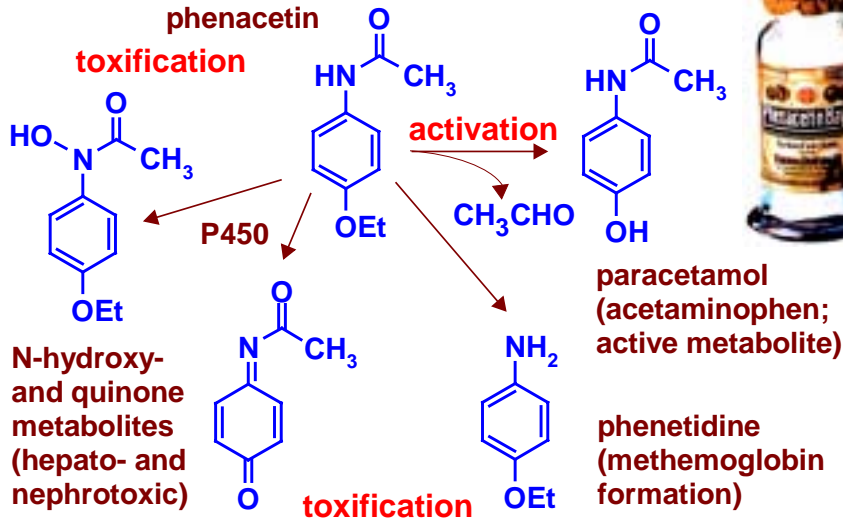
the linker is the prodrug  
of the active agent:



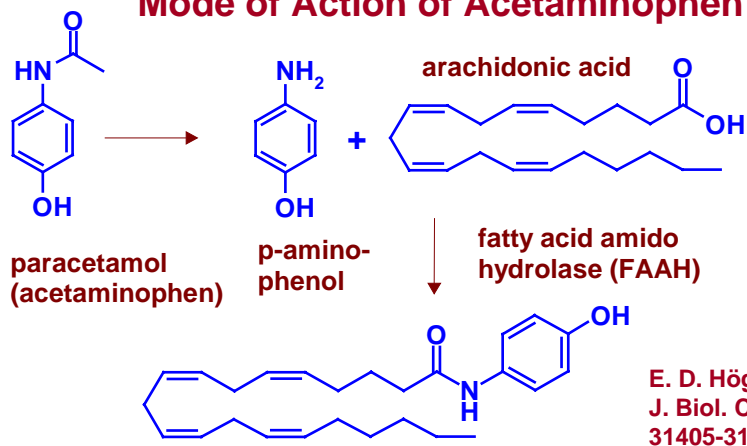
highly toxic, reacts with  
nucleophiles, e.g. GSH

about 10 times more active against  
colon cancer cells (N. Hulsman et al.,  
*J. Med. Chem.* **50**, 2424-2431 (2007);  
M. Wijtman, personal communication)

## Phenacetin, a Pro-Prodrug

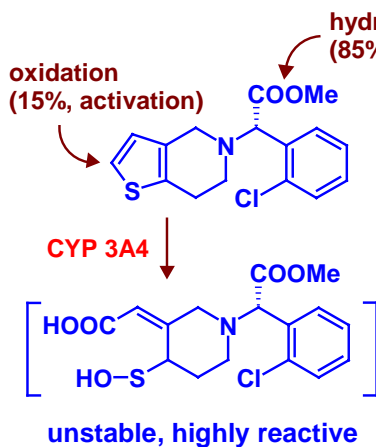


## Mode of Action of Acetaminophen



N-arachidonoyl phenolamine, a potent TRPV1 (transient receptor potential vanilloid 1, vanilloid receptor) agonist,  $pEC_{50} = 7.80$  (about 16 nM), binds also to the cannabinoid CB<sub>1</sub> receptor and inhibits cellular anandamide uptake.

## Clopidogrel, Mode of Action



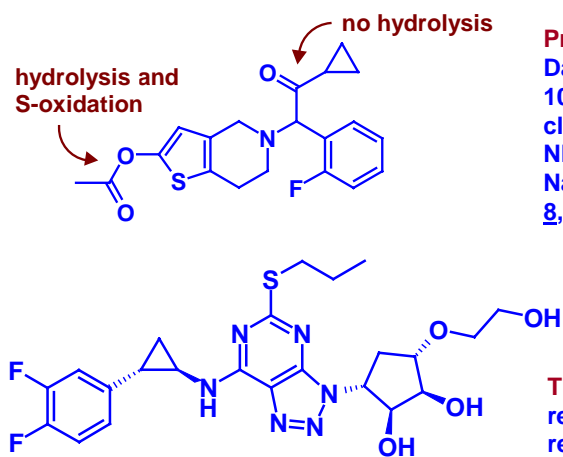
Plavix®, Iscover®  
(Sanofi-Aventis, BMS)  
worldwide net sales  
2005: about 6 bio US-\$

active metabolite, irreversibly reacts in the liver with platelet P2Y<sub>12</sub> (ADP) receptors

activation by CYP2C19  
(absent in 30% Caucasians)

