Prodrugs

2018

Prodrug – compound that is metabolised into pharmacologically active drug

IUPAC definition:
Compound that undergoes biotransformation before exhibiting pharmacological effect.

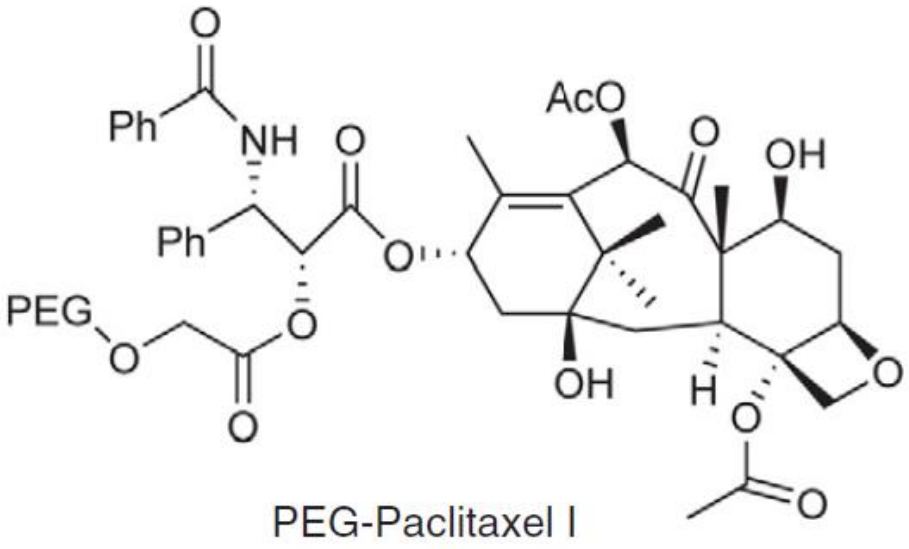
Drug development barriers that can be overcome by prodrugs

Barriers	Issues
Permeability	Not absorbed from GI tract because of polarity
	Low brain permeation
	Poor skin penetration
Solubility	Poor absorption and low oral bioavailability
	IV formulation cannot be developed
Metabolism	Vulnerable drug metabolized at absorption site
	Half-life is too short
	Sustained release is desired
Stability	Chemically unstable
	Better shelf life is needed
Transporter	Lack of specificity
	Selective delivery is desired
Safety	Intolerance/irritation
Pharmaceutics	Poor patient/doctor/nurse acceptance
	Bad taste or odor problems
	Painful injection
	Incompatibility (tablet desired but liquid is active)

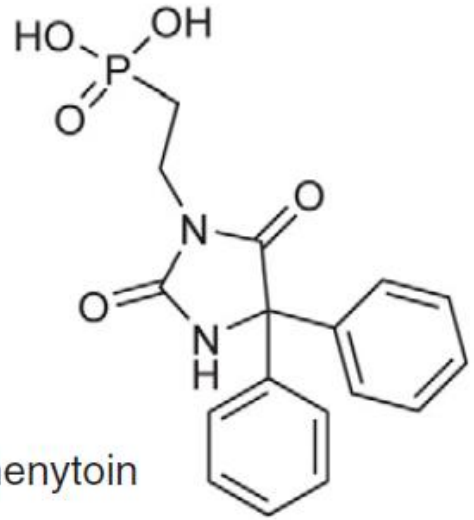
Improving solubility

Name	Solubility in water (mg/mL)
Clindamycin	0.2
Clindamycin-2-PO_4	150
Chloramphenicol	2.5
Succinate sodium	500
Metronidazole	10
N,*N*-dimethylglycinate	200
Phenytoin	0.02
Phosphate	142
Paclitaxel I	0.025
PEG-paclitaxel I	666
Celexicoxib	0.05
Parecoxib sodium	15

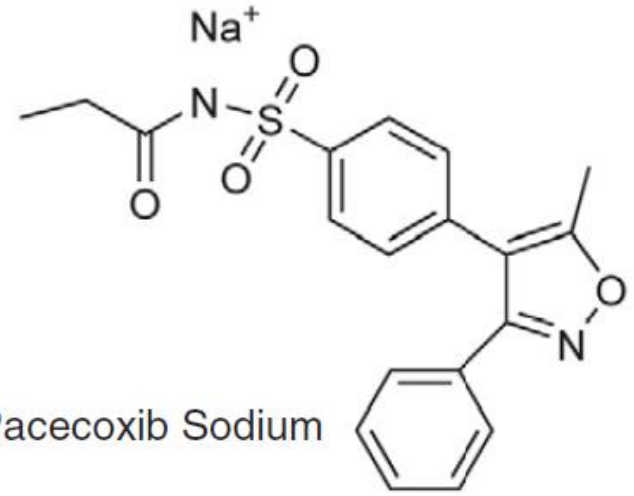
Improving solubility



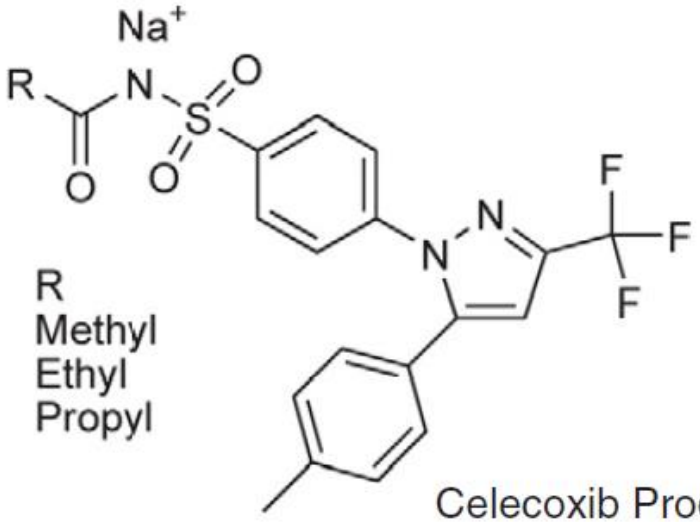
PEG-Paclitaxel I



Fosphenytoin



Pacecoxib Sodium

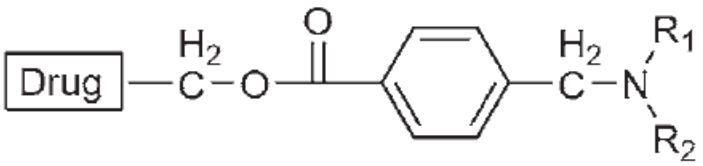


R
Methyl
Ethyl
Propyl

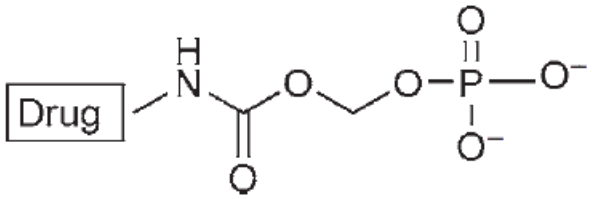
Celecoxib Prodrugs

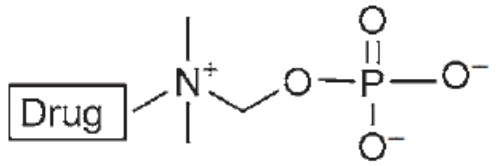
Improving solubility

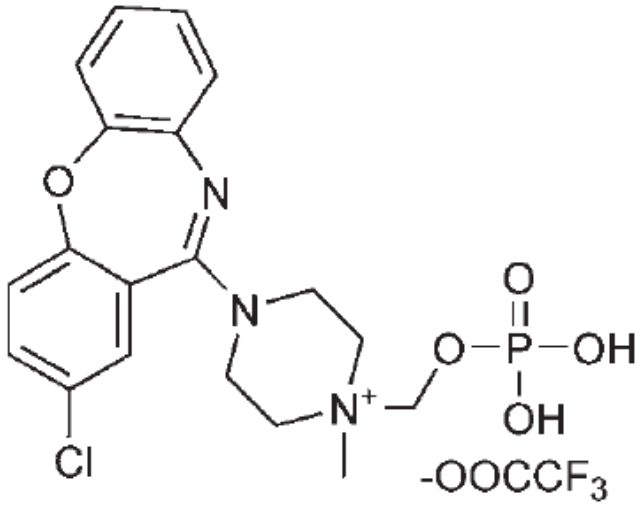
Amino-acid Type

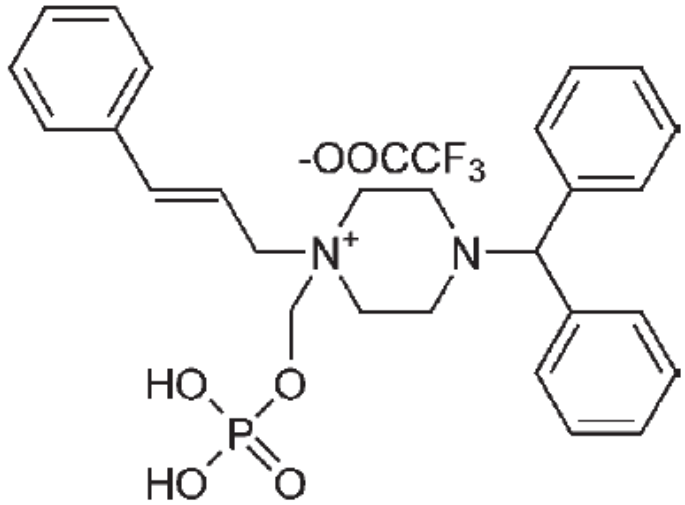


Phosphate Type









Loxapine

$pKa_2 = 7.5$

Free base solubility = 13 μg/mL

IM: 70% PG / 5% Tween 80

Cinnarizine

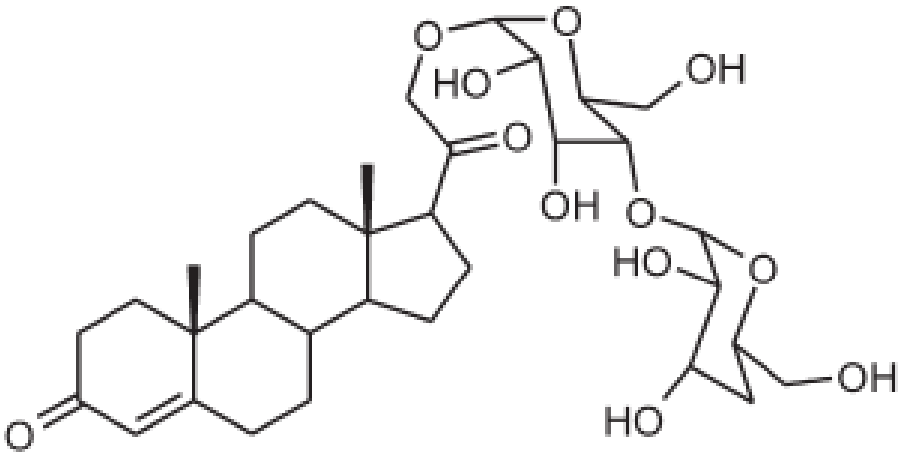
pKa = 1.95, 7.47

poor solubility

erratic oral bioavailability

Improving solubility

glucosides



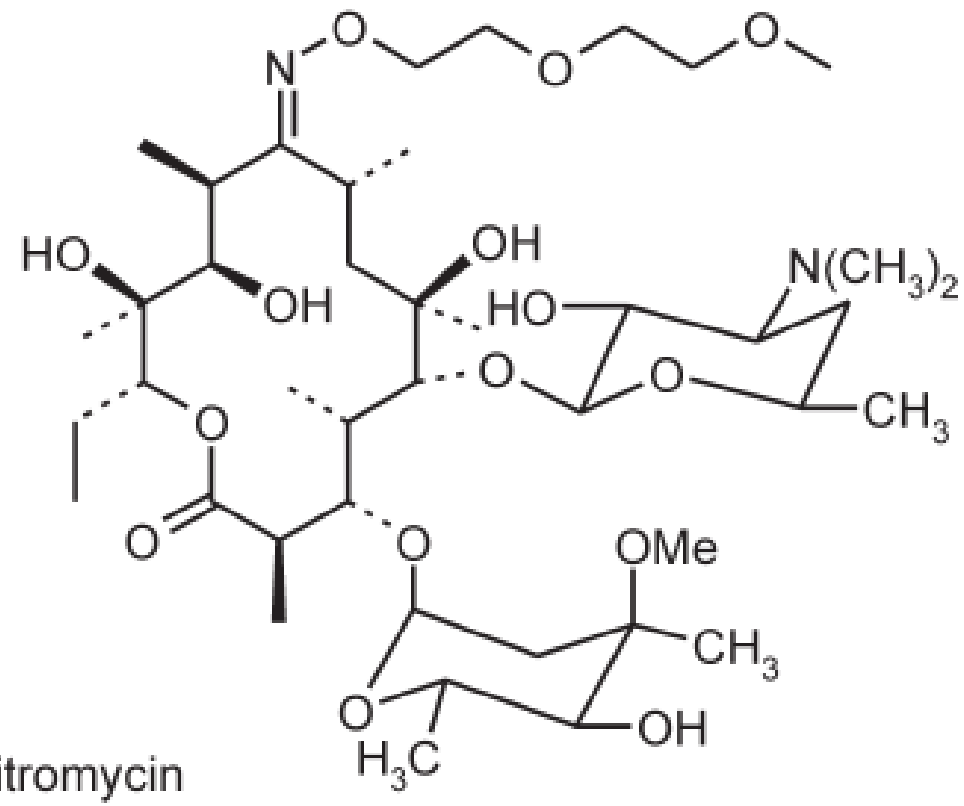
deoxycorticosterone β-maltoside

Deoxycorticosterone glycoside	Solubility in water
Glucoside	1.2‰
Galactoside	2.2‰
Lactoside	3.4‰
Lactosidoglucoside	Unlimited

