Peptidomimetics and Prodrugs

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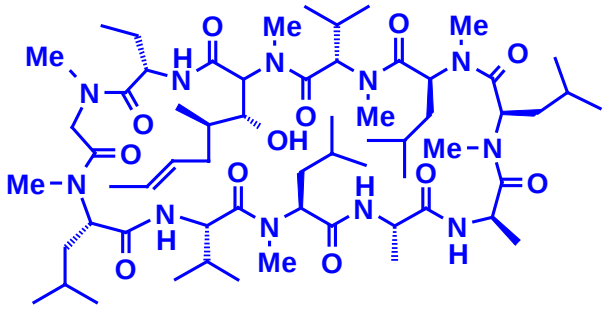
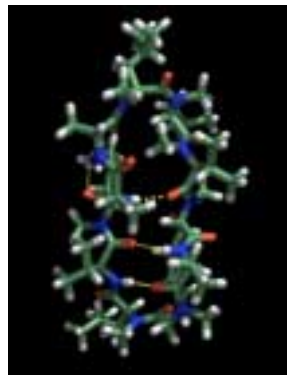
Physiological Role of Peptides

Endogeneous peptidic transmitters	Function
Leu-enkephalin, Met-enkephalin	Ligands of the morphine receptor (analgesics)
Angiotensin II	Blood pressure regulation
Endothelin	Blood pressure regulation
Neuropeptide Y	Blood pressure regulation
Substance P	Different effects, e.g. broncho-constriction, pain signalling
Fibrinogen	Blood platelet aggregation

Peptide Drugs





Cyclosporin A (immunosuppressant)

pGlu-His-Trp-Ser-Tyr-*D*-Leu-Leu-Arg-Pro-NHEt

Leuprolide (LHRH analog, prostate cancer)

H-Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Leu-Gly-NH_2

Oxytocin (labor induction)

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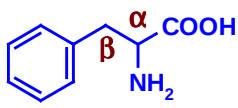
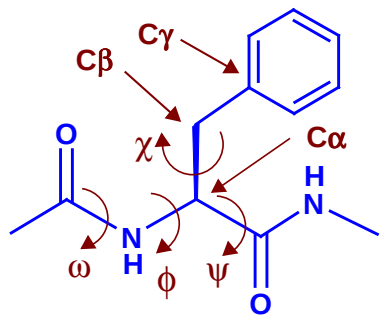
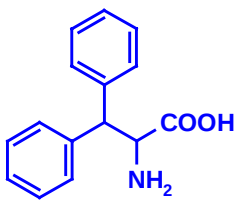
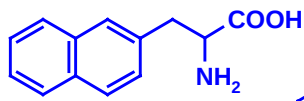
Phenylalanine and Some Analogs

