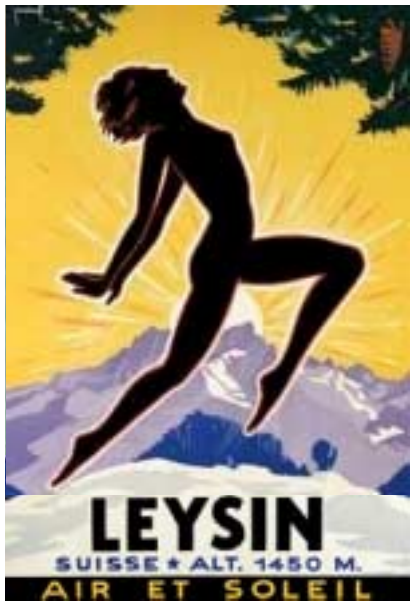

Prodrugs and Soft Drugs

Hugo Kubinyi

Germany

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HomePage www.kubinyi.de

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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)

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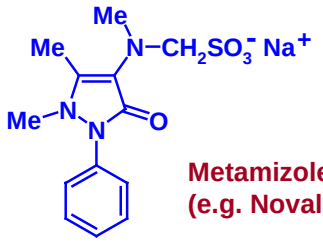
Introduction

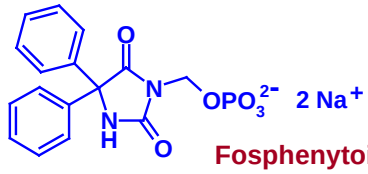
L	Liberation
A	Absorption
D	Distribution
M	Metabolism
E	Elimination
T	Toxicity

Reasons for Clinical Failure

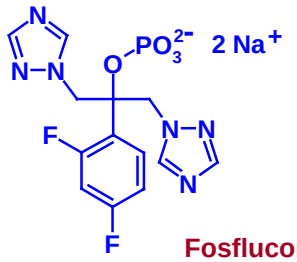
Liberation: Better Soluble Drug Derivatives



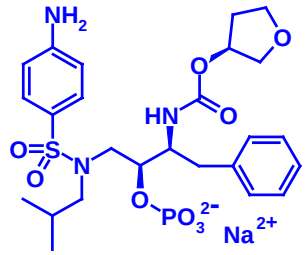
Metamizole
(e.g. Novalgin®)



Fosphenytoin

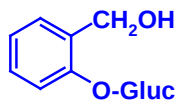


Fosfluconazole



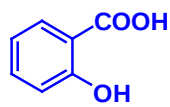
Fosamprenavir

The Doctrine of Signatures: „Nature helps Mankind“



salicin ,
a pro-prodrug

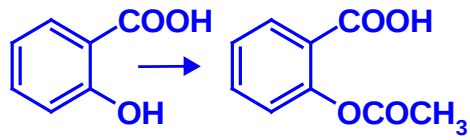
↓ hydrolysis, oxidation



salicylic acid

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

Aspirin®, a Prodrug? (Felix Hoffmann, 1897)



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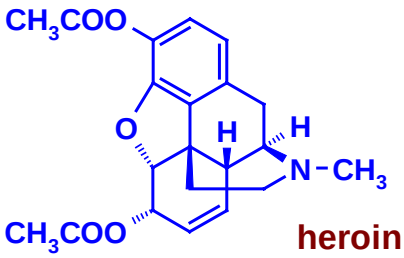
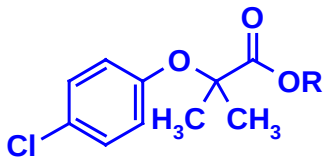
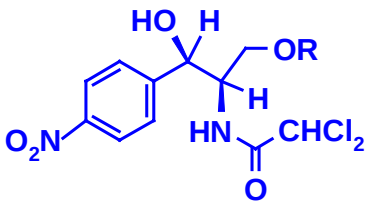
Prodrugs: Esters