J.-M. Pereillo et al., *Drug Metab. Dispos.* **30**, 1288-1295 (2002);  
E. J. Topol, *Nature Rev. Drug Discov.* **8**, 259 (2009);  
cf. P. M. Dansette et al., *Chem. Res. Toxicol.* **22**, 369-373 (2009)

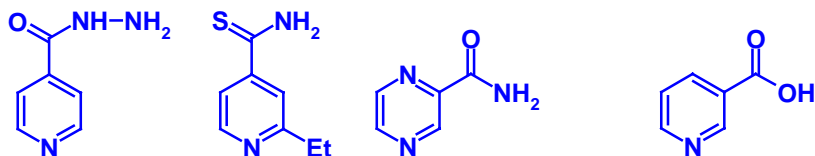
## Alternatives to Clopidogrel



Prasugrel (Eli Lilly and Daiichi Sankyo), clinically 10-15x more effective than clopidogrel (Europe, 2009; NDA pending)  
*Nature Rev. Drug Discov.* **8**, 449-450(2009)

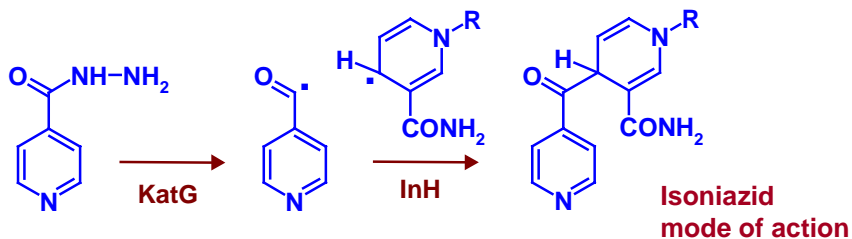
Ticagrelor (AstraZeneca), reversible platelet ADP receptor antagonist (in late phase III studies)

## Mode of Action of Isoniazid



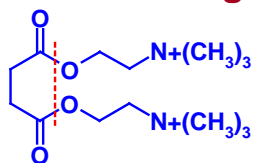
### Isoniazid and its analogs

considered to be prodrugs of antimetabolites of nicotinic acid

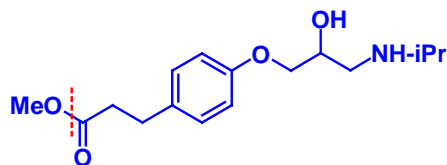


Z. Ma et al., Comprehensive Med. Chem II, Vol. 7, pp. 699-730 (2007)

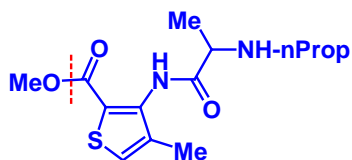
## Soft Drugs: Metabolically Labile Esters



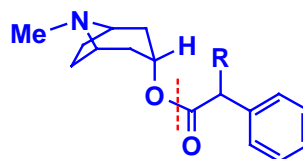
Succinylcholine, an acetylcholine analog; ester cleavage produces inactive choline



Esmolol, a soft  $\beta$ -blocker; ester cleavage produces weakly active acid



Articaine, a soft local anesthetic



R = CH<sub>2</sub>OH Atropin

R = COOR ester bioisoster,  
cleavage yields inactive acid

## Organ- and Cell-Specific Drug Delivery

### Organ Specificity, mediated by

- physicochemical properties (lipophilicity)
- transporters (uptake, efflux)
- metabolism only or preferentially in target organ

### Cell Specificity, mediated by

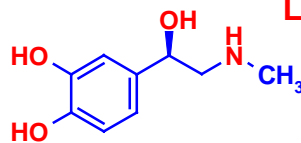
- cellular metabolism
- intracellular degradation

### Other mechanisms of organ-specific action

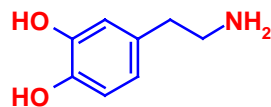
- local application (eye, skin, lung, spinal cord)
- antibody conjugates
- target localisation
- target type (e.g. microorganism targets)

## Lipophilicity and Blood-Brain Barrier

### Polar Compounds

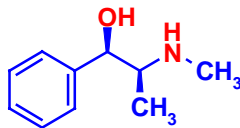


epinephrine



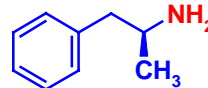
dopamine

### Intermediate Lipophilicity

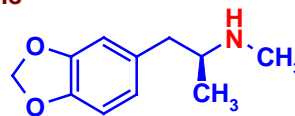


ephedrine

### Lipophilic Compounds

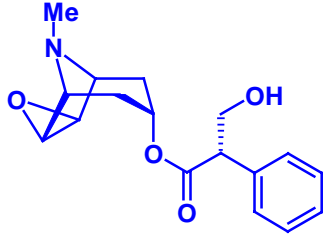


amphetamine  
(speed)