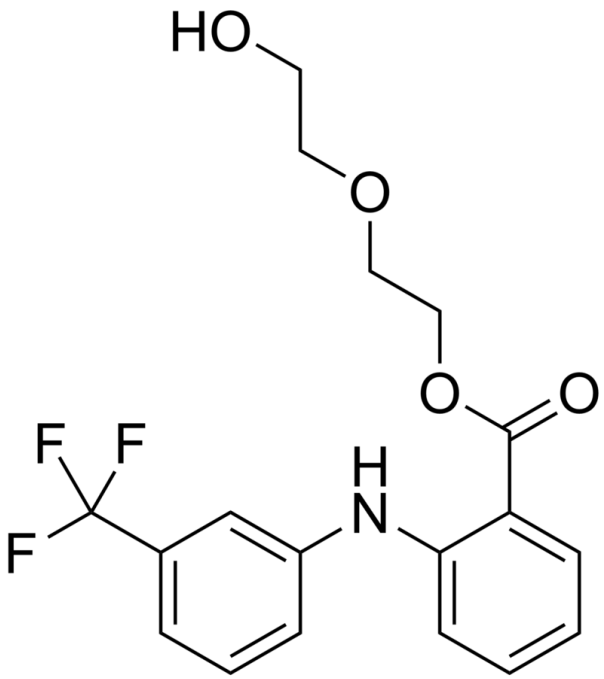
Improving solubility

Polyethyleneglycol

antibiotic roxithromycin, topic NSA Etofenamate



roxitromycin



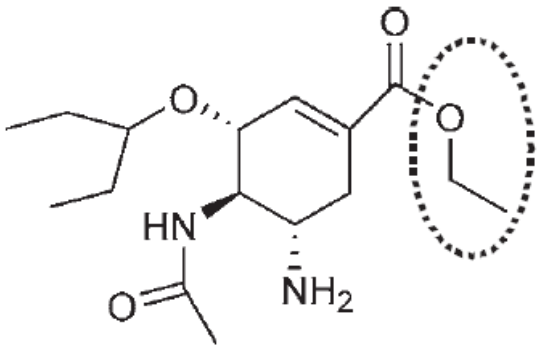
Improving permeability

Ideal ester/amide prodrug properties:

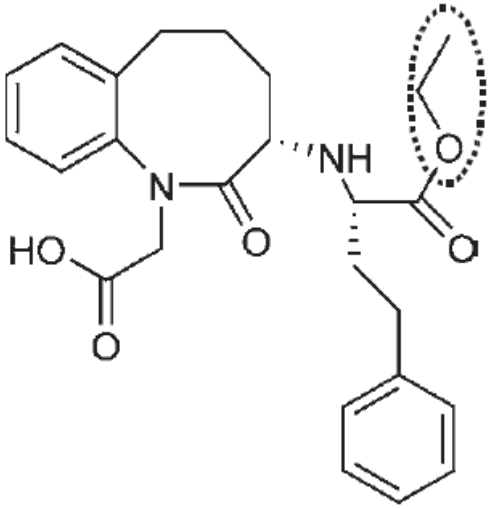
- Weak or no activity against any pharmacological target
- Good chemical stability at physiological pHs
- Sufficient aqueous solubility
- High passive permeability
- Resistance to hydrolysis during absorption
- Hydrolyzed to parent rapidly and quantitatively after absorption
- The released pro-moiety has no toxicity or unwanted pharmacological effects

Improving permeability

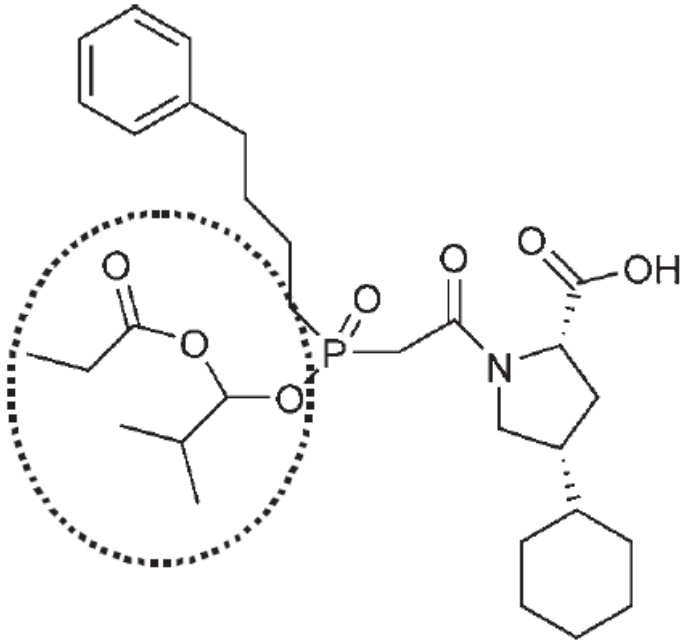
carboxylic acid esters



Oseltamivir, ethyl ester



Benazepril, ethyl ester

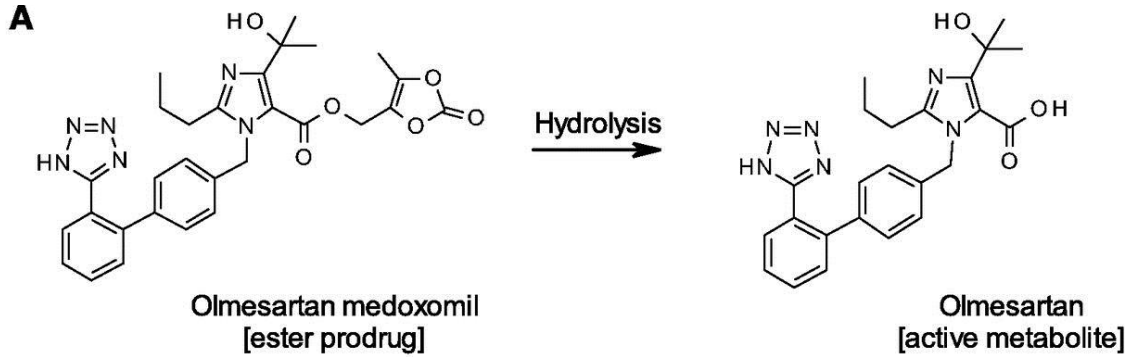


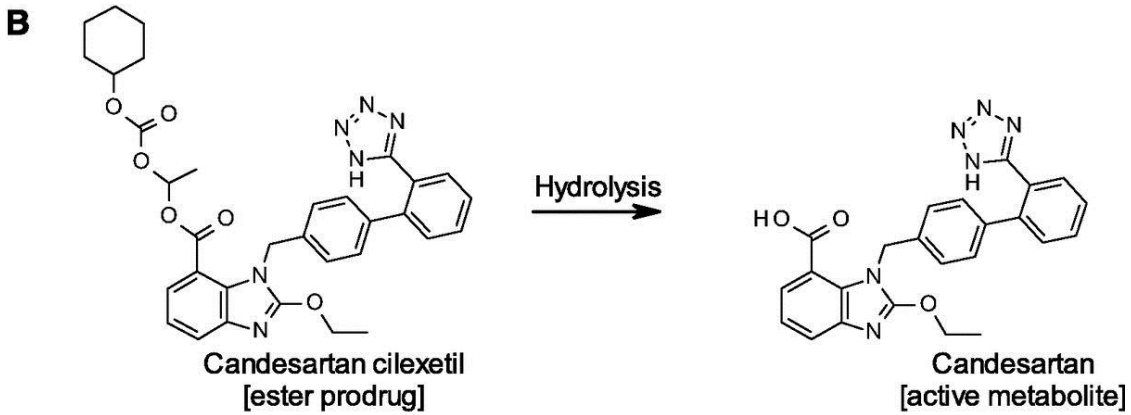
Fosinopril, double ester

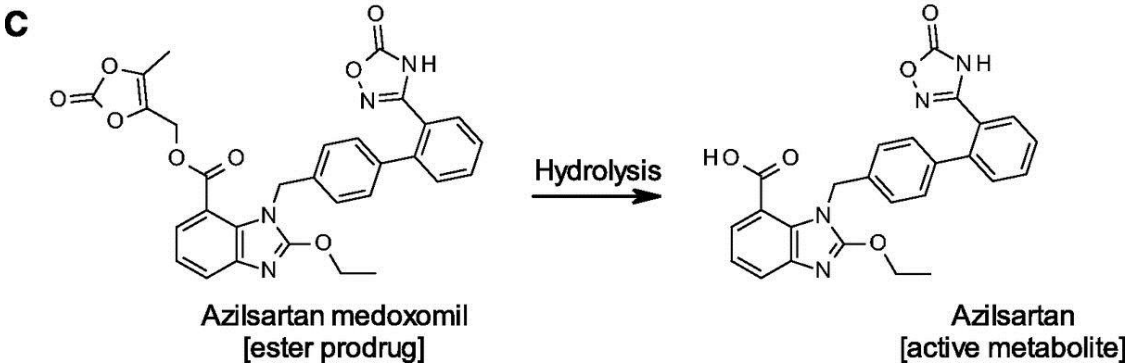
double esters are cleavaged more rapidly