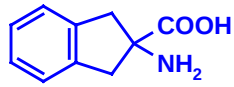


Phenylalanine

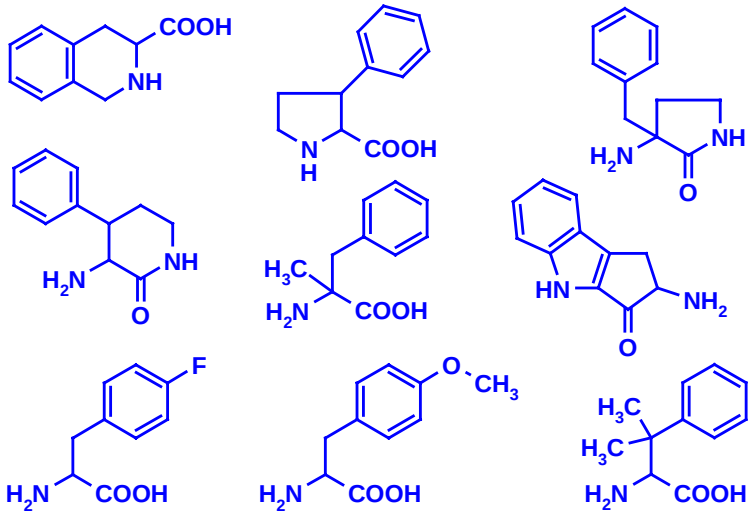




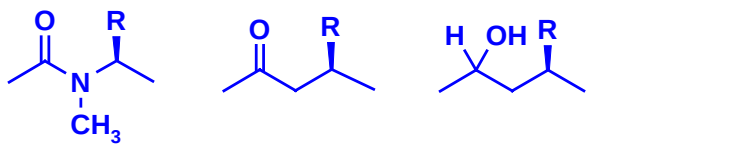




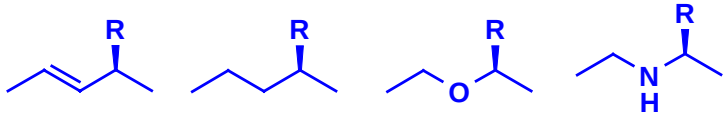
Other Phenylalanine Analogs



Replacement of the Peptide Bond



N-methyl **ketomethylene** **hydroxyethylene**

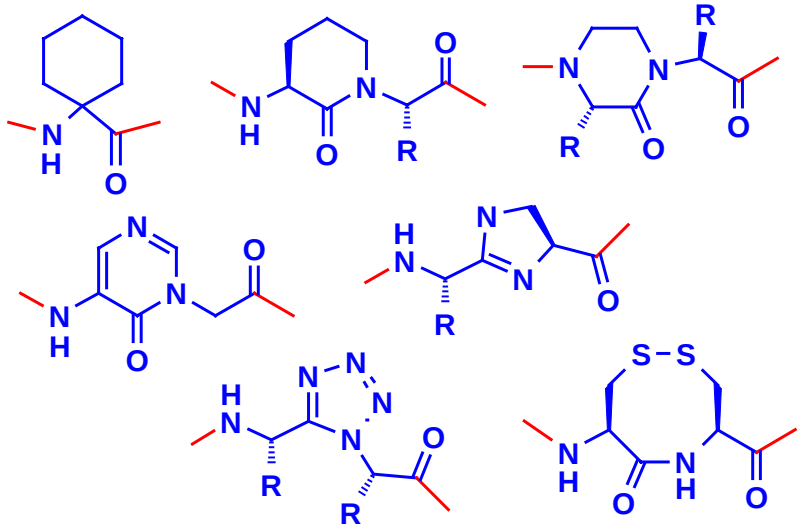


(E)-ethylene **carba** **ether** **reduced amide**

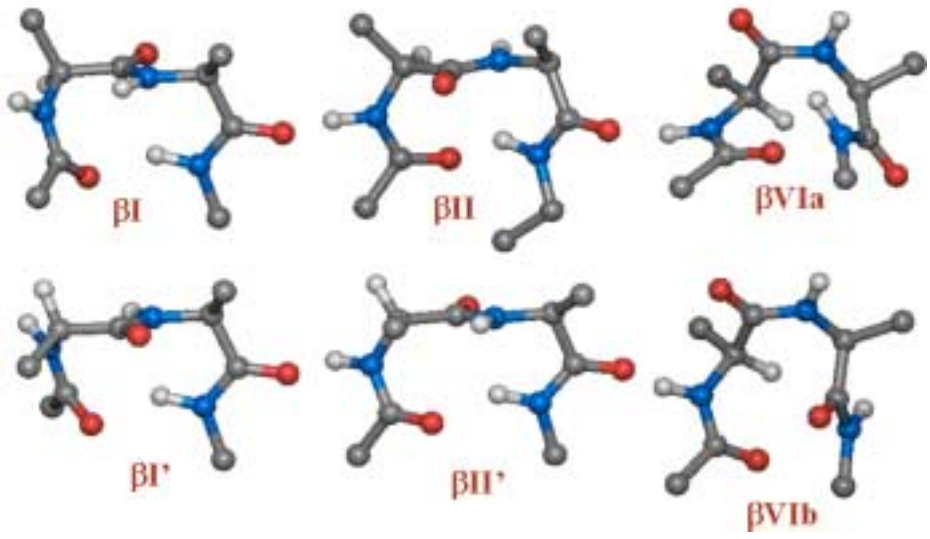
retro-inverso

phosphonamide, phosphonate, phosphinate; X = -NH-, -O-, -CH_2-

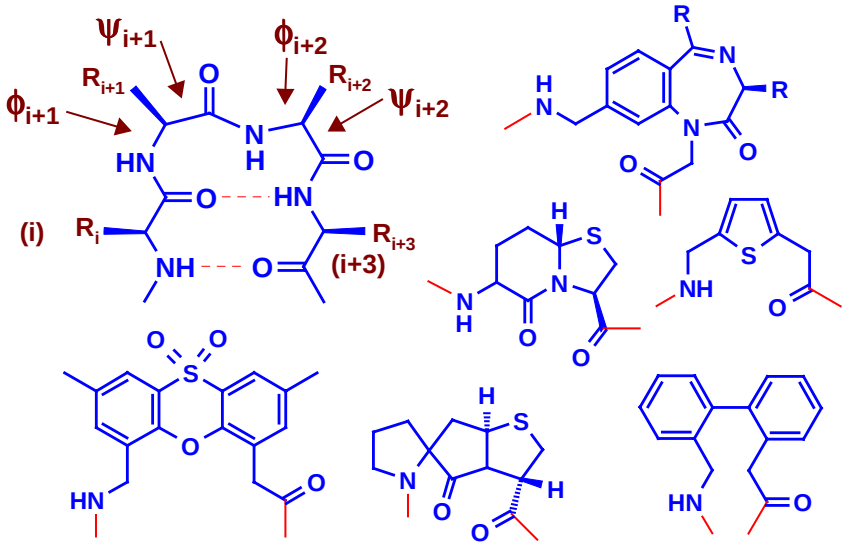
Conformational Stabilization by Cyclisation



Protein Secondary Structure Elements: ß turns



ß-Turn 3D Structure and ß-Turn Mimetics



Rational Design of NK_2 Receptor Antagonists

	Structure	K_i [nM]
Substance P	Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH_2	295
Active analog	Leu-Gln-Met-Trp-Phe-Gly-NH_2	11.7
Ala scan	Ala-Gln-Met-Trp-Phe-Gly-NH_2	40
	Leu-Ala-Met-Trp-Phe-Gly-NH_2	138
	Leu-Gln-Ala-Trp-Phe-Gly-NH_2	156
	Leu-Gln-Met-Ala-Phe-Gly-NH_2	>10,000
	Leu-Gln-Met-Trp-Ala-Gly-NH_2	8,300
	Leu-Gln-Met-Trp-Phe-Ala-NH_2	28
	Leu-Gln-Met-Trp-Phe-NH_2	200
Dipeptide	Z-Trp-Phe-NH_2	2,700

Rational Design of NK_2 Receptor Antagonists

	Structure	K_i [nM]
Dipeptide	Z-Trp-Phe-NH_2	2,700
Stabilize the bioactive conformation	Z-Trp-(*R*,*S*)-(α-Me)Phe-NH_2	327
Optimize the N-terminus	(2,3-di-OCH_3)C_6H_3-CH_2OCO-Trp-(*R*,*S*)-(α-Me)Phe-NH_2	37.6
Find active enantiomer	(2,3-di-OCH_3)$C_6H_3CH_2OCO$-Trp-(*R*)-(α-Me)Phe-NH_2	10,000
	(2,3-di-OCH_3)$C_6H_3CH_2OCO$-Trp-(*S*)-(α-Me)Phe-NH_2	17.2
Attach additional group	(2,3-di-OCH_3)$C_6H_3CH_2OCO$-Trp-(*S*)-(α-Me)Phe-Gly-NH_2	1.4

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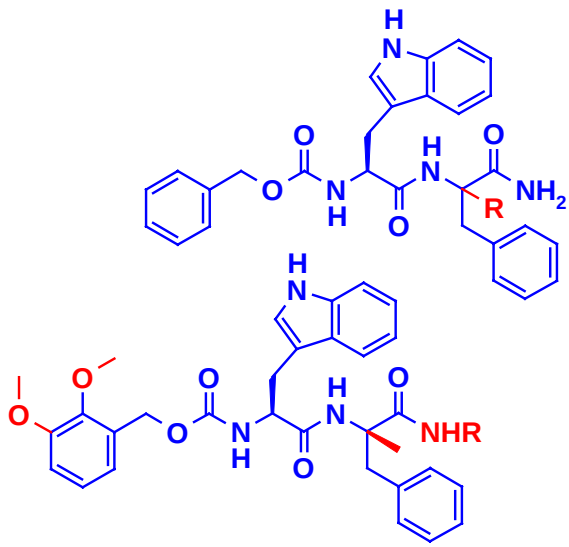
Rational Design of NK_2 Receptor Antagonists



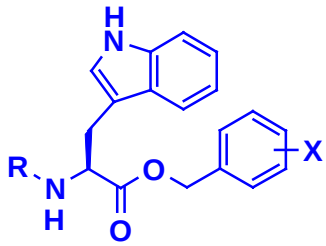
R = H
K_i = 2,700 nM

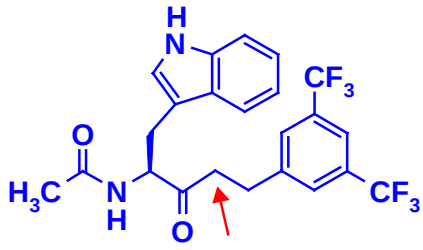
R = CH_3
K_i = 327 nM

R = H
K_i = 17.2 nM

R = CH_2CONH_2
K_i = 1.4 nM

Optimization of an NK1 Receptor Antagonist





orally available analog

IC_{50} = 3 nM

R = Et, X = H	IC_{50} = 3,800 nM
R = H, X = H	IC_{50} >10,000 nM
R = H, X = 3,5-di-CH_3	IC_{50} = 1,533 nM
R = Ac, X = 3,5-di-CH_3	IC_{50} = 67 nM
R = Ac, X = 3,5-di-CF_3	IC_{50} = 1.6 nM