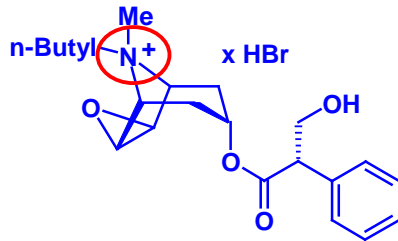
MDMA (Ecstasy, XTC)

## Avoidance of CNS Side Effects



**Scopolamine, (-)-Hyoscine**  
muscarinic AChR antagonist  
with varying oral bioavailability  
but good dermal absorption

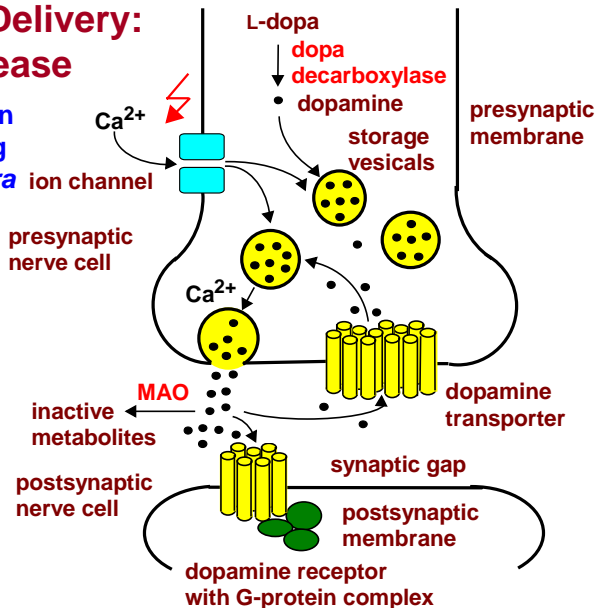
**dermal patch** against travel  
sickness  
toxic CNS side effects  
abuse as "truth drug"



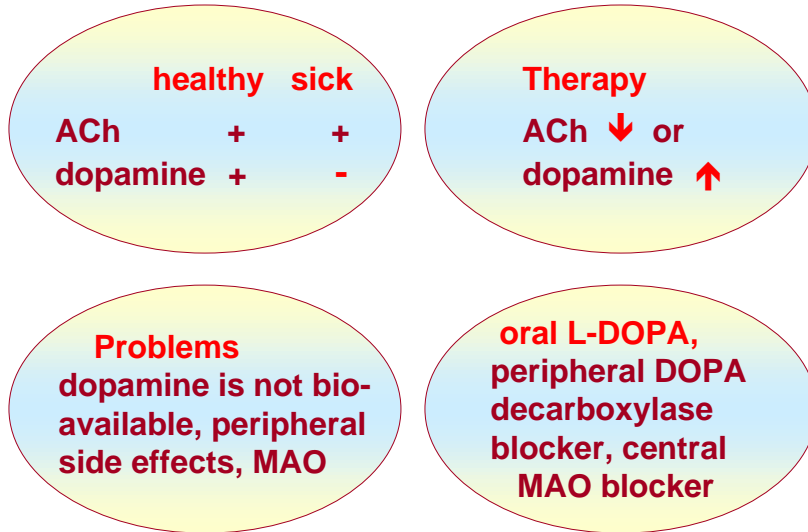
**N-Butyl-scopolamine  
hydrobromide, Buscopan®**  
smooth muscle spasmolytic,  
orally bioavailable,  
almost no CNS side effects

## Organ-Specific Delivery: Parkinson's Disease

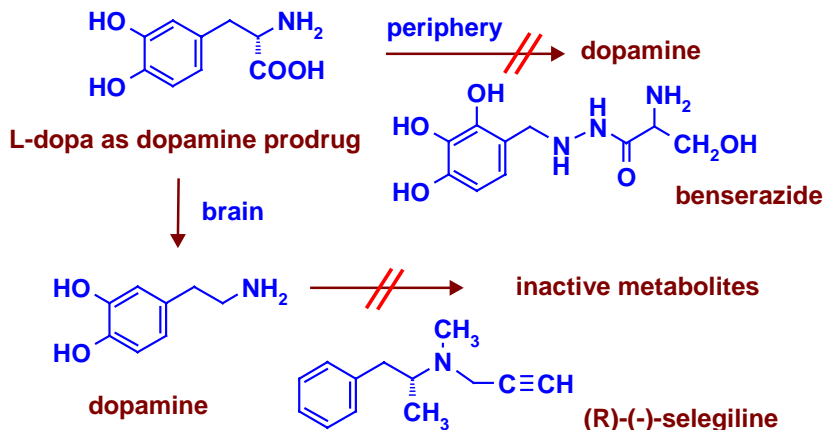
caused by degeneration  
of dopamine-producing  
cells in *Substantia nigra*