heroin



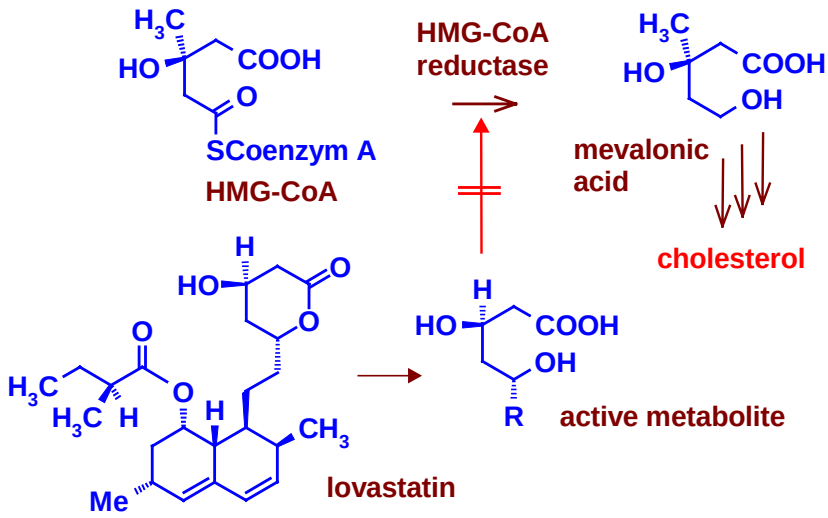
clofibrate, R = Et
clofibric acid, R = H



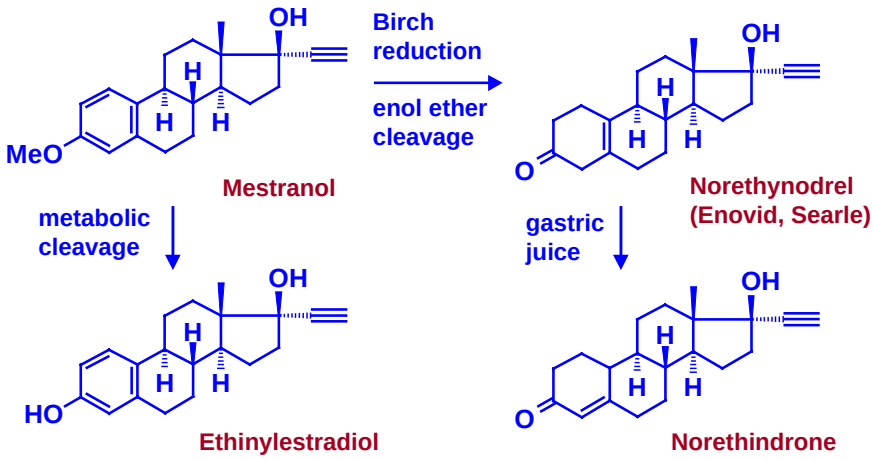
chloramphenicol, R = H
(very bitter taste)