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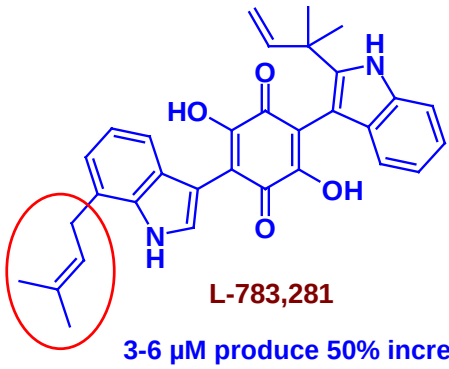
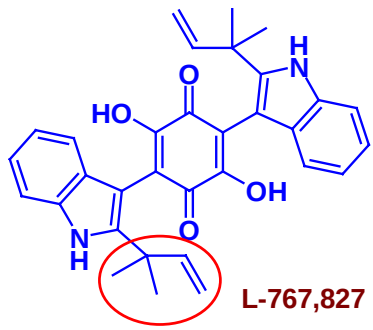
A Small Molecule Insulin Mimetic

screening of > 50,000 mixtures of synthetics and natural products yielded the insulin mimetic L-783,281



L-783,281



L-767,827

3-6 µM produce 50% increase of the maximal effect of insulin (in mice)

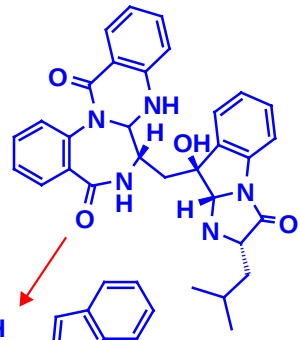
less active by a factor of 100

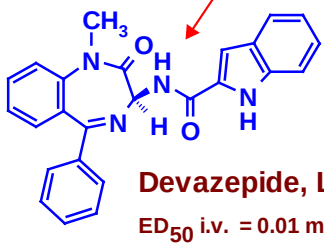
B. Zhang et al., Science 284, 974-977 (1999)

CCK-A and CCK-B Antagonists

Asperlicin (microbial product)

ED_{50} i.v. = 14.8 mg/kg
ED_{50} p.o. > 300 mg/kg



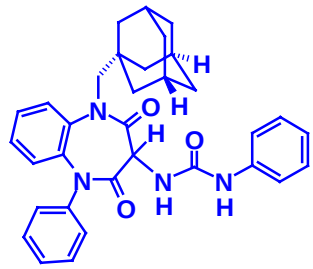


Devazepide, L-364 718

ED_{50} i.v. = 0.01 mg/kg
ED_{50} p.o. = 0.04 mg/kg
K_i CCK-A (rat) = 1,480 nM
K_i CCK-B (human) = 0.15 nM

A. Ursini et al., J. Med. Chem. 43, 3596-3613 (2000)

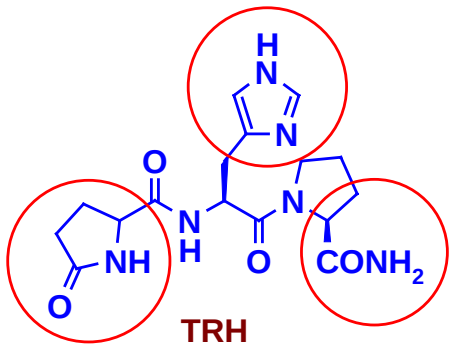
cf.



GV 150 013

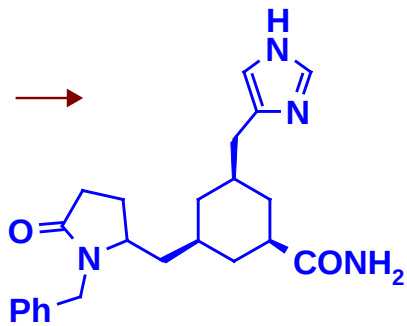
K_i CCK-A (rat) = 0.37 nM
K_i CCK-B (human) = 29.5 nM

Design of an Orally Active TRH Mimetic



TRH

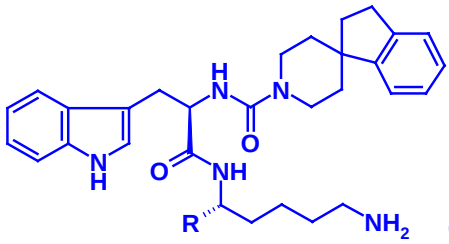
metabolically not stable, no oral bioavailability



peptidomimetic, orally bioavailable, sufficient half-life time

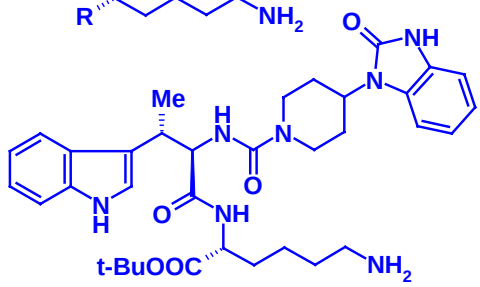
G. L. Olson et al., J. Med. Chem. 36, 3039-3049 (1993)

Amino Acid Amides as Somatostatin Mimics



R = H sst2 K_i = 5.9 nM

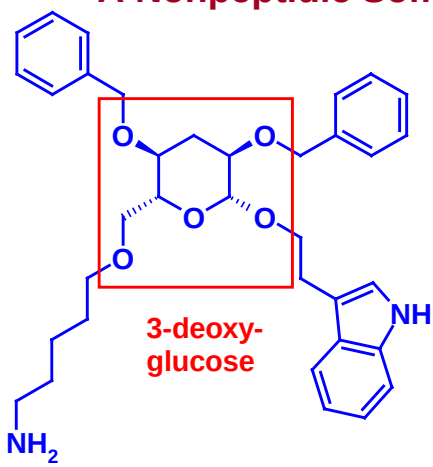
R = COOMe sst1 K_i = 3,794 nM
sst2 K_i = 1.0 nM
sst3 K_i = 360 nM
sst4 K_i = 2,402 nM
sst5 K_i = 2,105 nM



sst1 K_i = 2,392 nM
sst2 K_i = 0.01 nM
sst3 K_i = 31 nM
sst4 K_i = 81 nM
sst5 K_i = 163 nM

L. Yang et al., Proc. Natl. Acad. Sci. USA 95, 10836-10841 (1998)

A Nonpeptidic Somatostatin Mimic



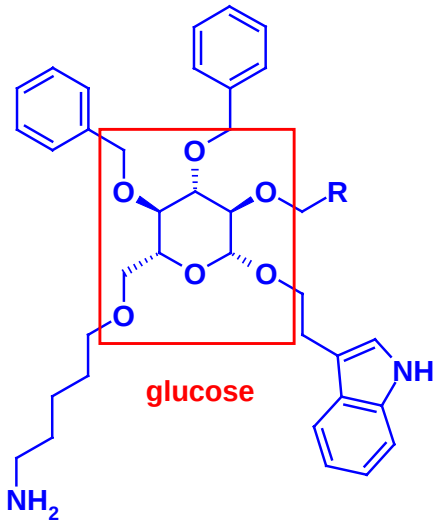
mimic of the receptor-recognizing ß-turn Phe7-Trp8-Lys9-Thr10 of somatostatin.