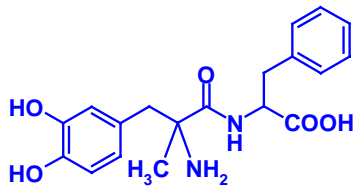
## A Rational Therapy of Parkinson's Disease



## Integrated Optimisation of Drug Therapy Dopamine Substitution in Parkinson's Disease



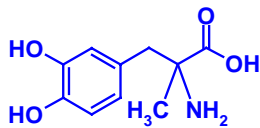
## A Most Elegant Pro-Drug Concept



$\alpha$ -Methyldopa-Phe

oral absorption by  
active transport  
(dipeptide transporter)

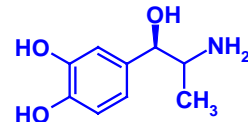
peptide cleavage  
in the liver



$\alpha$ -Methyldopa

BBB penetration by  
active transport  
(amino acid transporter)

decarboxylation  
and hydroxylation

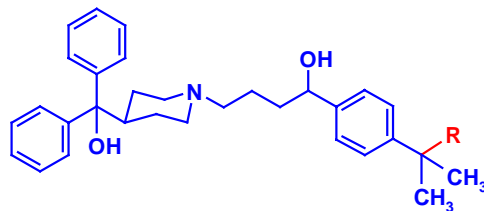


$\alpha$ -Methylnorepinephrine  
( $\alpha$ 2-agonist, "false  
neurotransmitter")

M. Hu et al., Pharm. Res. 6, 66-70 (1989)

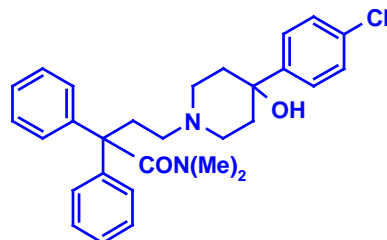
## Avoidance of CNS Effects by Active Efflux

Terfenadine, R = CH<sub>3</sub>  
lipophilic H<sub>1</sub> antagonist  
(no sedative side effect,  
due to active elimination  
by drug transporter)

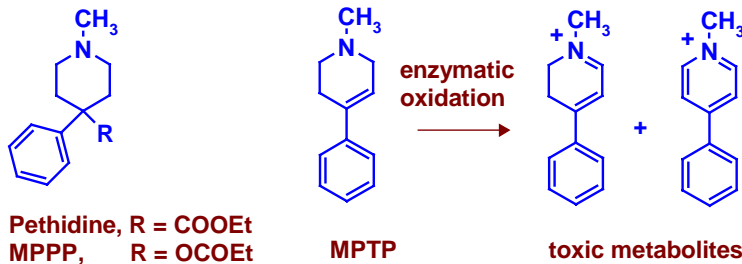


Fexofenadine, R = COOH  
active terfenadine metabolite

Loperamide  
antidiarrhoicum  
(opiate agonist without  
CNS activity)

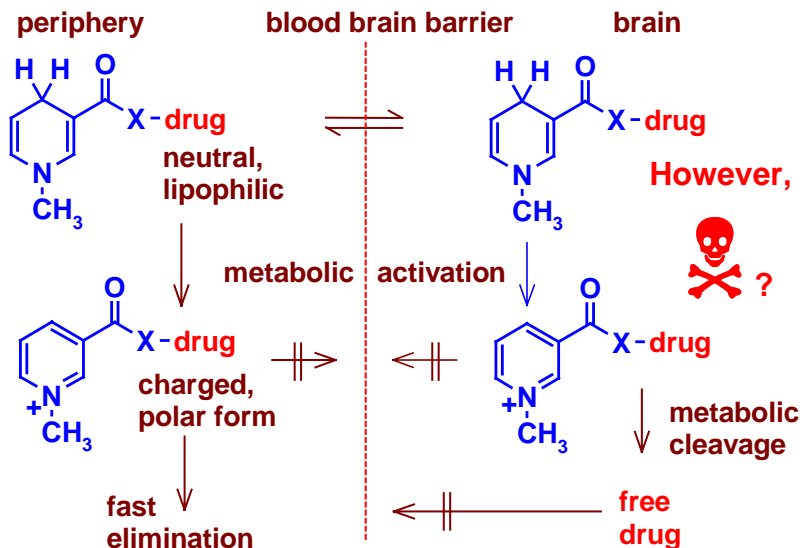


## Organ-Specific Formation of Toxic Metabolites

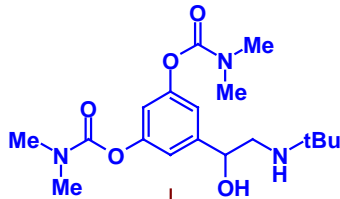


**1-methyl-4-phenyl-4-propionyloxy-piperidine (MPPP)** corresponds to pethidine but a “leaving group” results. Consumption of impure material leads to severe Parkinson symptoms, followed by early death. **MPTP is a “prodrug”** of permanently charged cytotoxic metabolites. The MAO inhibitor selegilin prevents this oxidation.