tasteless prodrug
R = $CO(CH_2)_{14}CH_3$

Prodrugs: Lactones

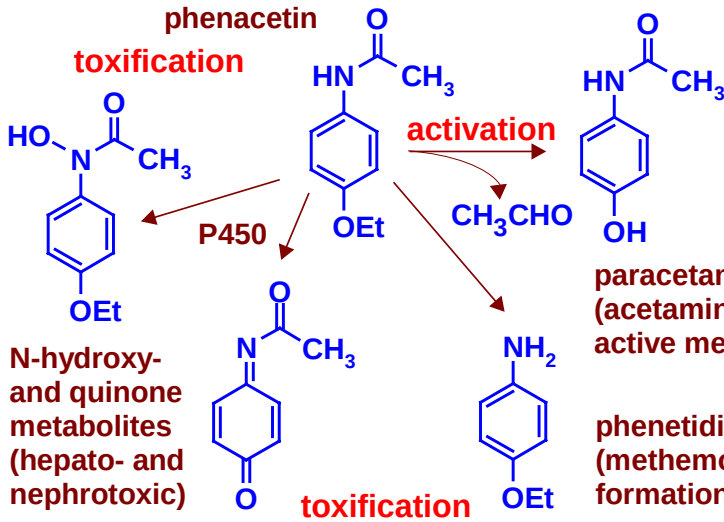


The Serendipitous Discovery of the Pill

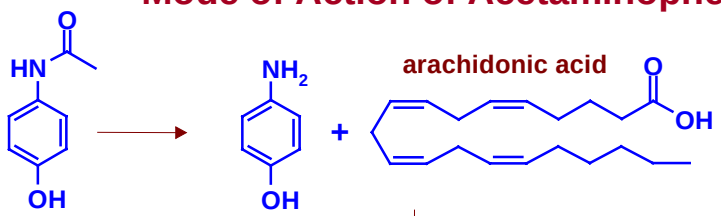


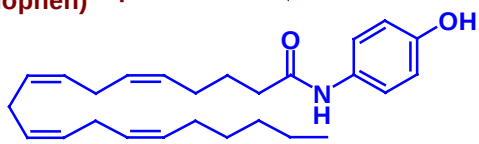
Source: J. Sutcliffe and N. Duin, A History of Medicine, Barnes & Noble Books, New York, 1992, p. 149; W. Sneader, Drug Prototypes and their Expolitation, Wiley, Chichester, 1996, p. 313 and 330-331

Phenacetin, a Pro-Prodrug



Mode of Action of Acetaminophen

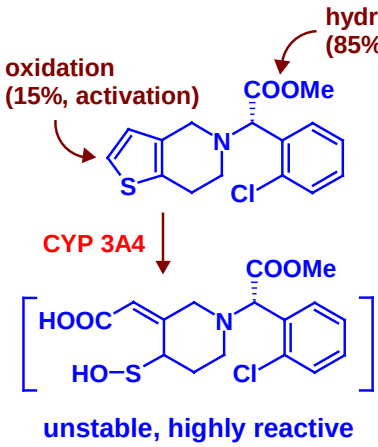




E. D. Högestätt et al., J. Biol. Chem. 280, 31405-31412 (2005); cf. D. A. Andersson et al., Nat. Commun. 2011 Nov 22;2:551

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_1 receptor and inhibits cellular anandamide uptake.

Clopidogrel, Mode of Action



unstable, highly reactive

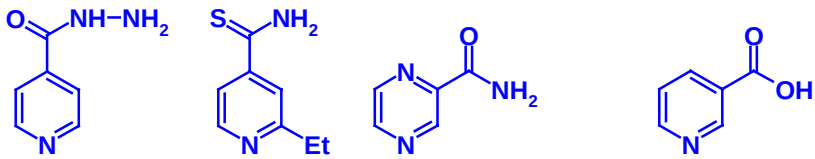
Plavix®, Iscover®
(Sanofi-Aventis, BMS)
worldwide net sales
2005: about 6 bio US-$

active metabolite, irreversibly reacts in the liver with platelet $P2Y_{12}$ (ADP) receptors

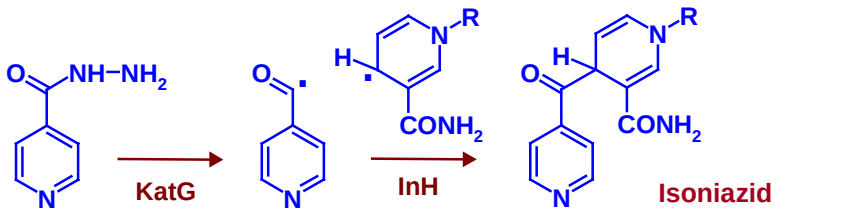
activation by CYP2C19
(absent in 30% Caucasians)

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)

Mode of Action of Isoniazid



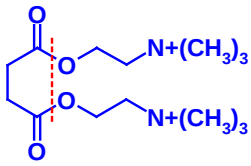
Isoniazid and its analogs
considered to be prodrugs of antimetabolites of nicotinic acid