IC_{50} = 1.3 µM (pituitary somatostatin receptor)

agonist activity in a functional assay at 3 µM

K. C. Nicolaou et al., Peptide Chem. Struct. Biol., Proceedings of the 11th Am. Peptide Symp., 1990, pp. 881-884; C. Wermuth, The Practice of Medicinal Chemistry, 1996, pp. 571 ff.

A Subtype-Specific Somatostatin Mimic



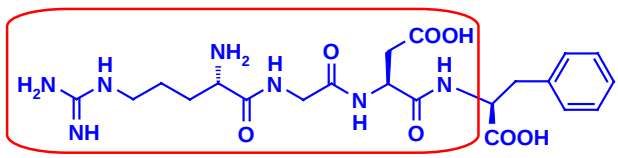
R = phenyl
non-selective, weak sst-receptor partial agonist

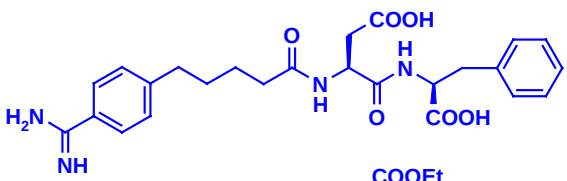
R = imidazol-4-yl
100 nM, selective sst4-receptor agonist

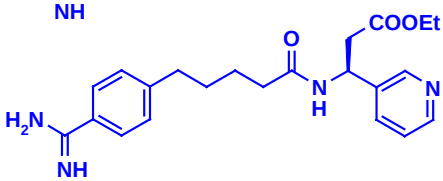
R. Hirschmann et al., J. Med. Chem. 41, 1382-1391 (1998).

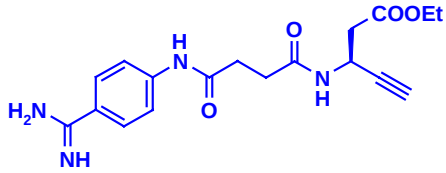
Stepwise Design of Nonpeptidic, Orally Available Fibrinogen Receptor Antagonists

RGD motif, the binding domain of integrin receptor ligands

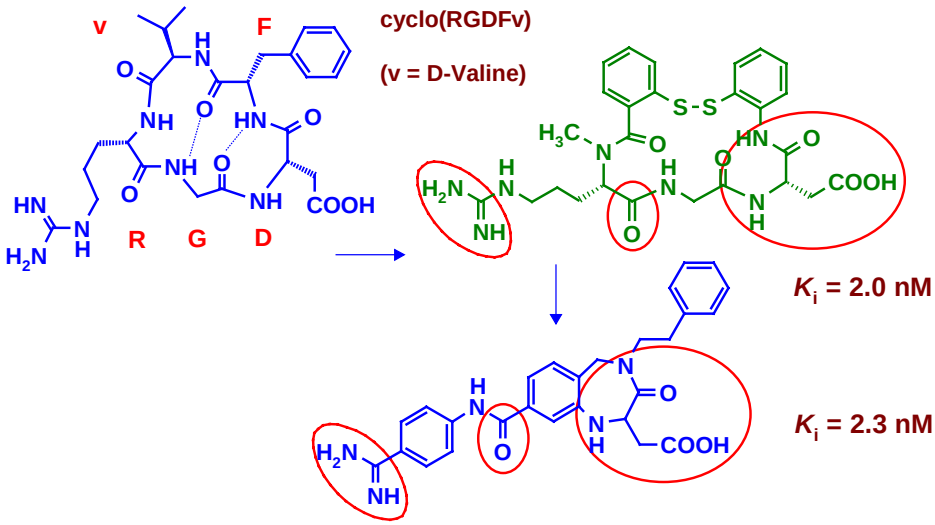




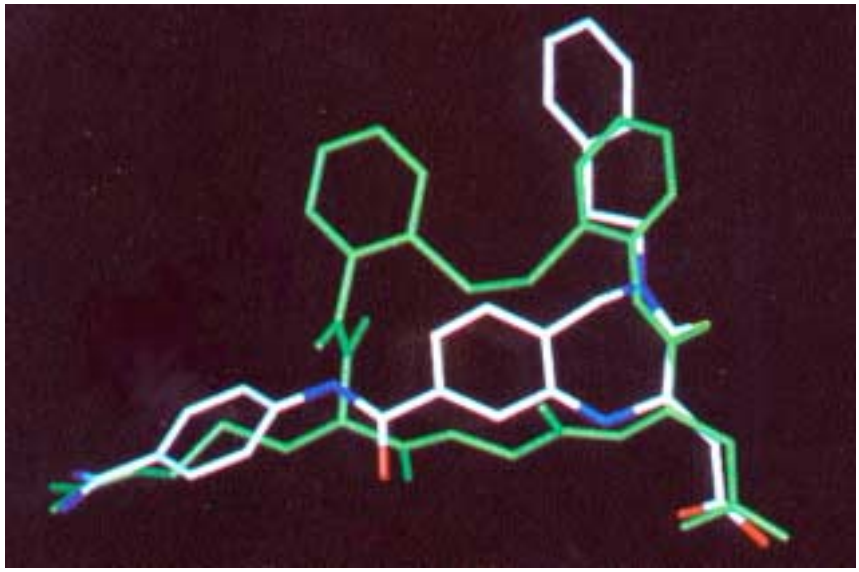




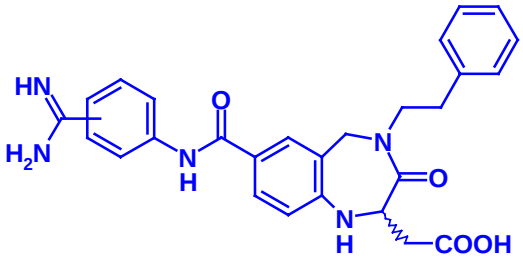
Rational Design of Integrin Receptor Ligands