## Brain Targeting of Drugs



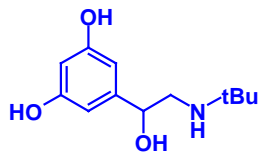
## Fast Onset but Long Duration of Action



**bambuterol**

(for the treatment of asthma;  
concentrates in lung tissue  
and is metabolized there)

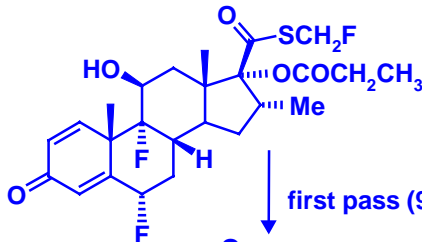
irreversible inhibition  
by serine carbamylation  
↓  
cleavage by butyrylcholinesterase



**terbutaline ( $\beta_2$  agonist)**

D. S. Sitar, Clin. Pharmacokin.  
31, 246-256 (1996)

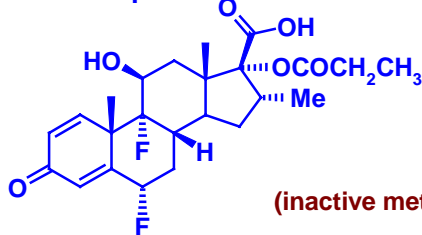
## Soft Drugs: Corticosteroid Esters



**fluticasone propionate**  
(Flonase; Advair, GSK)

(inhalation; topically active  
in asthma treatment)

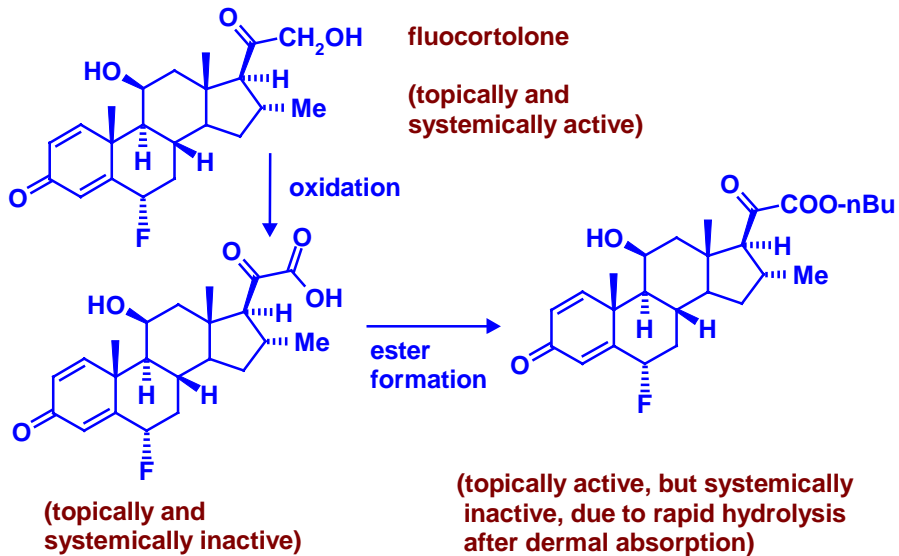
first pass (99%)



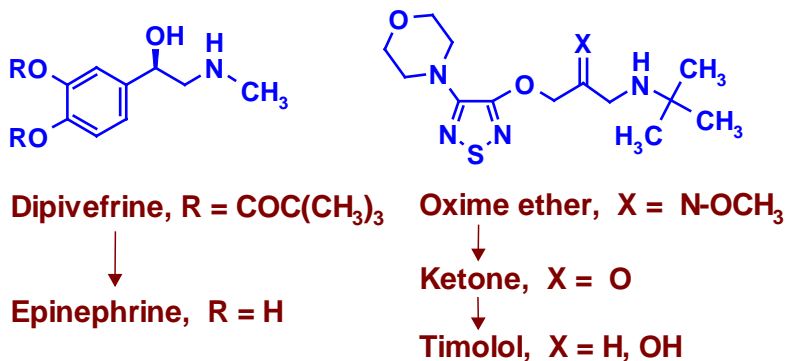
(inactive metabolite)

R. E. Pearce et al., Drug Metab. Dispos. 34, 1035-1040 (2006)

## Soft Drugs: Corticosteroid Esters

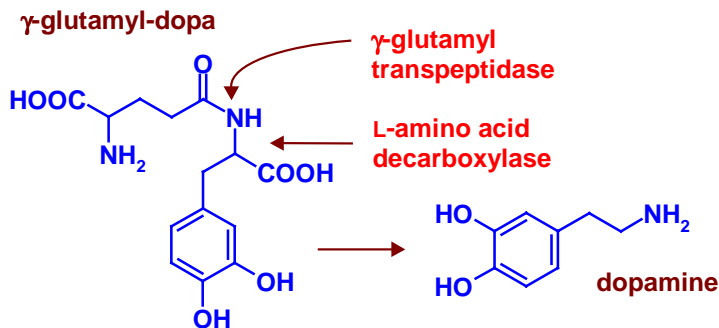


## Targeted Drugs: Eye-specific Prodrugs



**Dipivefrine** is 20x faster metabolized in the eye than in the periphery. The **timolol prodrug** is only metabolized in the eye. Both prodrugs are used for the therapy of glaucoma.