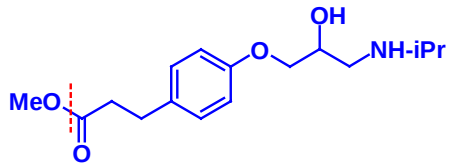
Isoniazid
mode of action

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

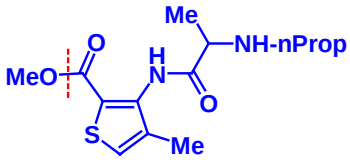
Soft Drugs: Metabolically Labile Esters



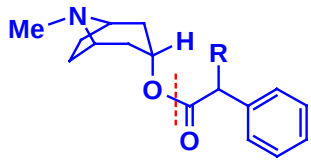
Succinylcholine, an acetylcholine analog; ester clevage produces inactive choline



Esmolol, a soft ß-blocker; ester cleavage produces weakly active acid



Articaine, a soft local anesthetic



R = CH_2OH Atropin

R = COOR ester bioisoster, cleavage yields inactive acid

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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

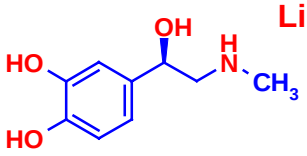
- cellular metabolism
- intracellular degradation

Other mechanisms of organ-specific action

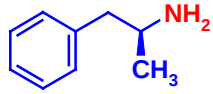
- local application (eye, skin, lung, spinal cord)
- antibody conjugates
- target localisation
- target type (e.g. microorganism targets)

Lipophilicity and Blood-Brain Barrier

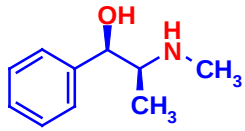
Polar Compounds — **Intermediate Lipophilicity** — **Lipophilic Compounds**



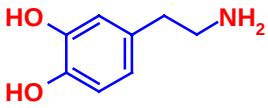
epinephrine



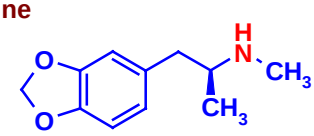
amphetamine (speed)



ephedrine



dopamine



MDMA (Ecstasy, XTC)

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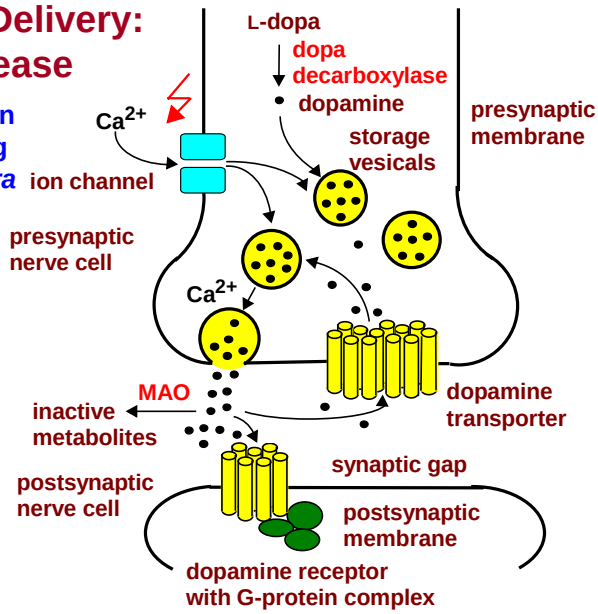
Organ-Specific Delivery: Parkinson's Disease