Superposition of Integrin Receptor Ligands

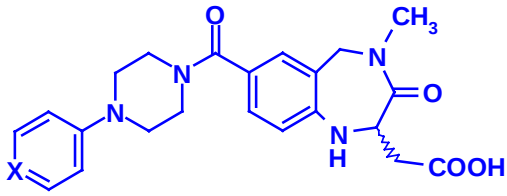


Selectivity of Integrin Receptor Ligands



p-amidine
K_i GPIIb/IIIa = 26 nM
K_i αvβ3 = 56,000 nM

m-amidine
K_i GPIIb/IIIa = 4,500 nM
K_i αvβ3 = 510 nM



X = N
K_i GPIIb/IIIa = 8 nM
K_i αvβ3 = 1,000 nM

X = CH
K_i GPIIb/IIIa >100,000 nM
K_i αvβ3 = 9,200 nM

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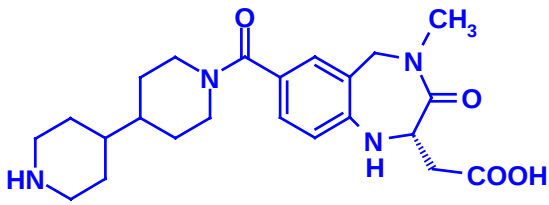
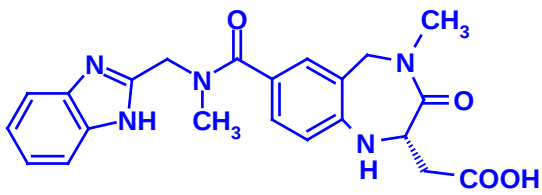
Highly Selective Integrin Receptor Ligands

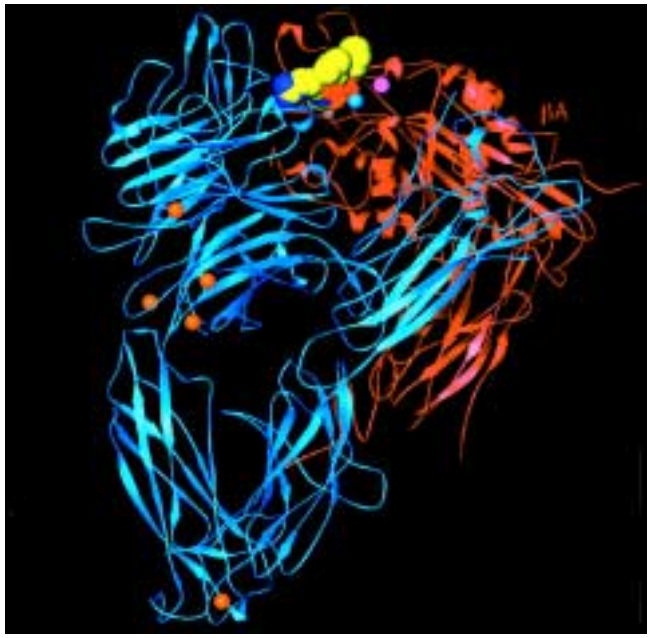


Iotrafiban (SB 214 857)
K_i GPIIb/IIIa = 2.5 nM
K_i αvβ3 = 10,340 nM



SB 223 245
K_i GPIIb/IIIa = 30,000 nM
K_i αvβ3 = 2 nM

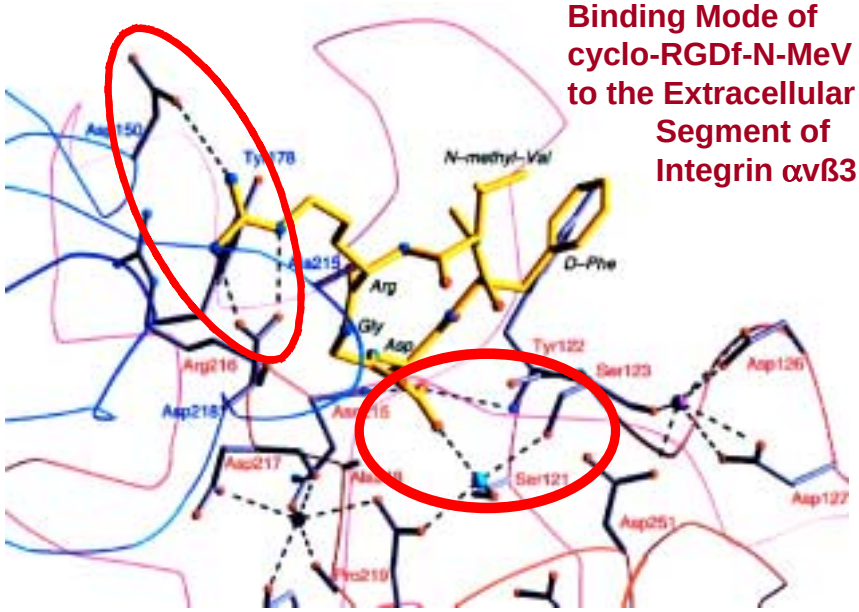
Lotrafiban failed in phase III, due to lack of activity and increased mortality (J.-M. Dogné et al., Curr. Med. Chem. 9, 577-589 (2002))



Crystal Structure of the Extracellular Segment of Integrin αvß3; complex with cyclo-RGDf-N-MeV

J.-P. Xiong et al., Science 296, 151-155 (2002)

Binding Mode of cyclo-RGDf-N-MeV to the Extracellular Segment of Integrin αvß3



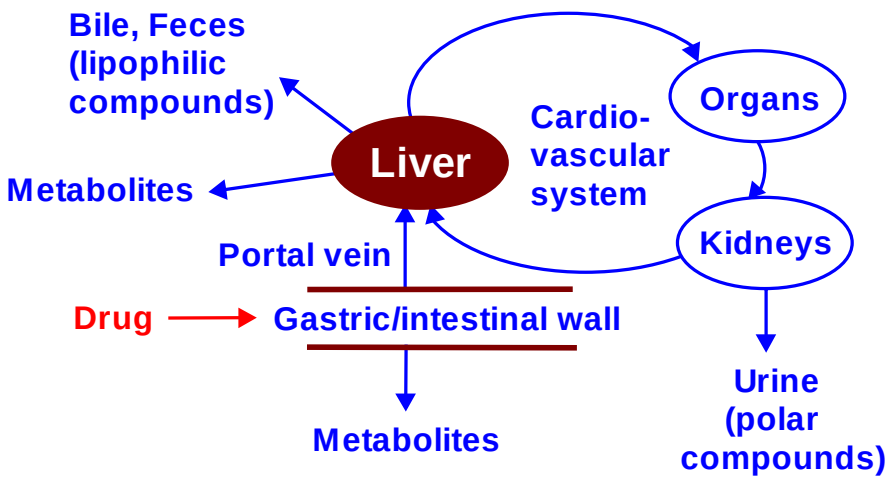
Prodrugs, Soft Drugs and Targeted Drugs

Prodrugs are inactive (or less active) drug analogs that have better pharmacokinetic properties (e.g. oral bioavailability, BBB penetration) than their parent drugs. They are (specifically) metabolized to the active form of the drug.