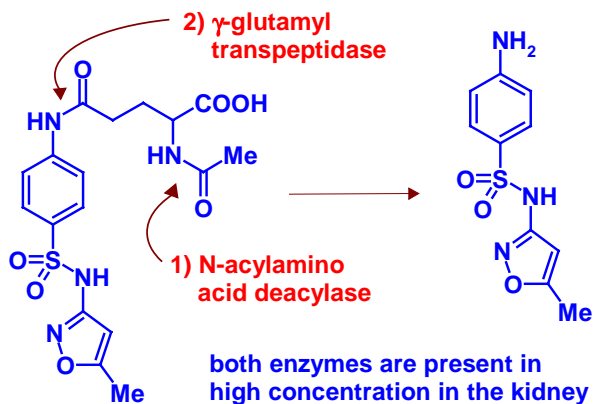
## Kidney-Selective Vasodilation



$\gamma$ -glutamyl derivatives of amino acids and peptides accumulate in the kidney, where they undergo selective metabolic activation

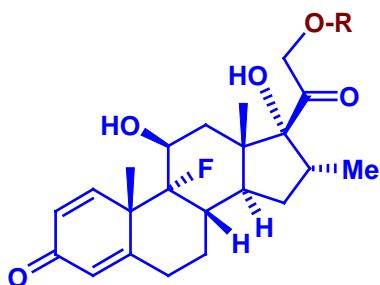
C. G. Wermuth, *The Practice of Medicinal Chemistry*, 3rd Edition, Elsevier/Academic Press, New York 2008, p. 729;  
S. D. J. Magnan et al., *J. Med. Chem.* 25, 1018-1021 (1982)

## Kidney-Selective Release of the Antiinfective Sulfonamide Sulfamethoxazole



C. G. Wermuth, *The Practice of Medicinal Chemistry*, 3rd Edition, Elsevier/Academic Press, New York 2008, p. 729-730;  
M. Orłowski et al., *J. Pharmacol. Exp. Ther.* 212, 167-172 (1979)

## Colon-Selective Delivery of Corticosteroids in Inflammatory Bowel Disease

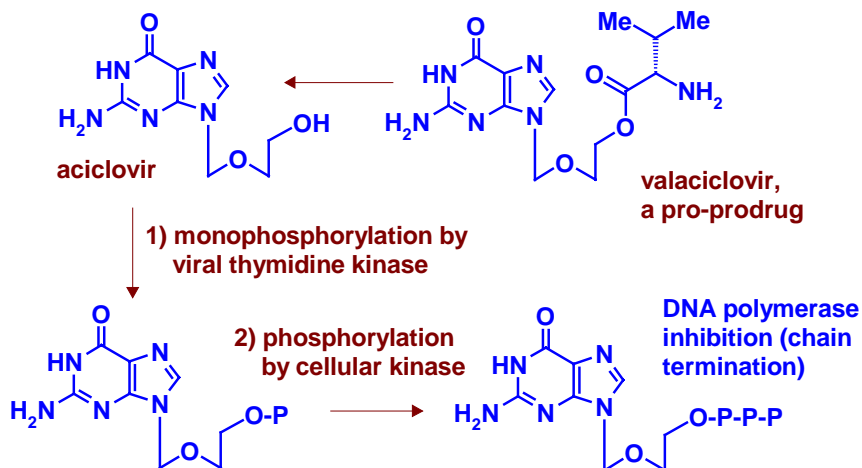


R = H, Dexamethasone  
oral dose almost exclusively  
absorbed in the intestine,  
only about 1% reach the cecum