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



A Rational Therapy of Parkinson's Disease

	healthy	sick
ACh	+	+
dopamine	+	-

Therapy

ACh ↓ or

dopamine ↑

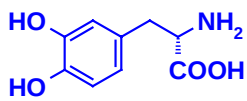
Problems

dopamine is not bio-available, peripheral side effects, MAO

oral L-DOPA, peripheral DOPA decarboxylase blocker, central MAO blocker

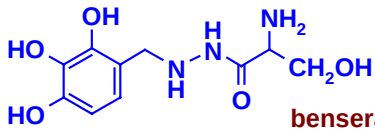
Integrated Optimisation of Drug Therapy

Dopamine Substitution in Parkinson's Disease



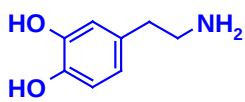
L-dopa as dopamine prodrug

periphery ⫽→ dopamine



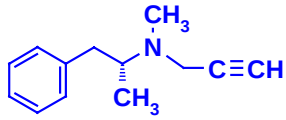
benserazide

brain ↓



dopamine

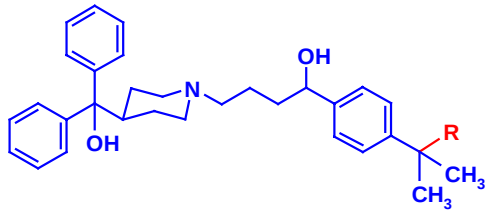
⫽→ inactive metabolites



(R)-(-)-selegiline

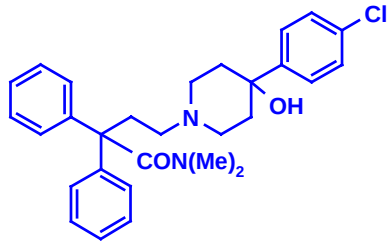
Avoidance of CNS Effects by Active Efflux

Terfenadine, R = CH_3
lipophilic H_1 antagonist
(no sedative side effect, due to active elimination by drug transporter)

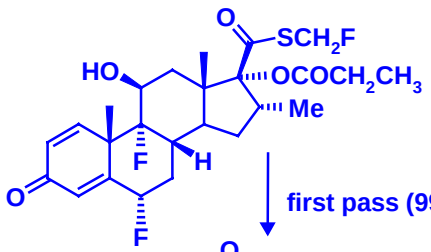


Fexofenadine, R = COOH
active terfenadine metabolite

Loperamide
antidiarrhoicum
(opiate agonist without CNS activity)



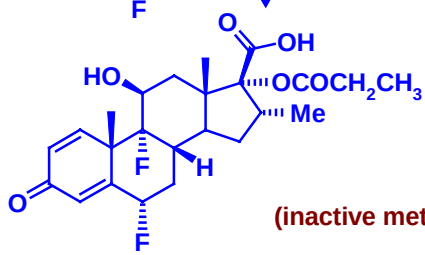
Soft Drugs: Corticosteroid Esters



fluticasone propionate
(Flonase; Advair, GSK)

(inhalation; topically active in asthma treatment)

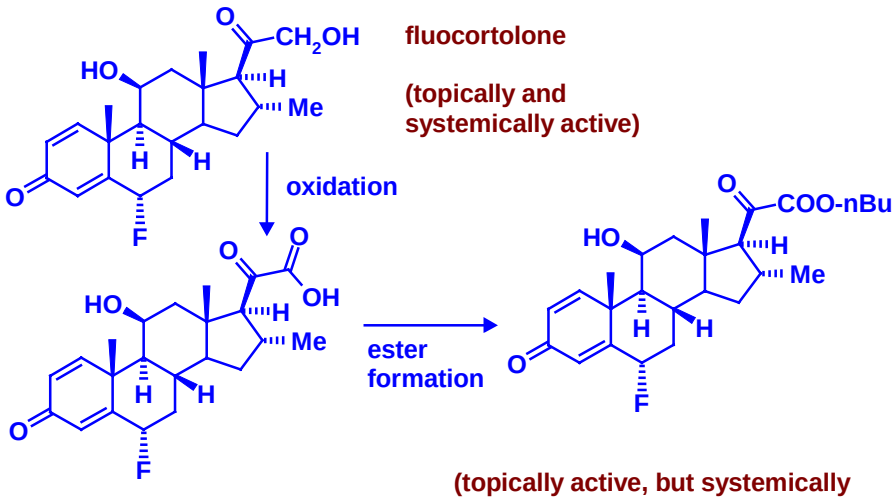
first pass (99%)



(inactive metabolite)