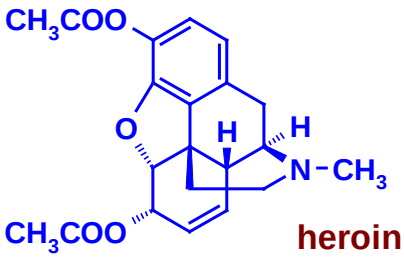
Soft drugs are biologically active derivatives of inactive drug analogs , e.g. esters of corticosteroid carboxylic acids. These esters are (topically) active; after dermal absorption they are readily degraded by metabolic enzymes to inactive analogs.

Targeted drugs are drugs or prodrugs that exert their biological action only in certain organs or cells (e.g. Omeprazole, Aciclovir).

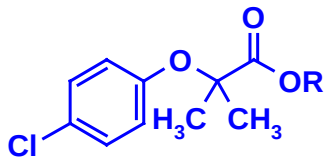
Distribution and Metabolism of Drugs in a Biological System



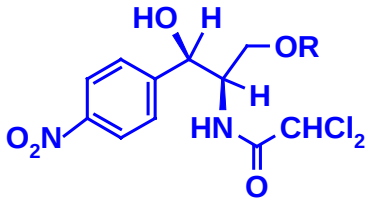
Prodrugs: Esters



heroin



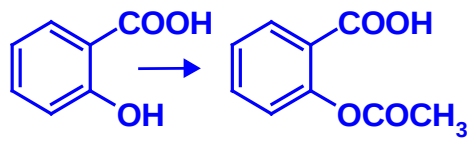
clofibrate, R = Et
clofibric acid, R = H



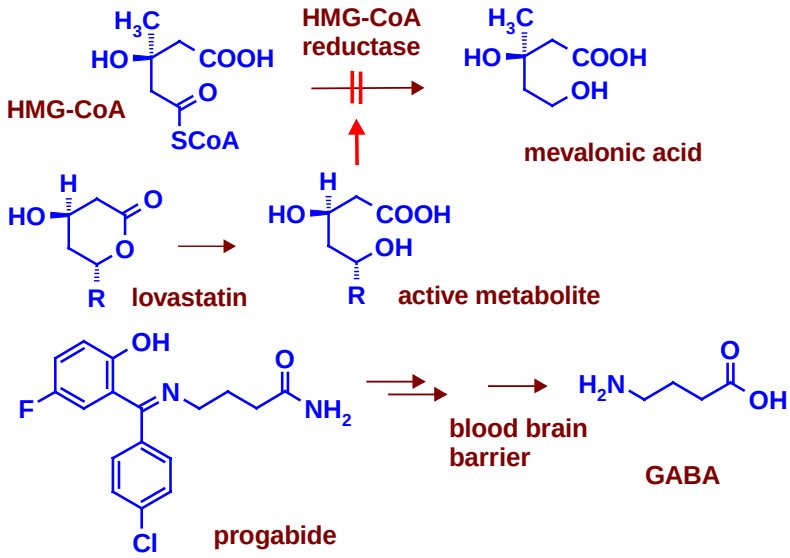
chloramphenicol
(bitter taste), R = H

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

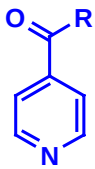
Aspirin®, a Prodrug? (Felix Hoffmann, 1897)



Prodrugs: Lactones and Amides

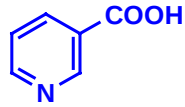


Prodrugs: Hydrazides and Azo Compounds

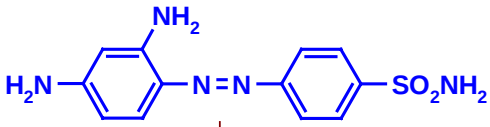


isoniazide,
R = -NH-NH$_2$
(tuberculostatic)

the metabolite isonicotinic acid (R = -OH) is an antimetabolite of nicotinic acid

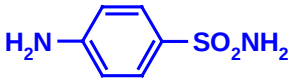


nicotinic acid

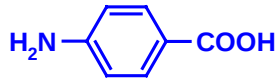


sulfamidochrysoidine
("prontosil rubrum")

metabolic degradation

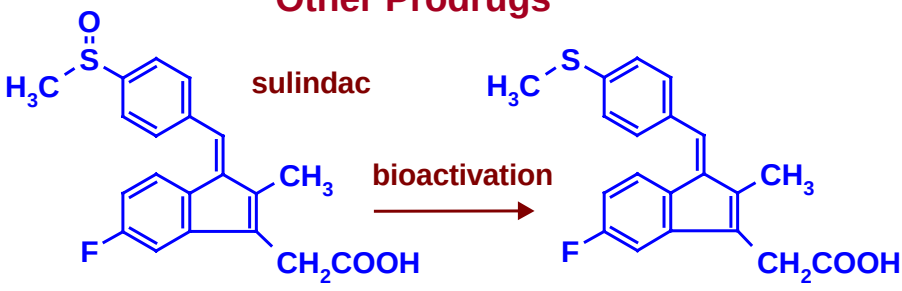


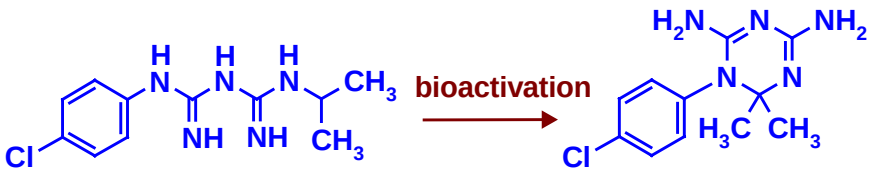
cf.



sulfanilamide, an antimetabolite of p-aminobenzoic acid

Other Prodrugs

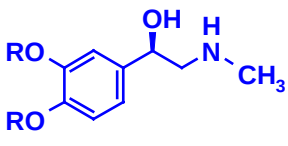


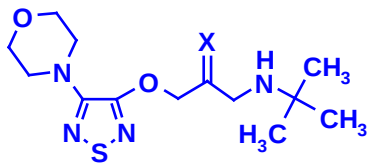


proguanil

cycloguanil

Drug Targeting into the Eye





Dipivefrine, R = $COC(CH_3)_3$

↓

Epinephrine, R = H

Oxime ether, X = N-OCH_3

↓

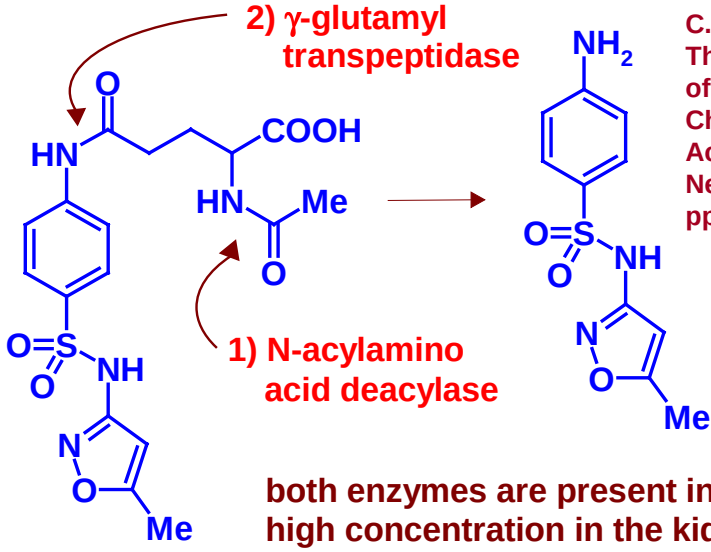
Ketone, X = O

↓

Timolol, X = H, OH

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.