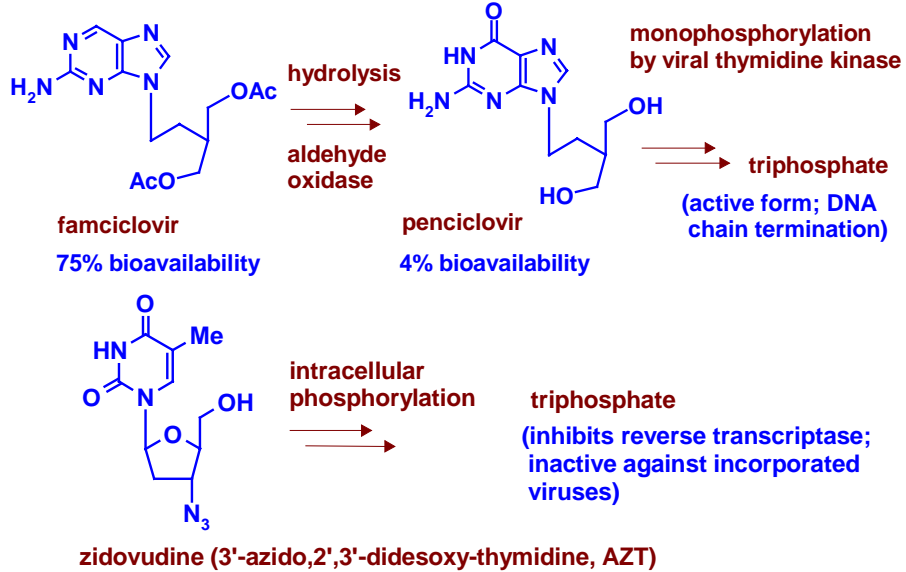
R = glucose, Dexamethasone-  
21 $\beta$ -D-glucoside  
cleaved by the colonic  
microflora, about 60% of the  
free steroid reach the cecum

C. G. Wermuth, *The Practice of Medicinal Chemistry*,  
3rd Edition, Elsevier/Academic Press, New York 2008, p. 730;  
D. R. Friend and G. W. Chang, *J. Med. Chem.* **28**, 51-57 (1985)

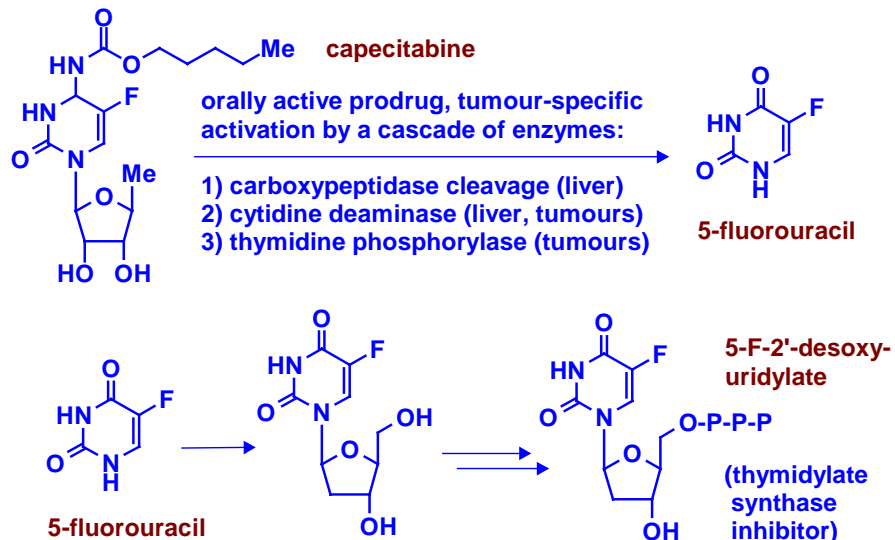
## Antiviral Prodrugs are Trojan Horses



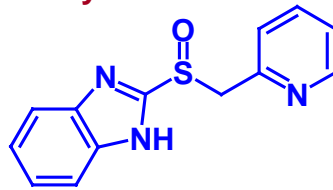
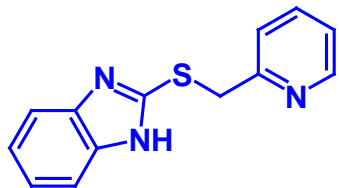
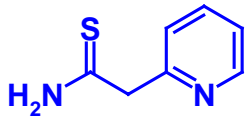
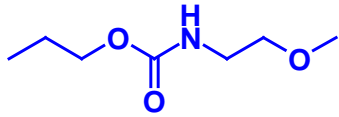
## Antiviral Prodrugs are Trojan Horses



## Tumor Cell-Specific Trojan Horses



## Omeprazole: A Cell-Specific Anti-Ulcer Agent



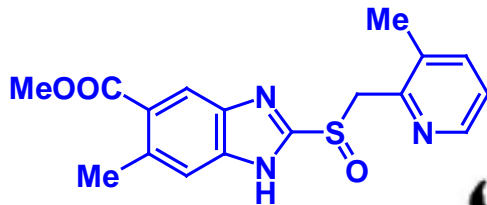
1966: Local anesthetics reduce gastric secretion (Hässle)

1966-1972: First lead

1972-1979: New lead pyridyl-acetamide (from screening of antiviral compounds)