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

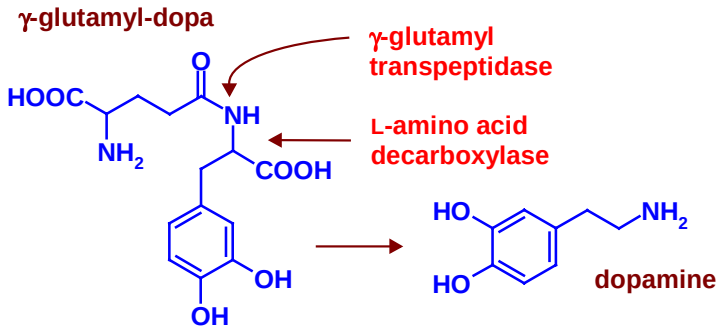
Soft Drugs: Corticosteroid Esters



(topically and systemically inactive)

(topically active, but systemically inactive, due to rapid hydrolysis after dermal absorption)

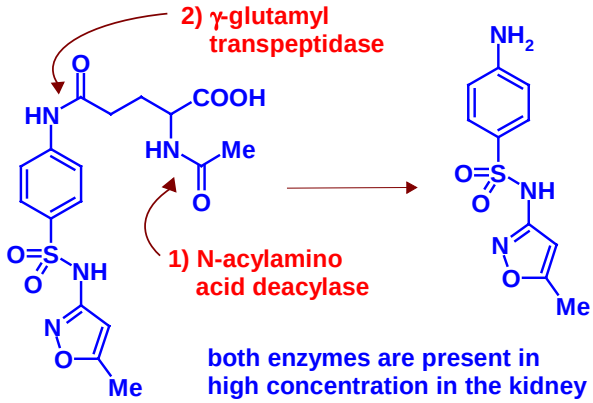
Kidney-Selective Vasodilation



γ-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)

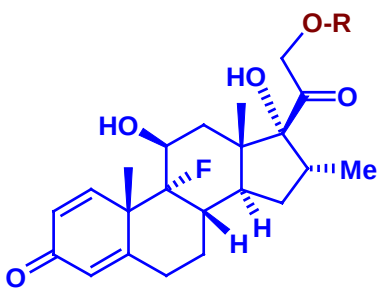
Kidney-Selective Release of the Antiinfective Sulfonamide Sulfamethoxazole



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

Hugo Kubinyi, www.kubinyi.de

Colon-Selective Delivery of Corticosteroids in Inflammatory Bowel Disease

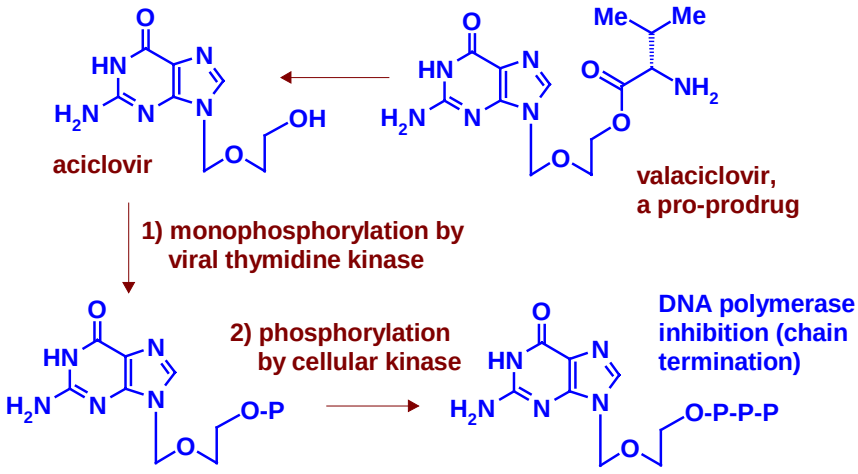


R = H, Dexamethasone
oral dose almost exclusively absorbed in the intestine, only about 1% reach the cecum

R = glucose, Dexamethasone-21β-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