Improving permeability

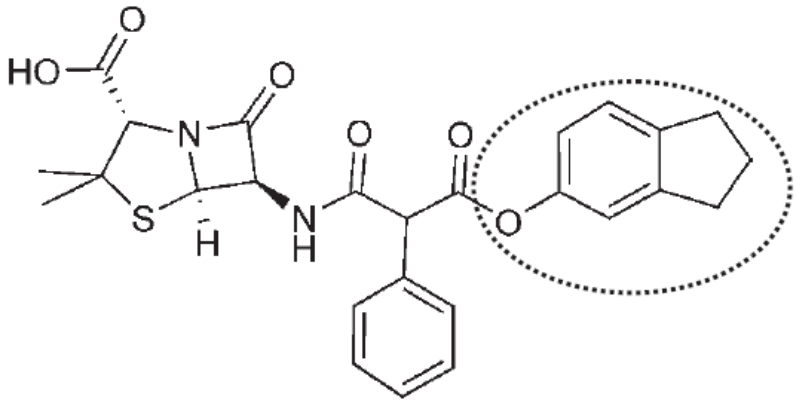
carboxylic acid esters - sartans



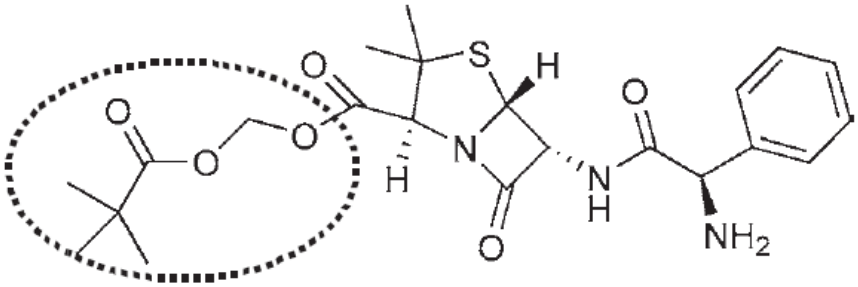




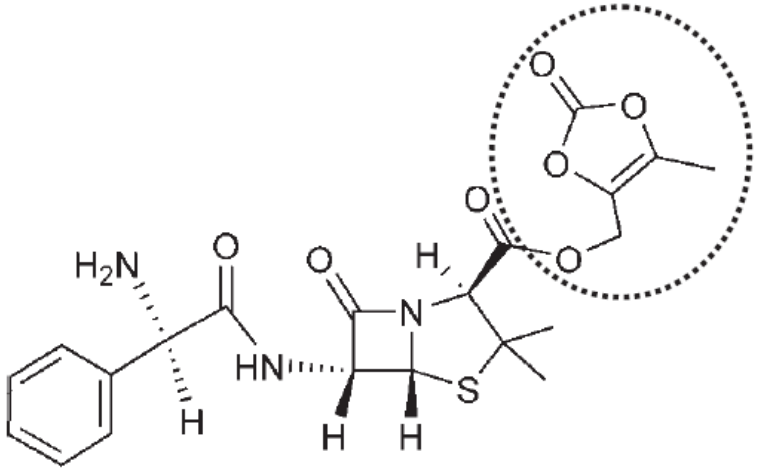
Improving permeability
carboxylic acid esters



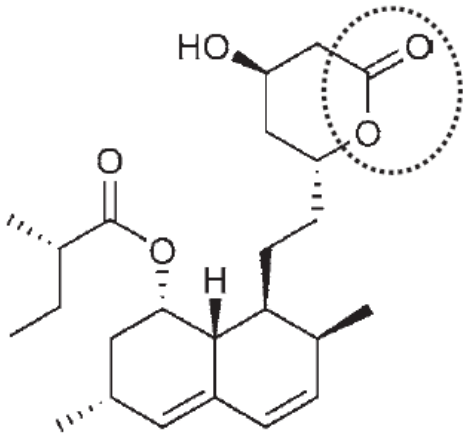
Carbinicillin indanyl ester, aryl ester



Pivampicillin, double ester



Lenampicillin, cyclic carbonate

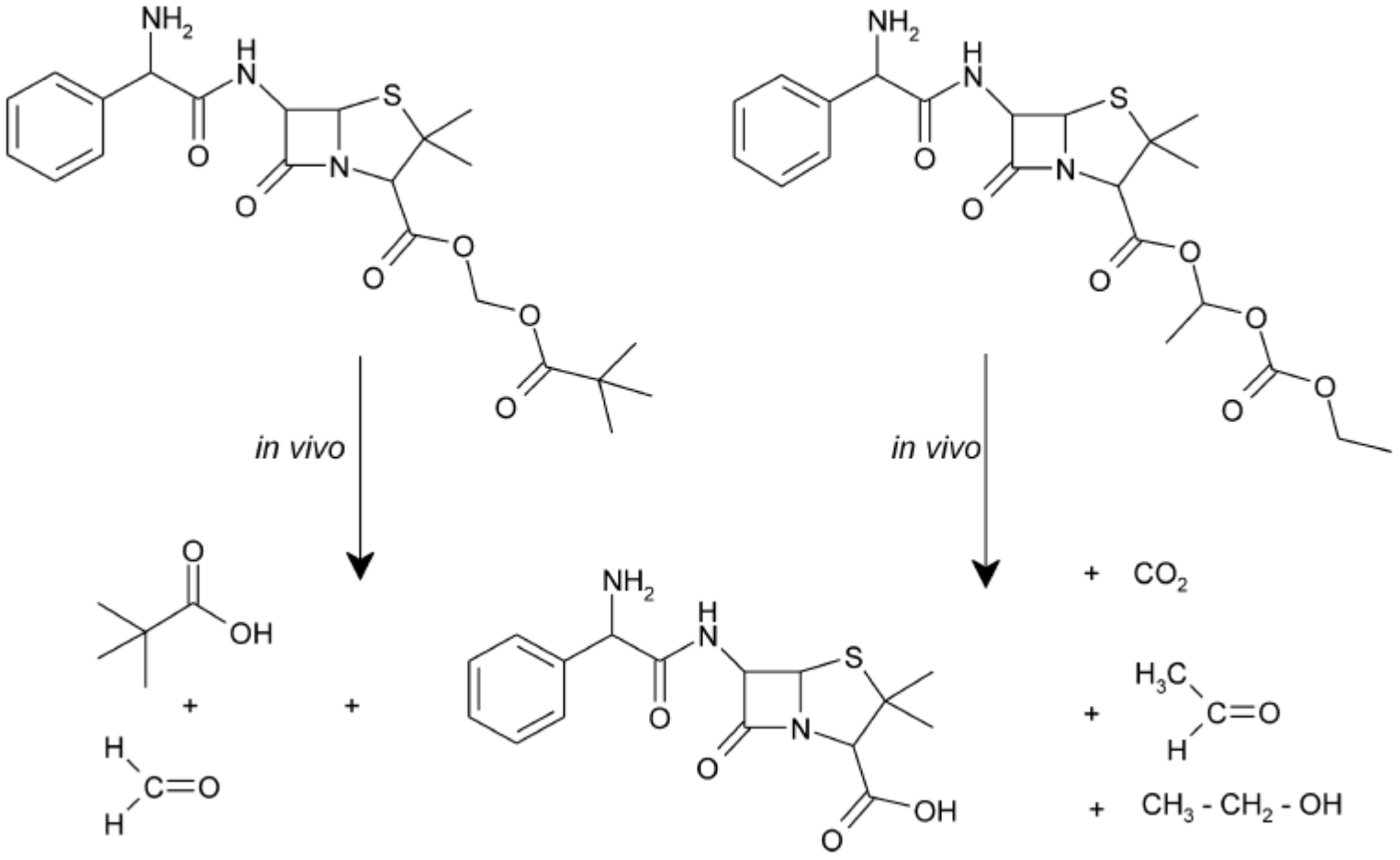


Lovastatin, lactone

Improving permeability

carboxylic acid esters – bacampicillin, pivampicillin

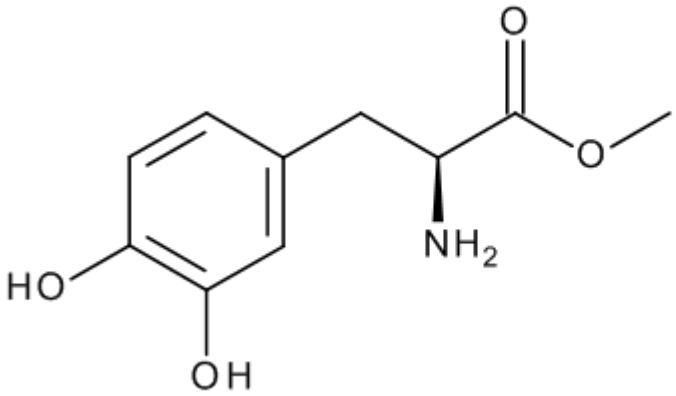
98-99% peroral absorption compared to 40% of ampicillin



Improving permeability

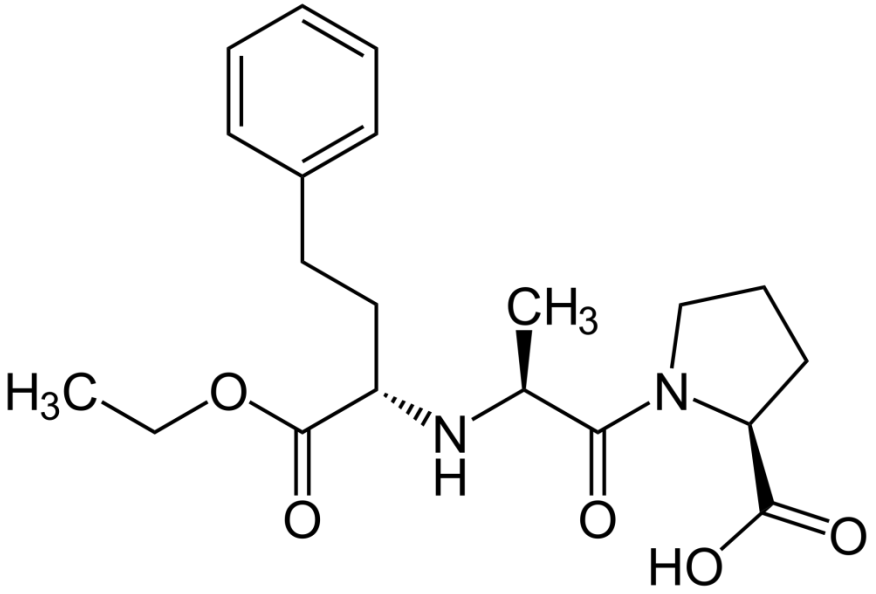
carboxylic acid esters

levodopa methylester,



HCl

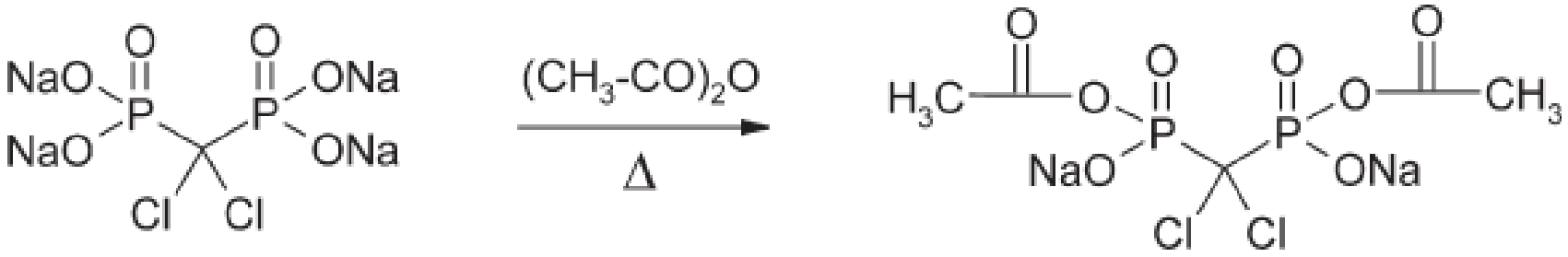
enenalapril = ethylester



Improving permeability

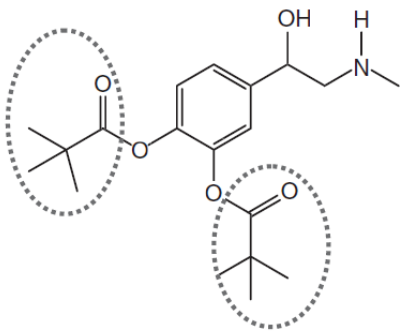
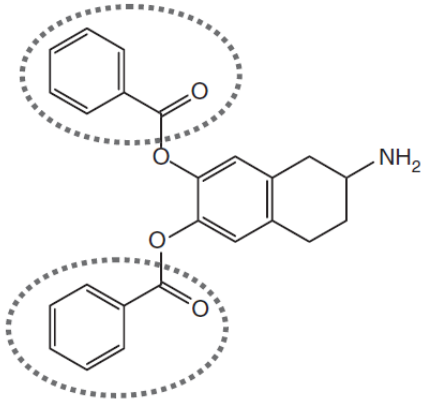
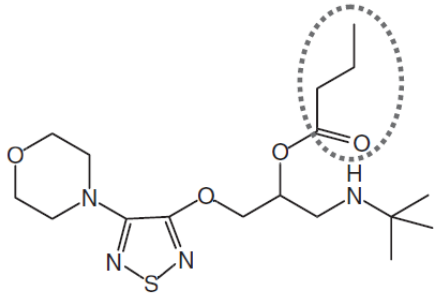
carboxylic acid anhydrides

clodronate anhydride



Improving permeability

Alcohol and phenol esters

Prodrugs	Limitations of parent	Benefits of prodrug
 Dipivaloyl-epinephrine	Log P = –0.04 Low corneal penetration	Log P = 2.08 Four- to six-fold increase in corneal penetration
 Dibenzoyl-Amino-Dihydroxy-tetrahydronaphthalene (ADTN)	No CNS penetration	Reaches CNS
 Butyryl-Timolol	Low oral exposure	High oral exposure Enable IV formulation