Active analogs; metabolite with higher antisecretory activity

## Omeprazole Analog: Toxic or not Toxic?



Picoprazole, 1976 preclinical candidate

Tox study:



breeding dog Fabian

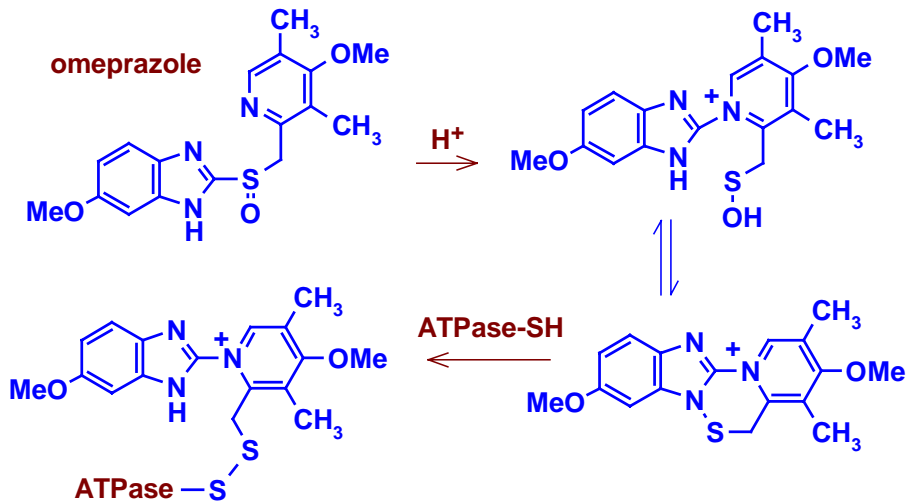
vasculitis



picoprazole group

placebo group

## Drug Activation in Acid-Producing Cells - The Serendipitous Discovery of a Targeted Drug



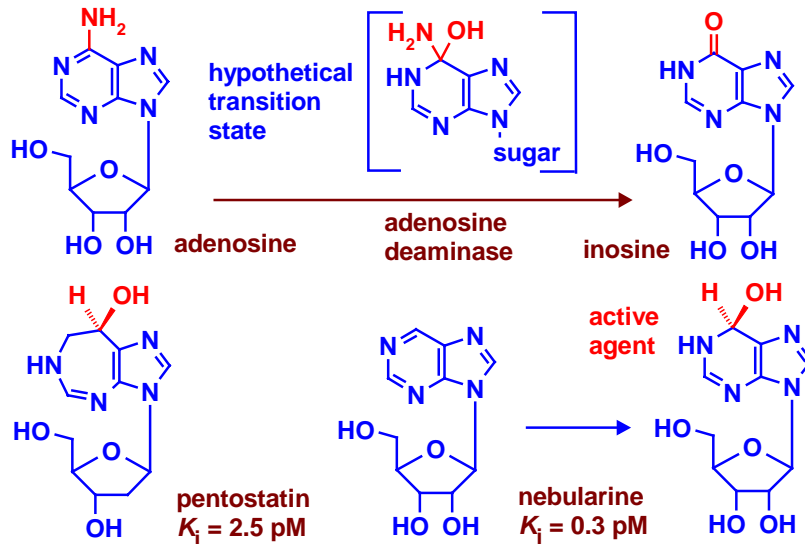
## Omeprazole Activation in Acid-Producing Cells



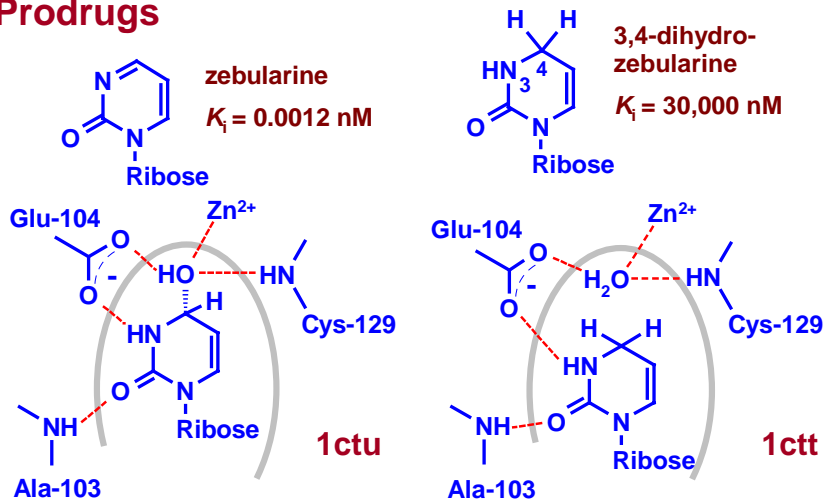
Distribution of  
radio-labelled  
omeprazole,  
one minute after  
i.v. injection, rat

sixteen hours  
after i.v.  
injection, rat

## Transition State Mimics and Their Prodrugs



## Nebularine and Zebularine are Target-Specific Prodrugs



S. Xiang et al., *Biochemistry* **34**, 4516-4523 (1995)

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