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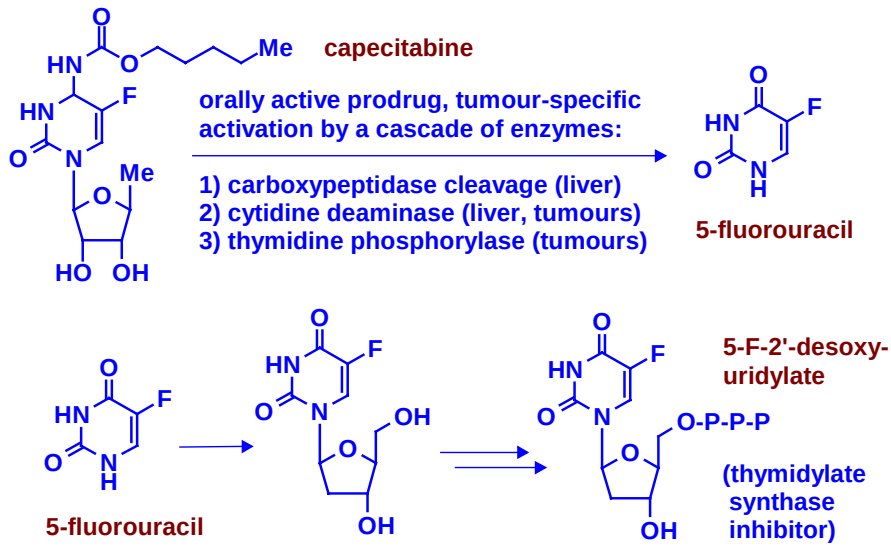
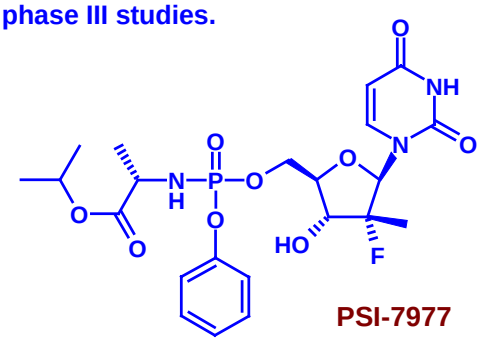
Tumor Cell-Specific Trojan Horses



Promising Prodrugs Are Expensive

In 2012, Gilead Sciences was going to pay 11 billion US-$ for Pharmasset, a company with only 82 employees and no product in the market. However, they have PSI 7977 in early clinical phase III studies.



PSI-7977

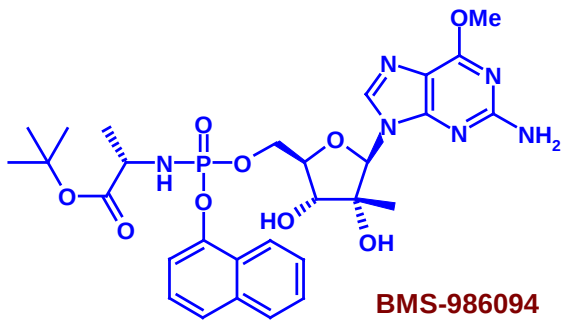
tested in combination with Ribavirin, as the first oral treatment for hepatitis C.

M. J. Sofia et al., J. Med. Chem. 53, 7202-7218 (2010); Chem. & Eng. News, November 28, 2011, p. 8.

Hugo Kubinyi, www.kubinyi.de

Why Drugs Are So Expensive

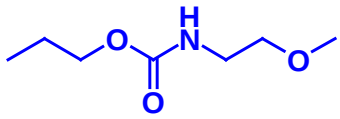
In January 2012, Bristol-Myers Squibb acquired Inhibitex for $ 2.5 billion, to get access to an NS5b inhibitor for the potential treatment of hepatitis C. Because of a heart failure-associated death case in one patient and hospitalization of eight others, phase II clinical trials were terminated August 01, 2012.

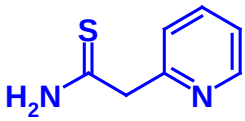


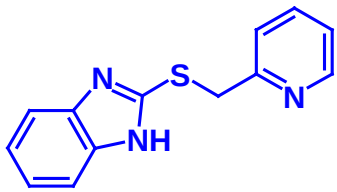
BMS-986094

Chem. & Eng. News, Aug. 13, 2012, p. 8, and Sept. 03, 2012, p. 10.