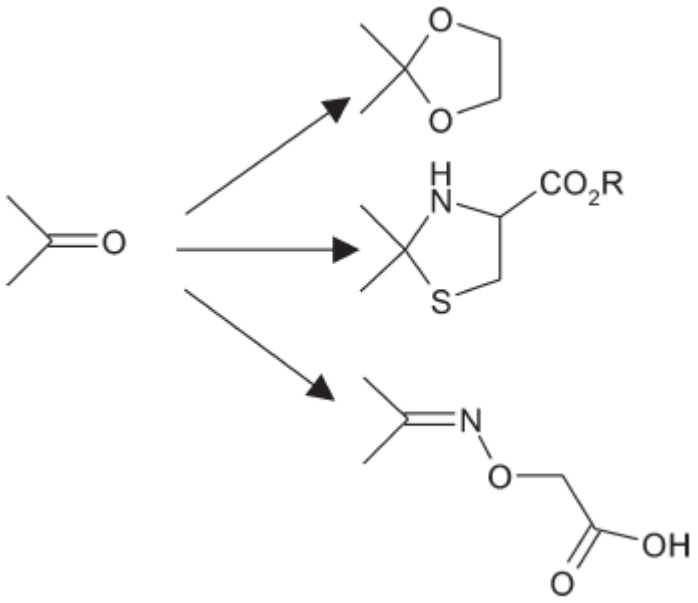
Improving permeability

aldehydes and ketones:

ethylene ketals

spirothiazolidines

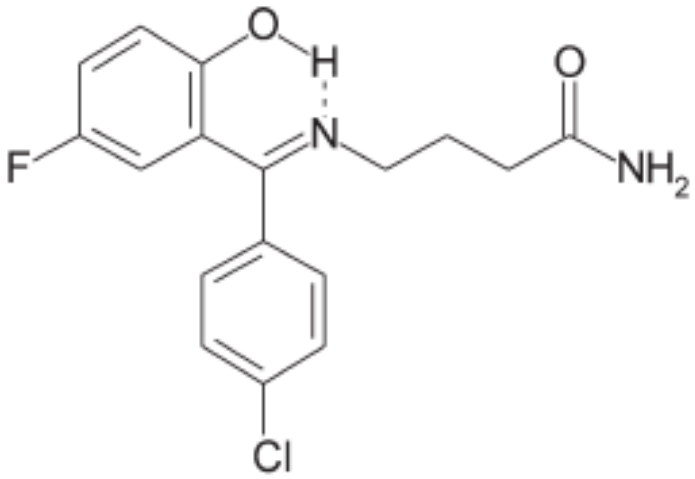
oxime derivatives



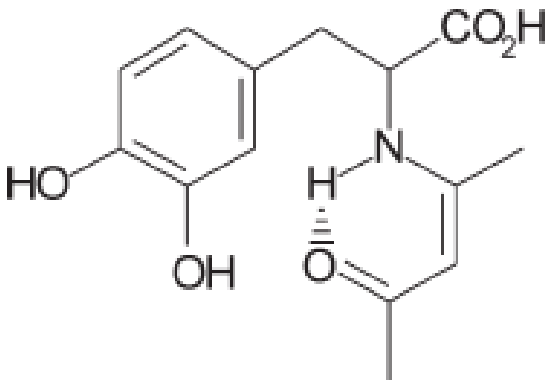
Improving permeability

Nitrogen containing compounds

imides, peptides



progabide

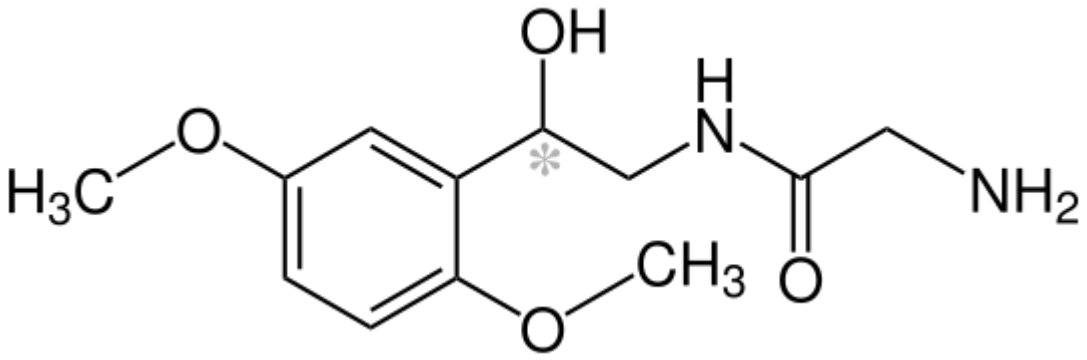


DOPA enamine

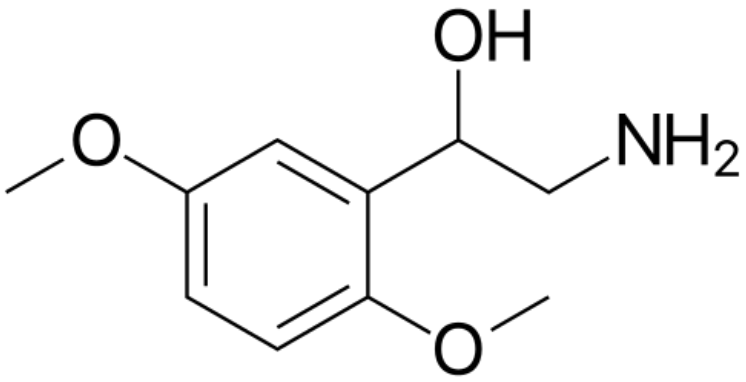
Improving permeability

Nitrogen containing compounds

peptide prodrug of alpha adrenergic agonist Midodrine



desglymidodrine = active metabolite

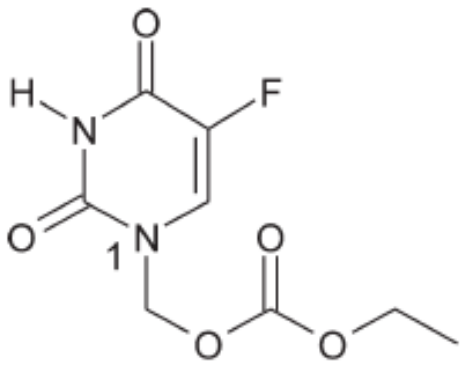


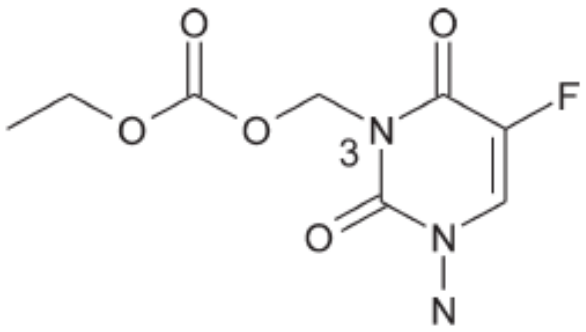
Improving permeability

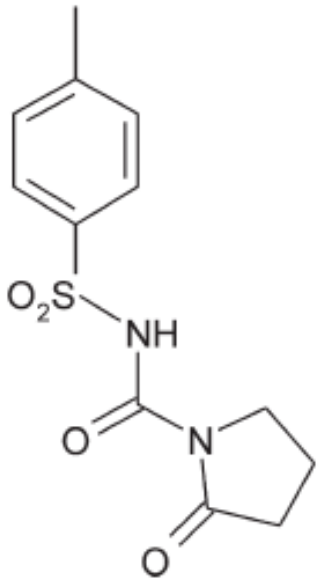
Nitrogen containing compounds

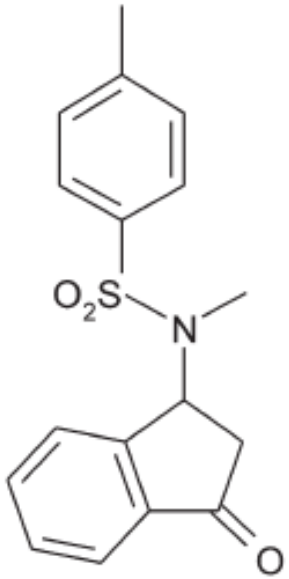
acidic nitrogen

- unstable amides of fluorouracil and sulfonamides



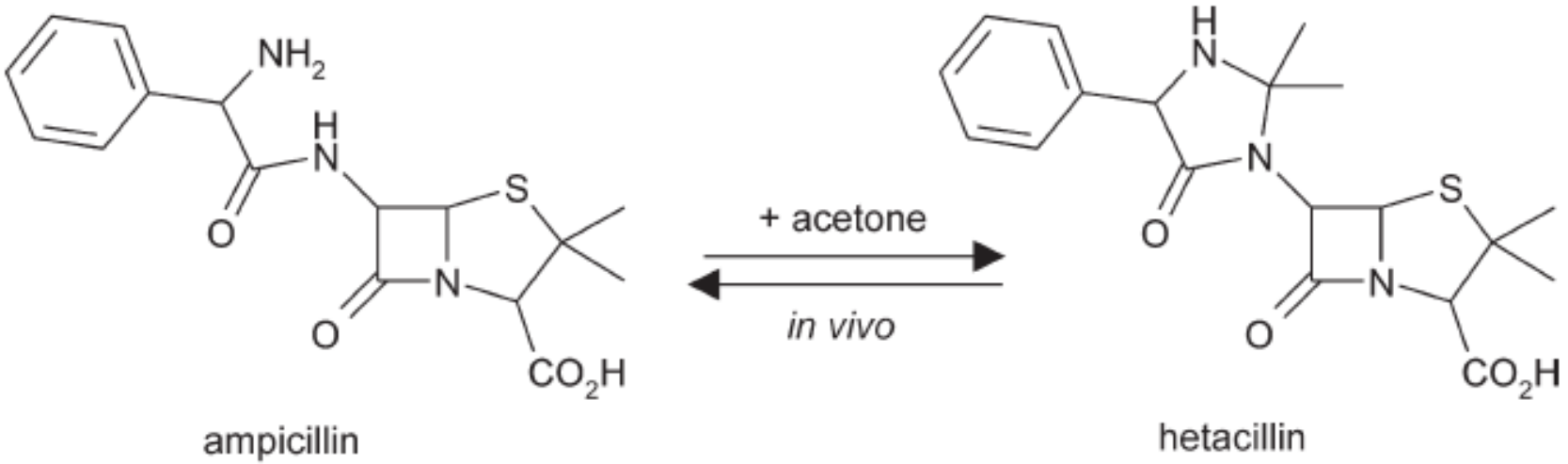






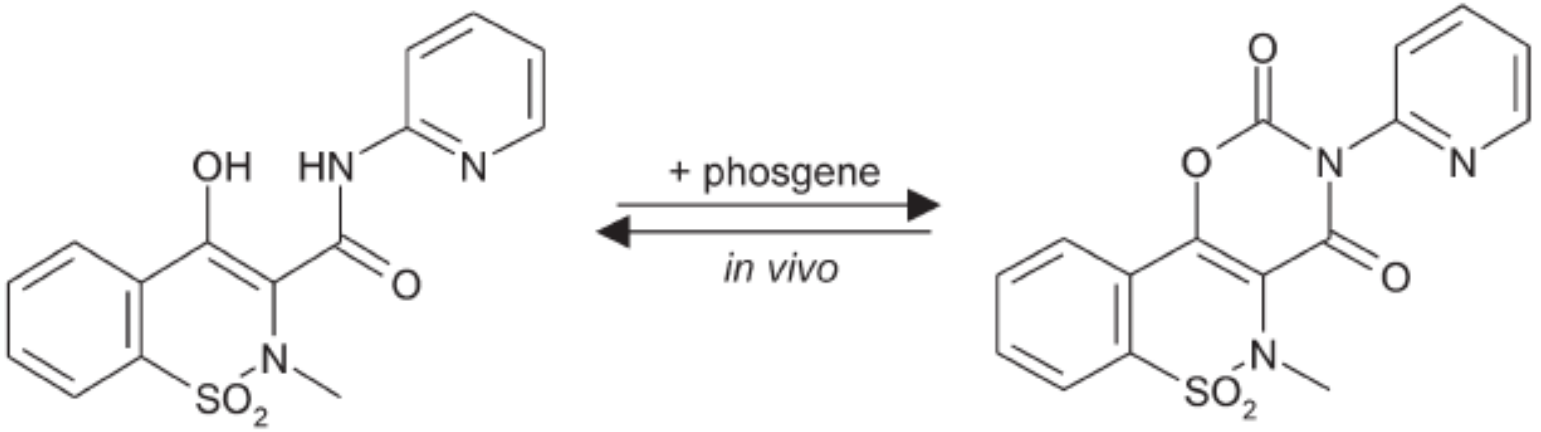
Improving permeability

cyclic protection of neighbouring functional groups



ampicillin

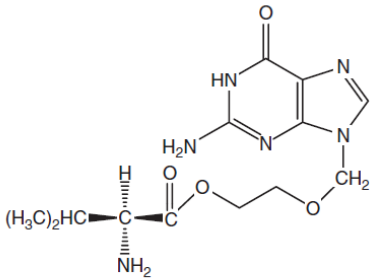
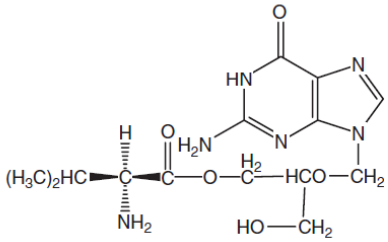
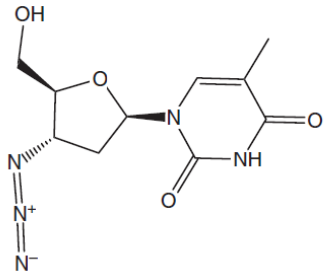
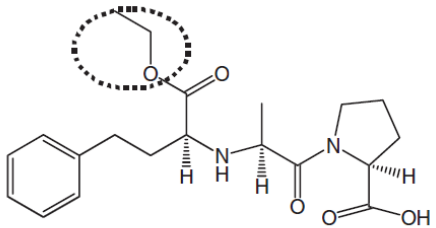
hetacillin



piroxicam

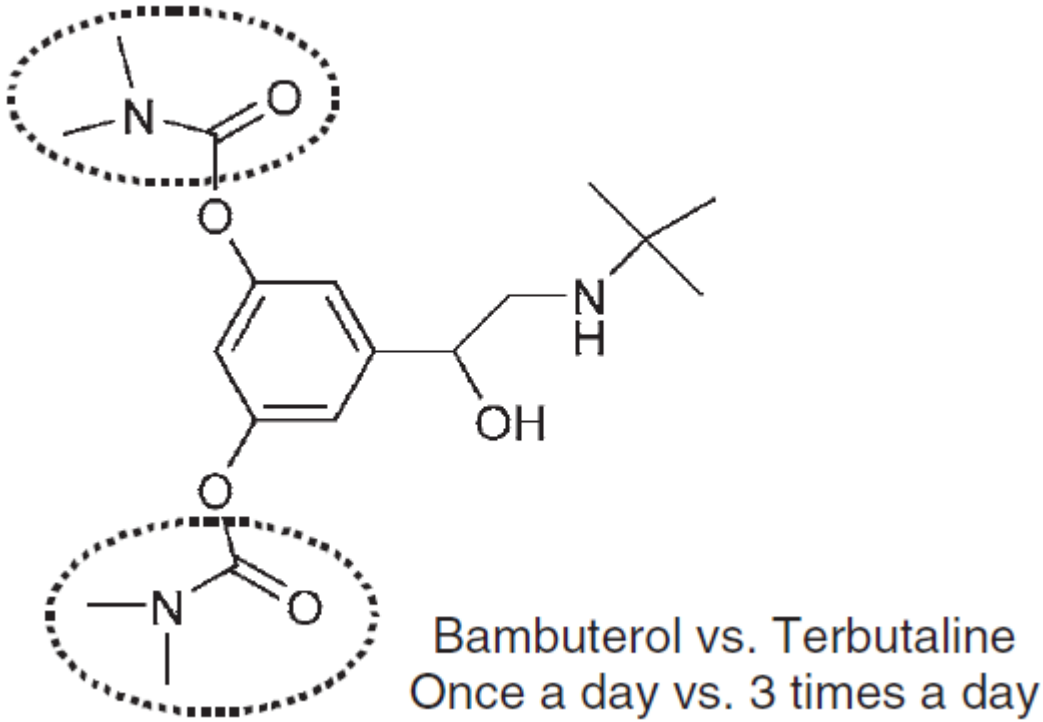
droxicam

Improving permeability
targeting transporters

Prodrugs	Transporters	Benefits of prodrug
 Valacyclovir (Valtrex)	PEPT1 and PEPT2[10]	Oral bioavailability Three- to five-fold higher than acyclovir
 Valganciclovir	PEPT1 and PEPT2[9]	Oral bioavailability Ten-fold higher than ganciclovir
 Zidovudine (AZT, Retrovir)	Nucleoside transporter[11]	Oral bioavailability 64%[14]
 Enalapril	PEPT1[6]	Oral bioavailability is 36%–44% due to increase in lipophilicity and transporter-mediated absorption. Oral bioavailability of diacid parent is 3%.

Prodrugs reducing metabolism

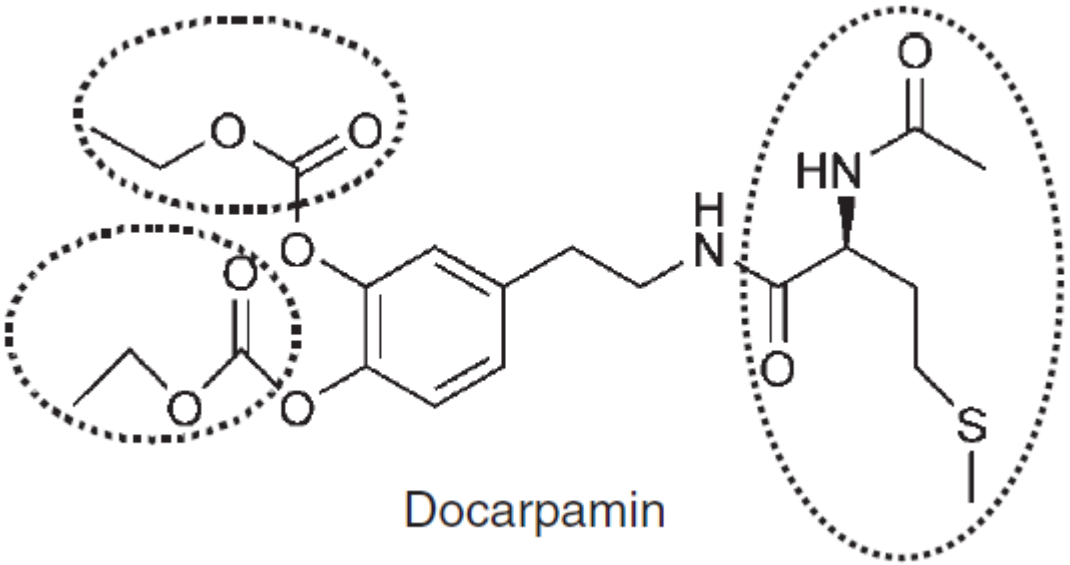
carbamates of bambuterol are slowly hydrolyzed to terbutaline



Bambuterol vs. Terbutaline
Once a day vs. 3 times a day

Prodrugs reducing metabolism

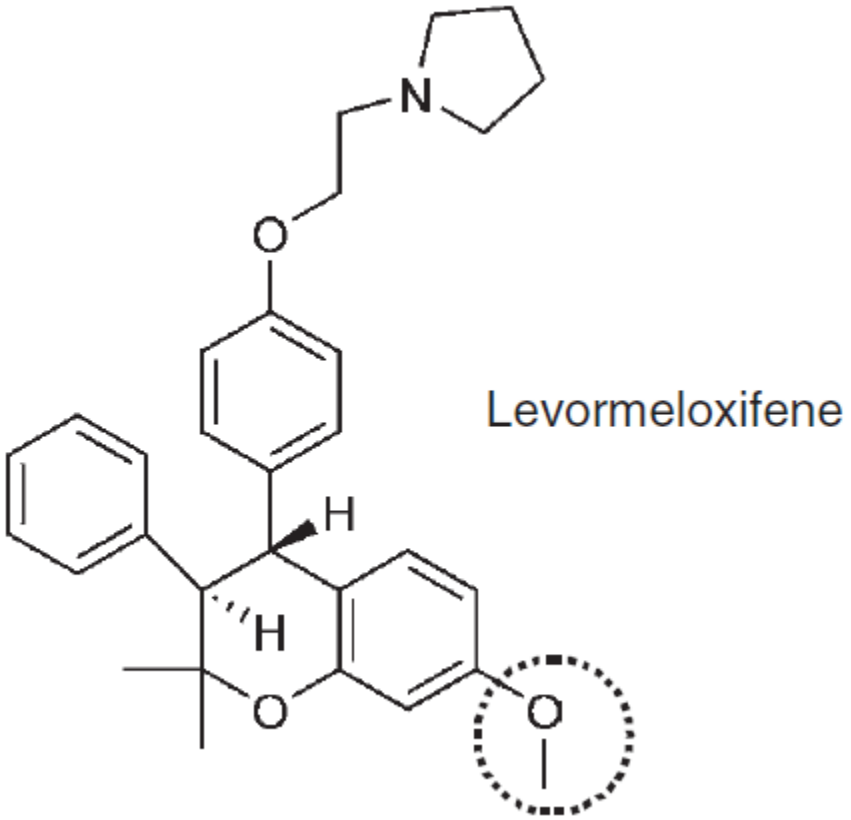
docarpamine – orally available dopamine supply activated in liver