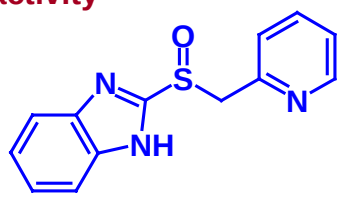
Omeprazole: A Cell-Specific Anti-Ulcer Agent





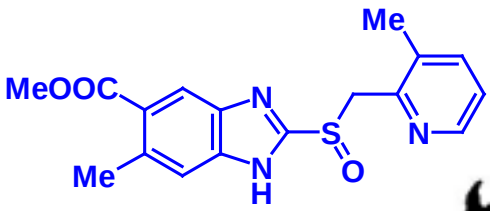


- 1966: Local anesthetics reduce gastric secretion (Hässle)
- 1966-1972: First lead
- 1972-1979: New lead pyridyl-acetamide (from screening of antiviral compounds)
- Active analogs; metabolite with higher antisecretory activity



Hugo Kubinyi, www.kubinyi.de

Omeprazole Analog: Toxic or not Toxic?



Picoprazole, 1976
preclinical candidate

breeding dog
Fabian

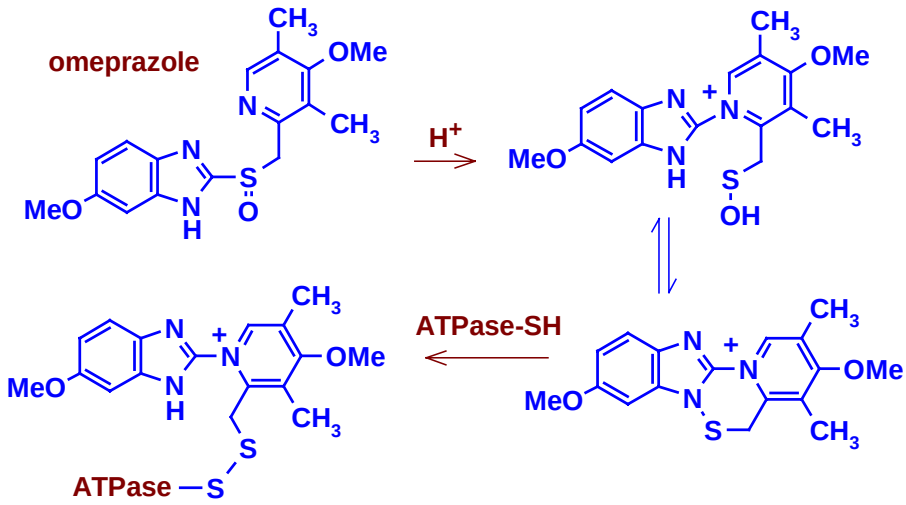
Tox study:

vasculitis

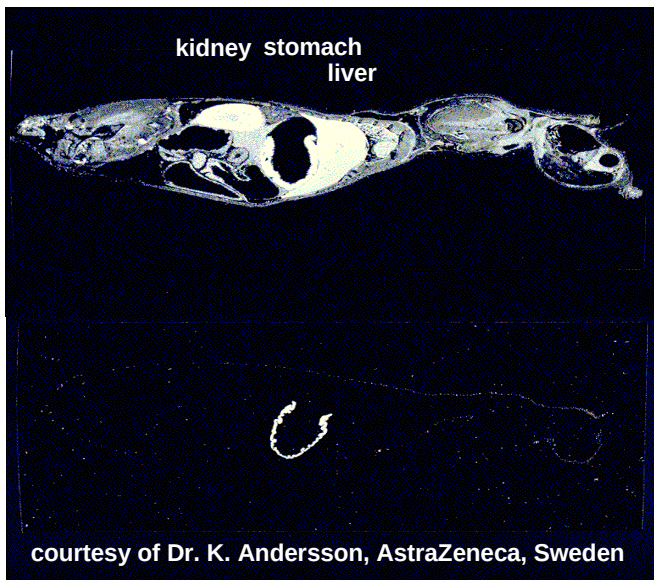
picoprazole group

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

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