Docarpamin

Prodrugs reducing metabolism

levormeloxifene is demetylated to active estrogen receptor modulator

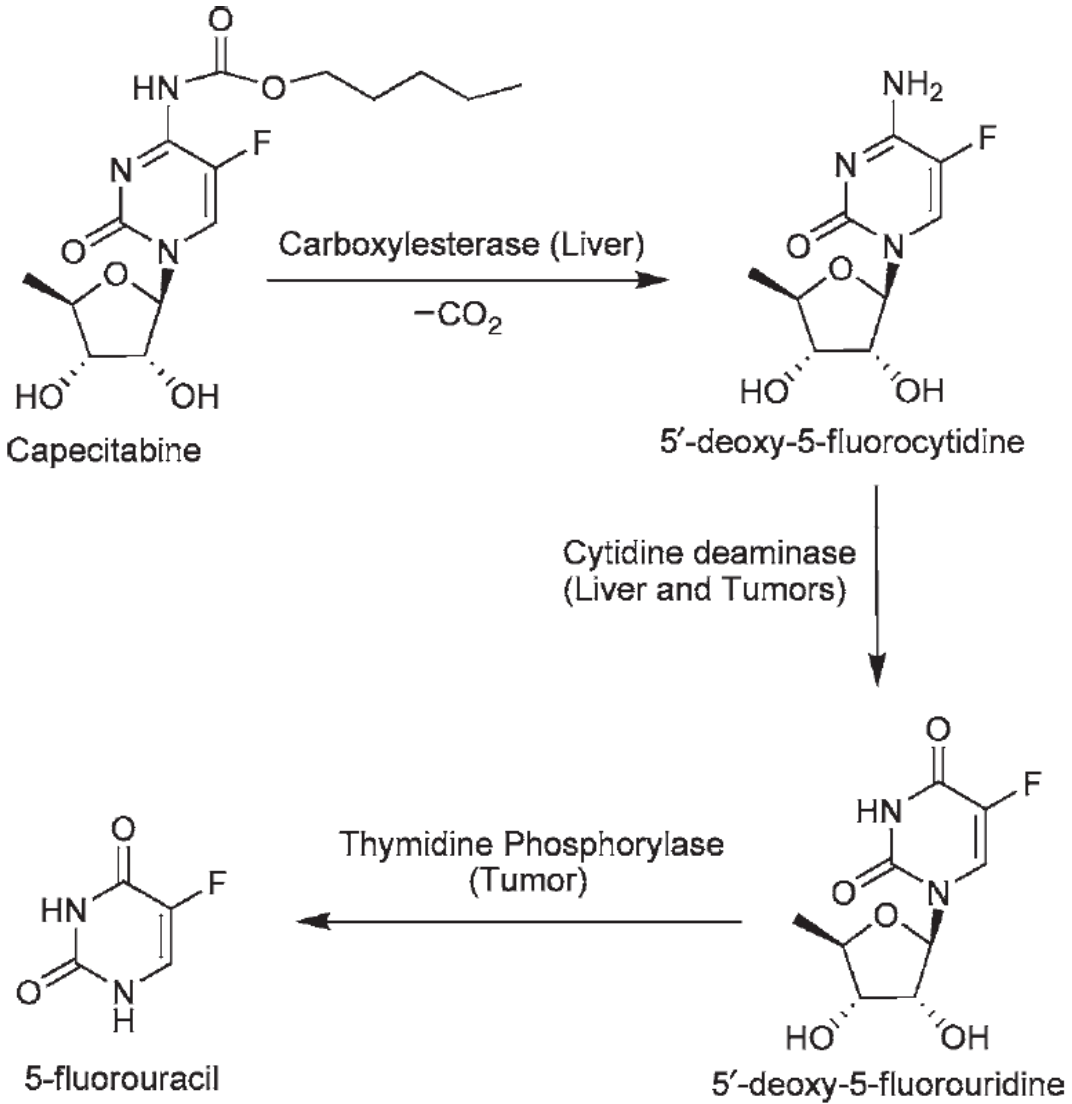


Levormeloxifene

Prodrugs targeting tissue

capecitabine predominantly metabolized in tumor cells

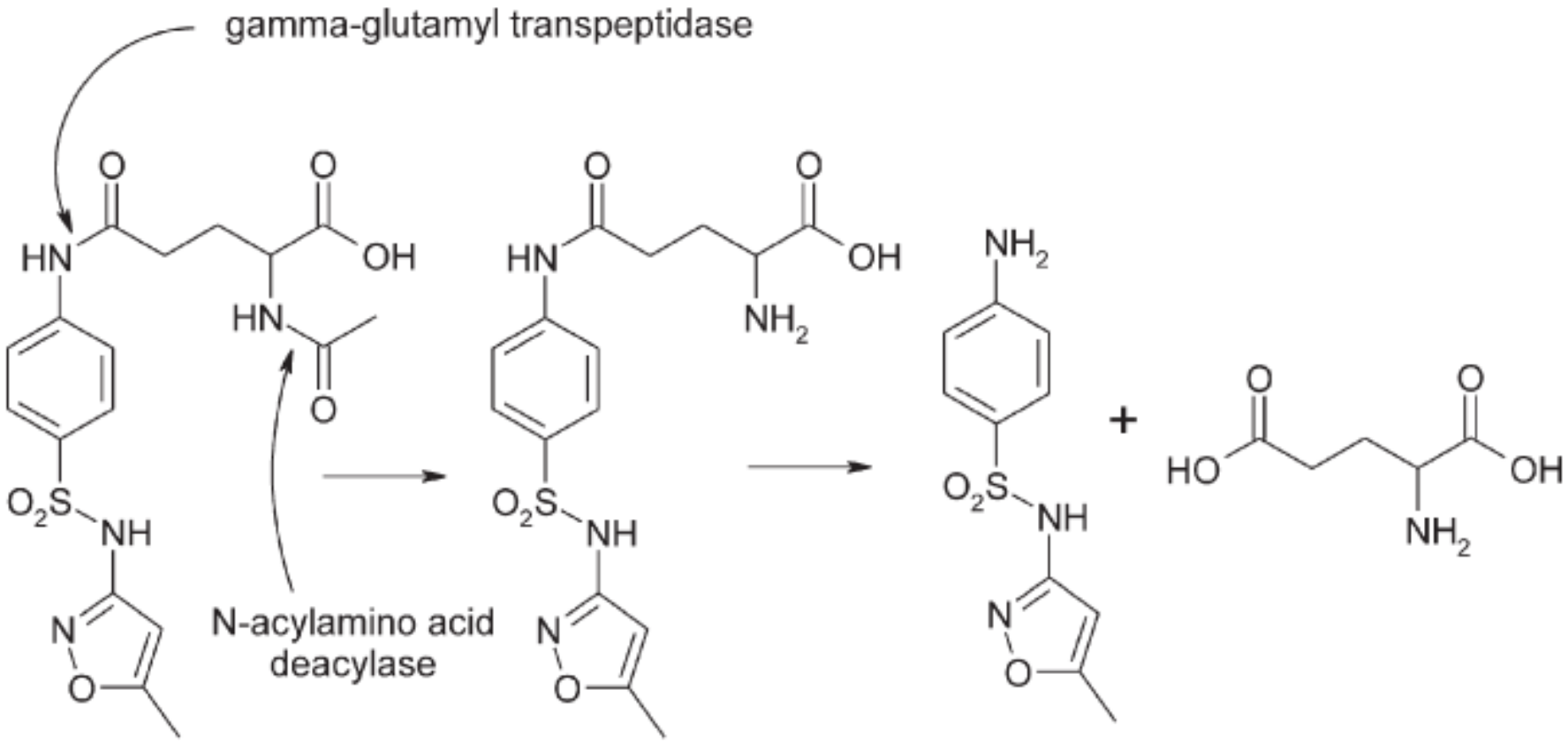
16x higher tumor concentration of 5-FU compared to plasma



Prodrugs targeting tissue

kidney-selective release of sulfamethoxazole

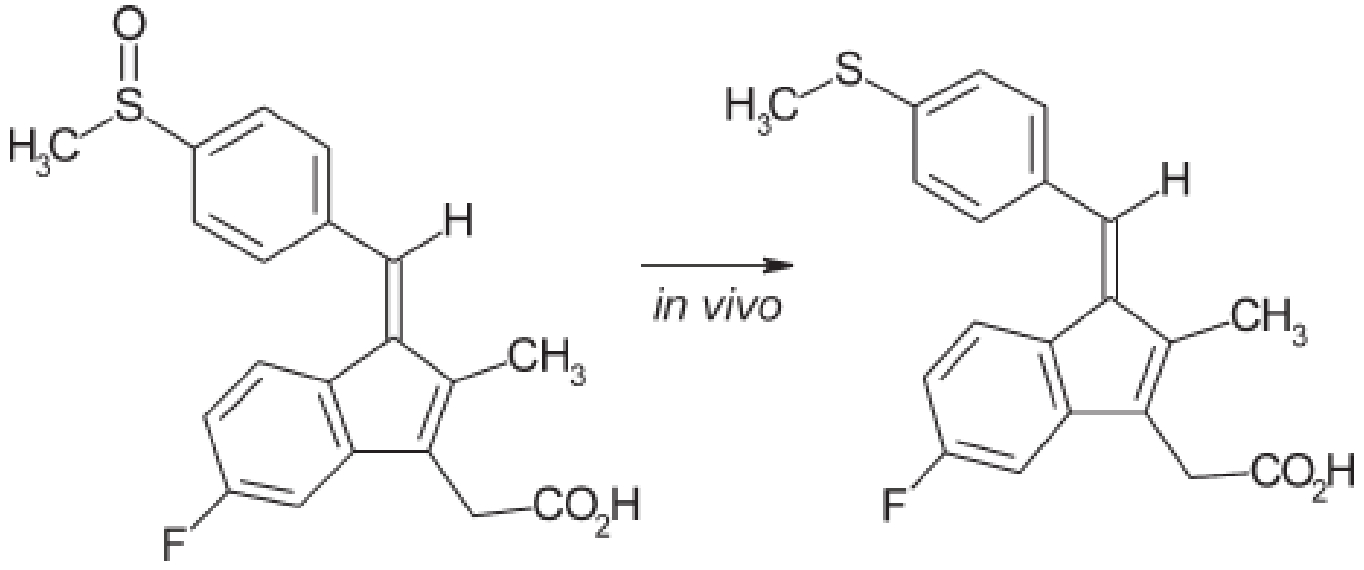
peptide selective cleavaged by kidney enzymes



Bioprecursors

inactive molecules metabolised to active drug of different structure

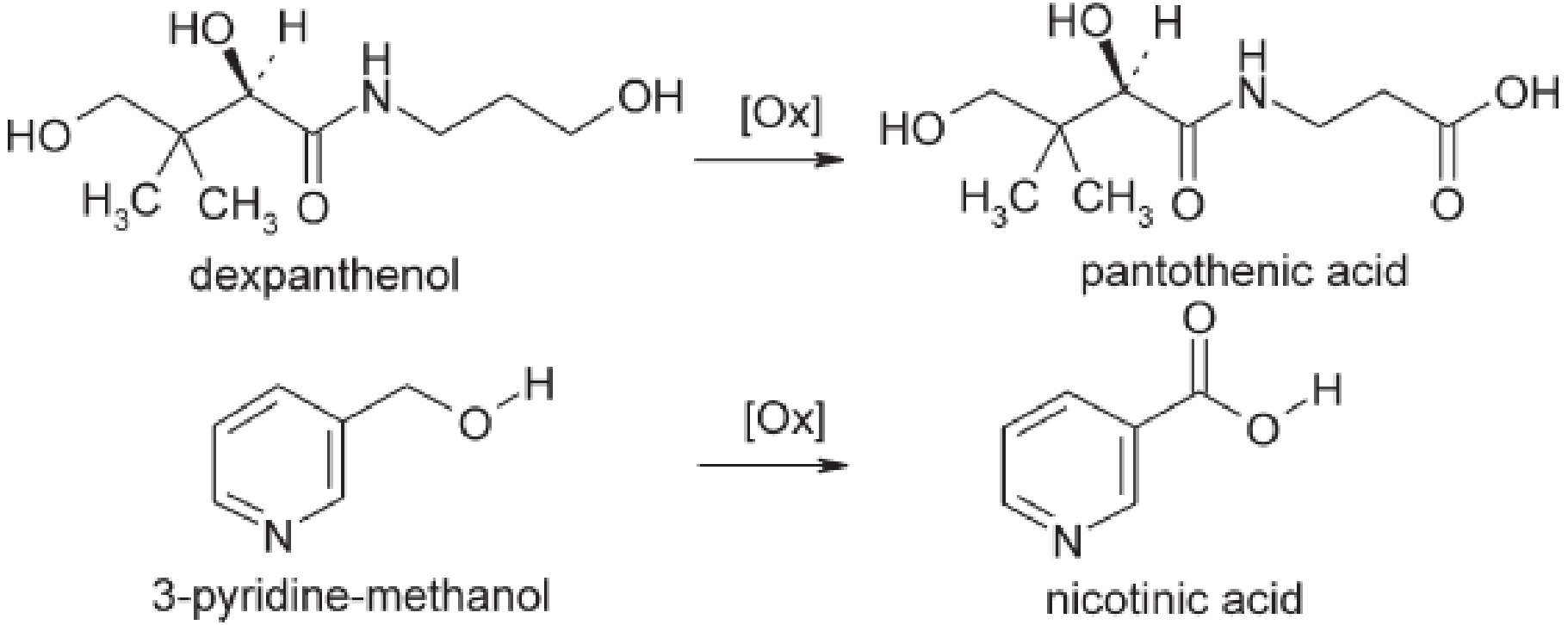
oxidative bioactivation of sulindac



Bioprecursors

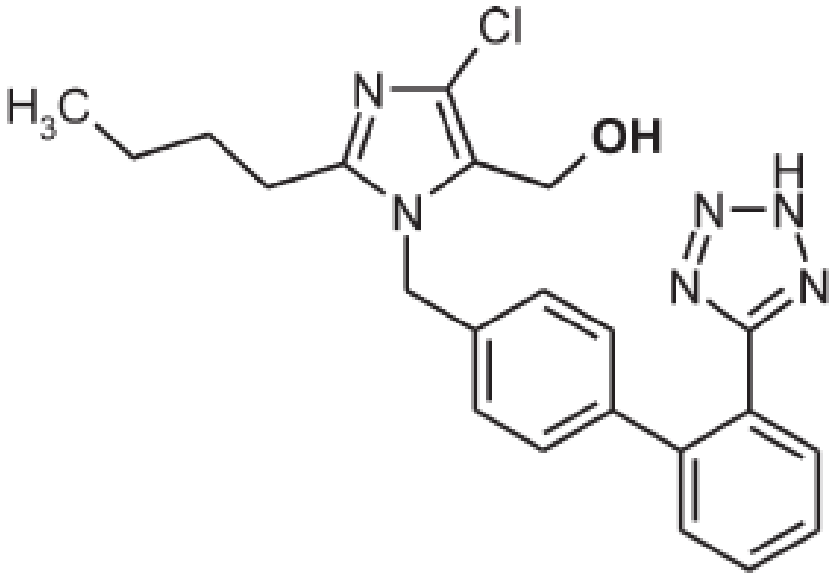
oxidative bioactivation of provitamines

provitamins are more stable and better orally absorbed

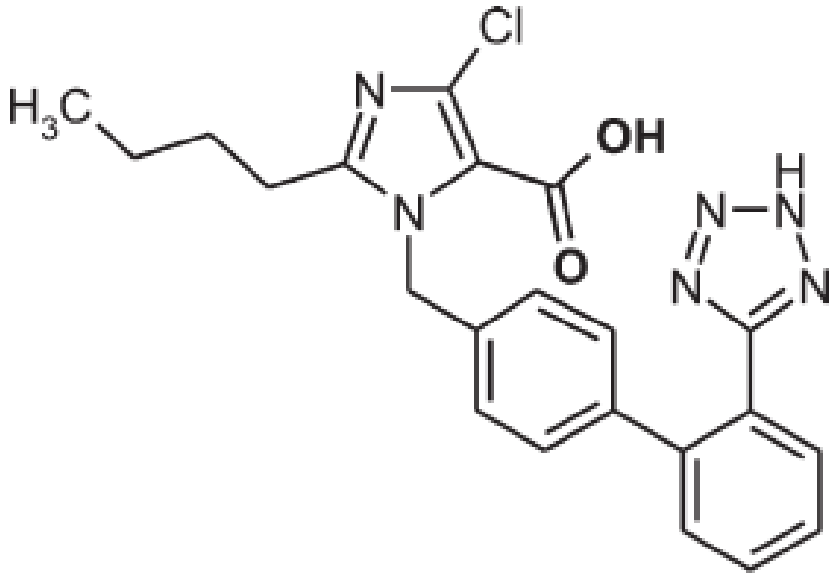


Bioprecursors

oxidative bioactivation of losartan



Lozartan

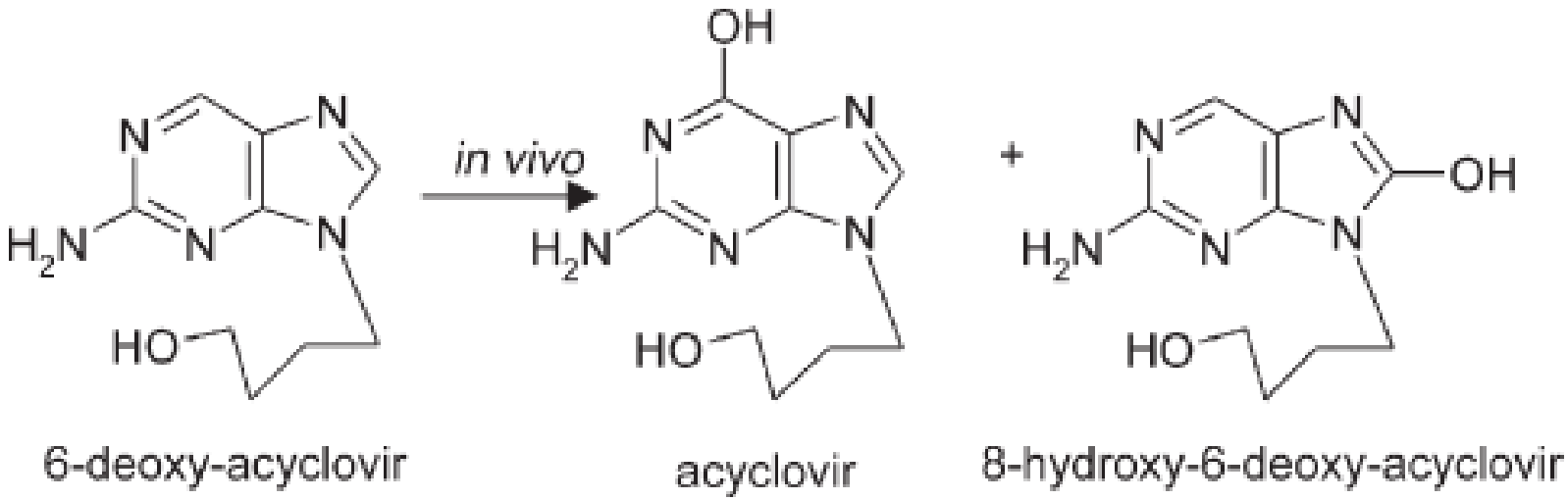


Active metabolite

Bioprecursors

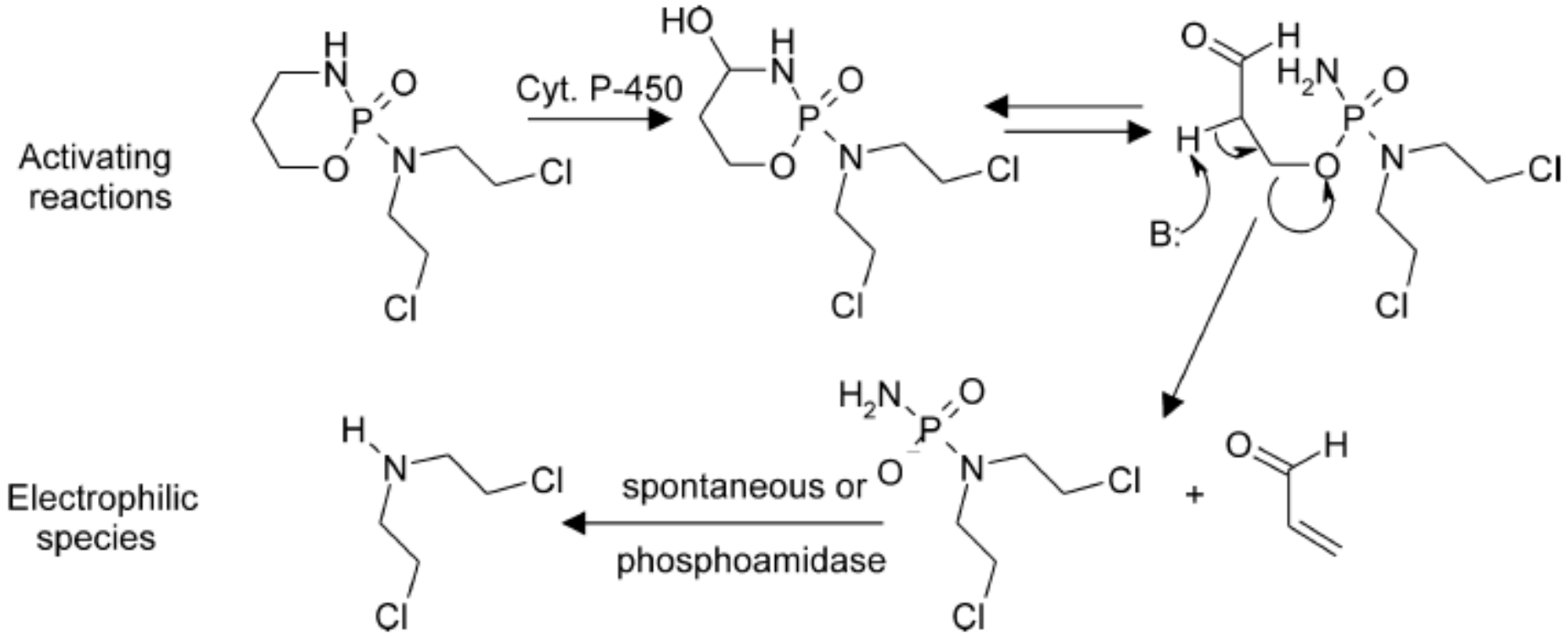
oxidative bioactivation of acyclovir precursor

6-deoxyacyclovir posses 6x better oral biovailability



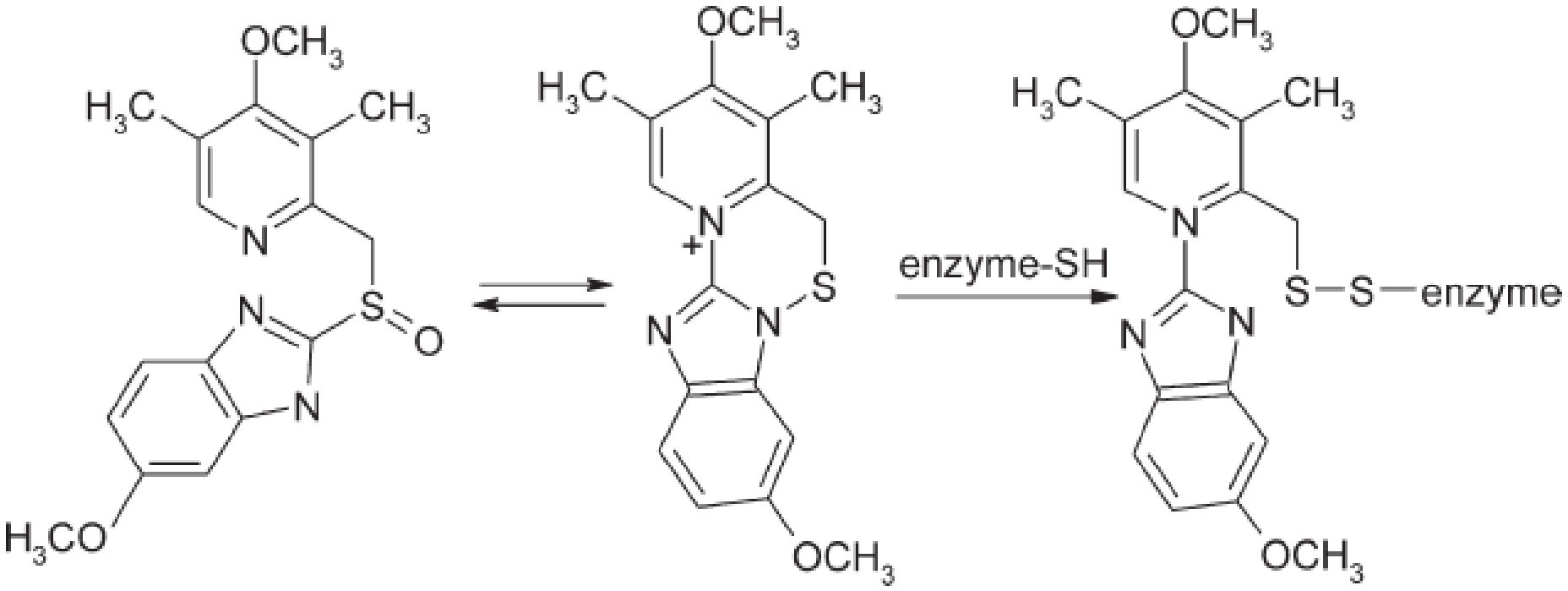
Bioprecursors

oxidative activation of cyclophosphamide –
active metabolites are reactive phosphamide and acrolein



Bioprecursors

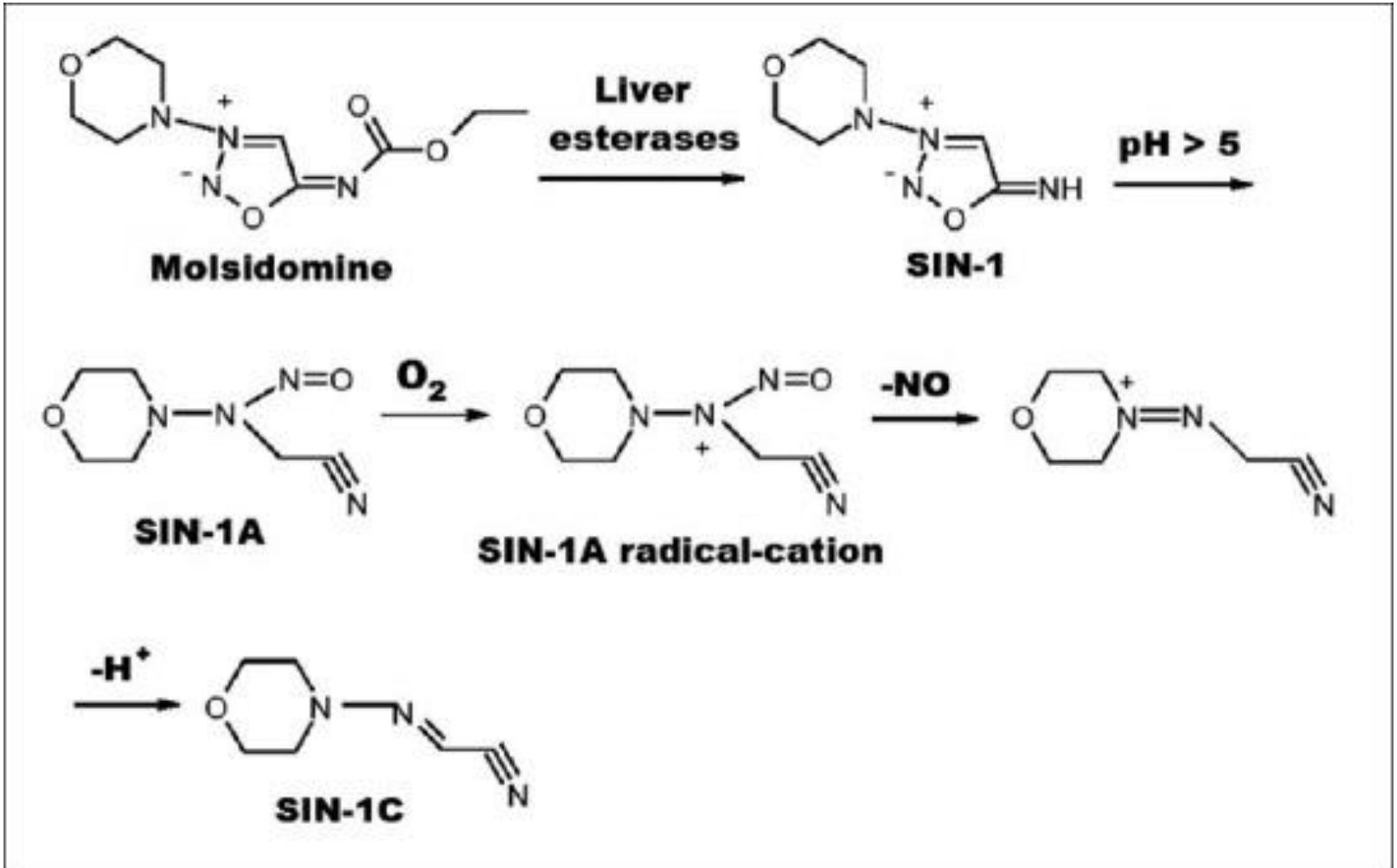
reductive bioactivation of omeprazole in acidic environment



Bioprecursors

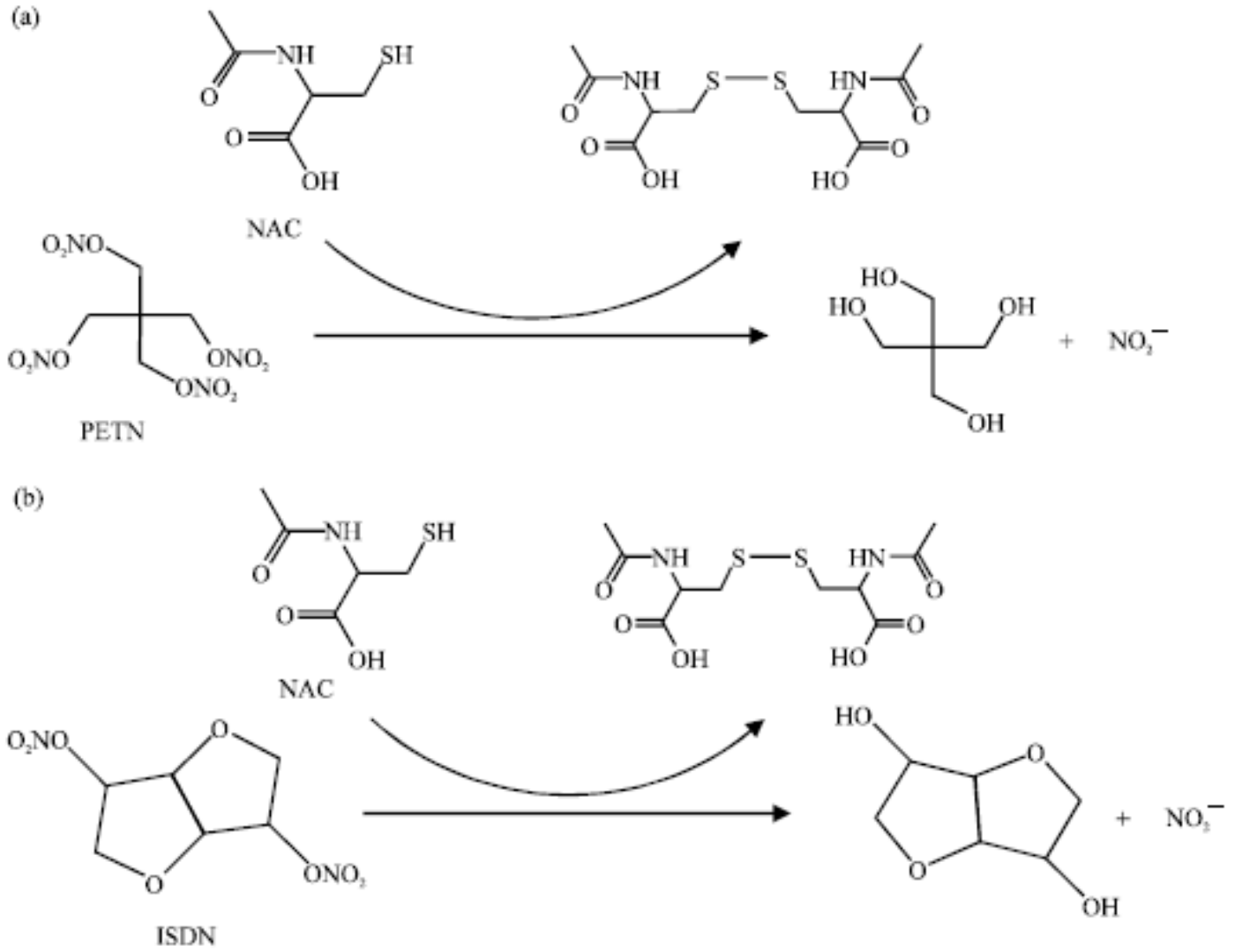
molsidomine is oxidatively deesterificated in liver to linsidomine.

Linsidomine is plasma sensitive and releases NO



Bioprecursors

nitrates are converted by N-acetylcystein and glutathion to nitrites, nitrites are reduced and binds to nitrosothiols



Soft drugs

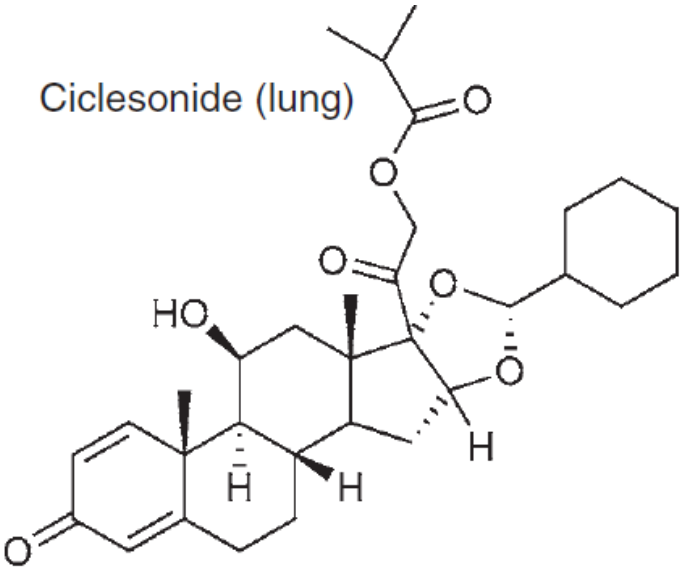
„reverse prodrugs“

- Metabolically unstable functionality is introduced to shorten biological half-time
- protects from system effect (and connected side effects)
- controlled site of effect and time of duration

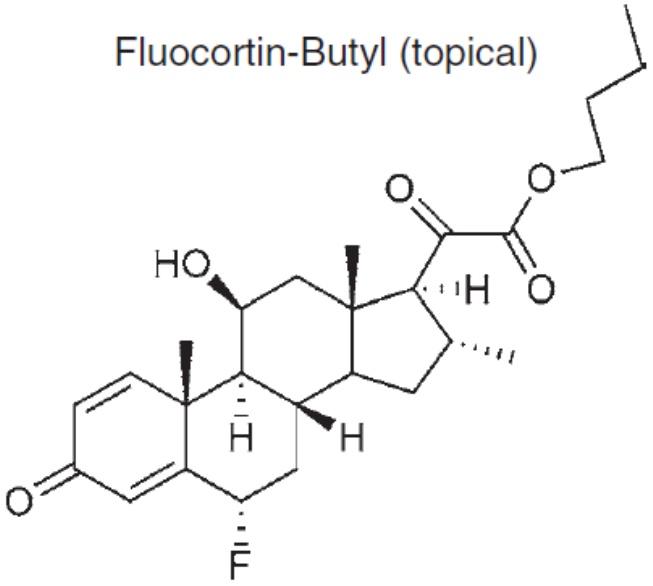
Soft drugs

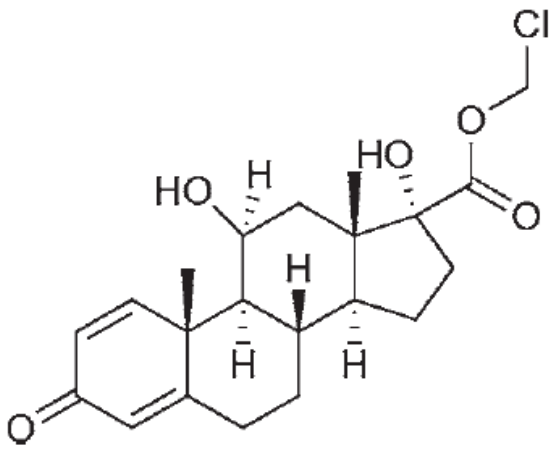
locally administrated corticosteroids are destroyed in plasma

Ciclesonide (lung)



Fluocortin-Butyl (topical)





Loteprednol Etabonate (eye)

Soft drugs: drugs for local delivery (skin, eyes, lungs), active locally and readily inactivated systemically.

Soft drugs

Esmolol administred by infusion.

Inactivated in plasma within 15 min.