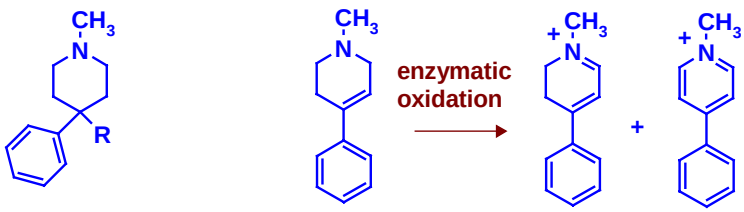
Kidney-Selective Release of Sulfamethoxazole



C. G. Wermuth
The Practice of Medicinal Chemistry, Academic Press, New York 1996, pp. 684-685

both enzymes are present in high concentration in the kidney

Drug Abuse Leads to a New Prodrug Concept



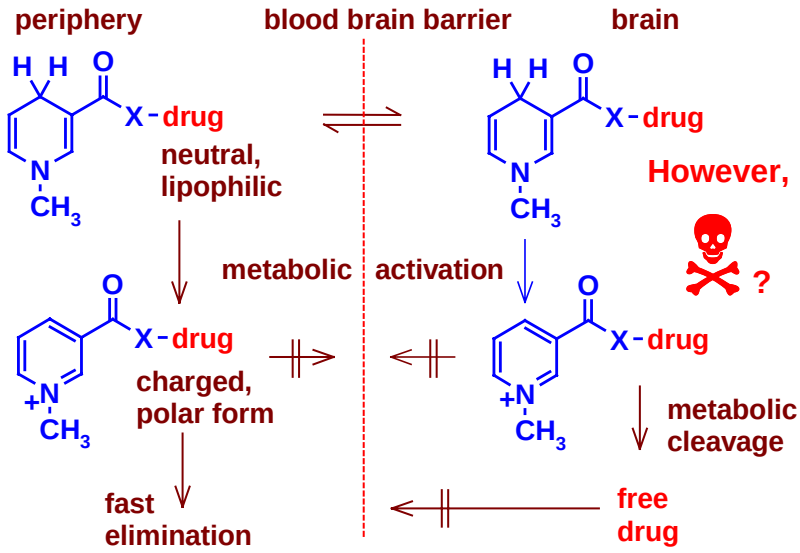
Pethidine, R = COOEt
MPPP, R = OCOEt

MPTP

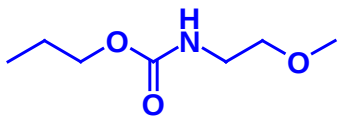
toxic metabolites

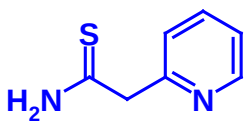
1-methyl-4-phenyl-4-propionyloxy-piperidine (MPPP) corresponds to pethidine but a "leaving group" results. Consumption of impure material leads to severe Parkinson symptoms, followed by early death. MPTP is a "prodrug" of permanently charged cytototoxic metabolites. The MAO inhibitor selegilin prevents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

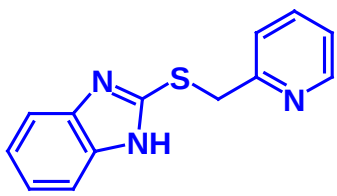
Brain Targeting of Drugs



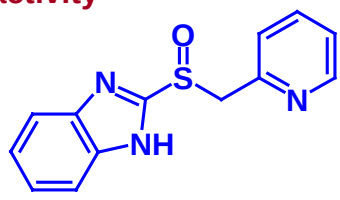
Omeprazole Case Study



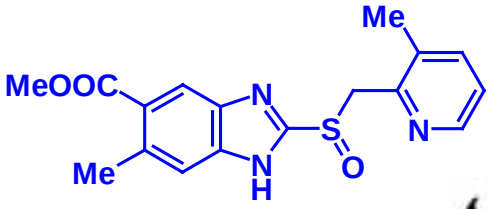




- 1966: Local anesthetics reduce gastric secretion (Hässle)
- 1966-1972: First lead
- 1972-1979: New lead pyridyl-acetamide (from screening of antiviral compounds)
- Active analogs; metabolite with higher antisecretory activity



Omeprazole Case Study

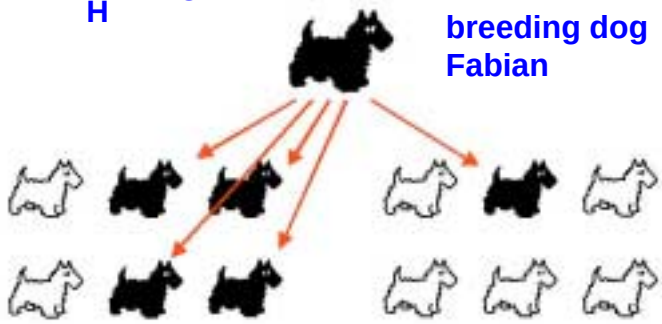


Picoprazole, 1976
preclinical candidate

breeding dog
Fabian

Tox study:

vasculitis

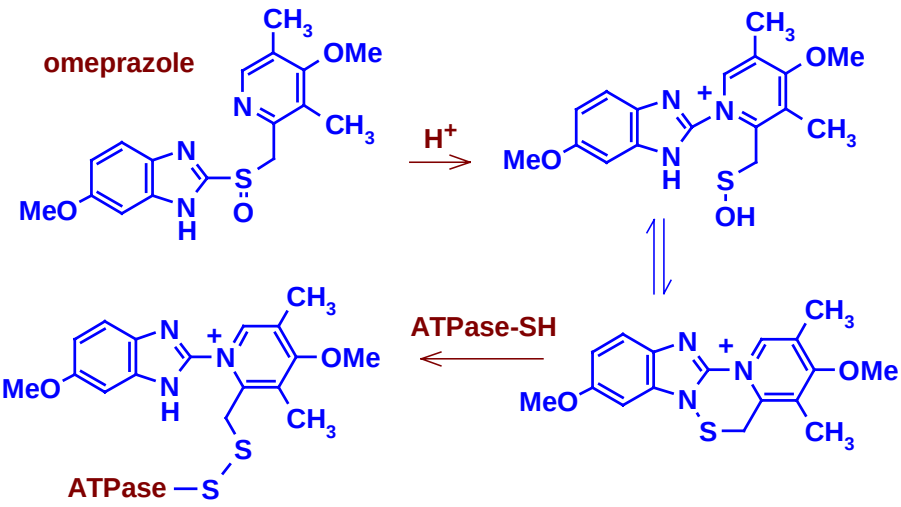


picoprazole group

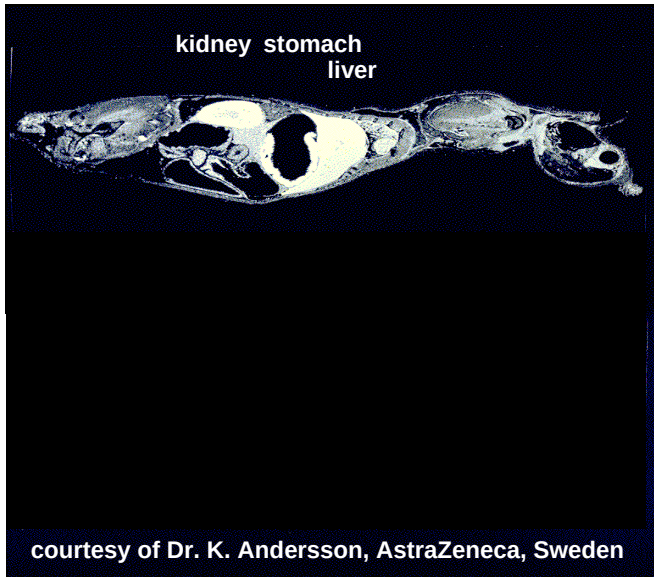
placebo group

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

omeprazole



Omeprazole Activation in Acid-Producing Cells

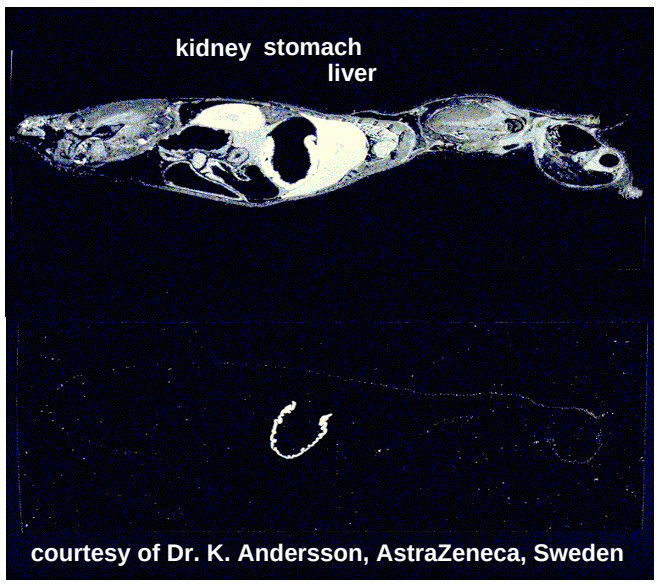


courtesy of Dr. K. Andersson, AstraZeneca, Sweden

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

Hugo Kubinyi, www.kubinyi.de

Omeprazole Activation in Acid-Producing Cells

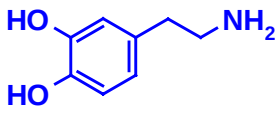


courtesy of Dr. K. Andersson, AstraZeneca, Sweden

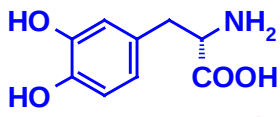
Distribution of radio-labelled omeprazole, one minute after i.v. injection, rat

sixteen hours after i.v. injection, rat

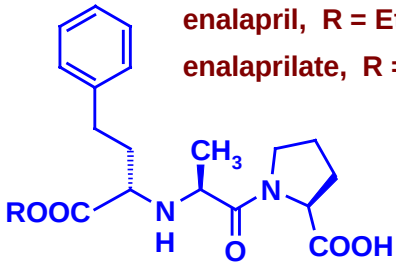
Use of the AA and Dipeptide Transporters



dopamine

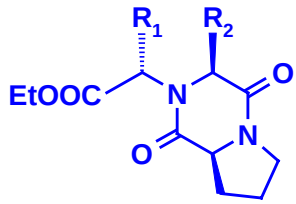


L-dopa



enalapril, R = Et

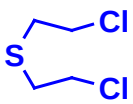
enalaprilate, R = H



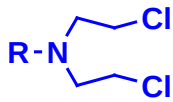
diketopiperazine

R_1 = phenethyl, R_2 = Me

Pro-Prodrugs

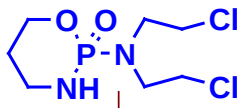


Mustard gas



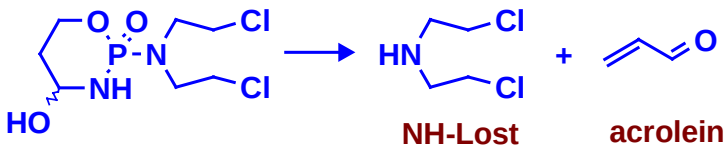
N-Lost, R = CH_3

N-Aryl-Lost, R = Aryl



Cyclophosphamide

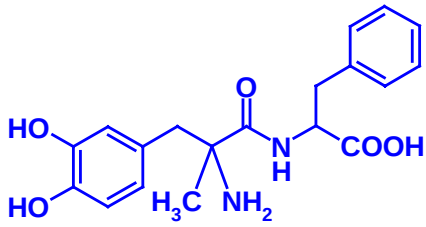
metabolic activation in the liver



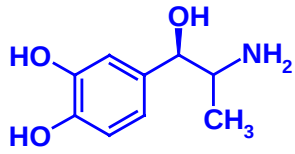
NH-Lost

acrolein

A Most Elegant Prodrug Concept



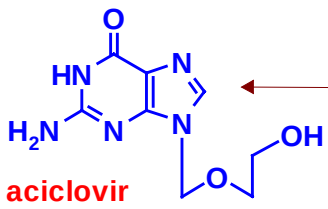
α-Methyldopa-Phe



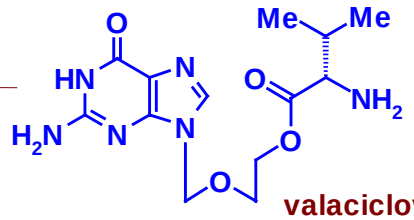
α-Methylnorepinephrine

The dipeptide α-Methyldopa-Phe is readily absorbed as a substrate of the dipeptide transporter. In the first pass, α-Methyldopa is produced, a substrate of the amino acid transporter. Transport into the brain, decarboxylation and hydroxylation produces a „false neurotransmitter", the α_2 agonist α-Methylnorepinephrine.

Antiviral Prodrugs are Trojan Horses



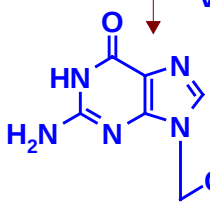
aciclovir

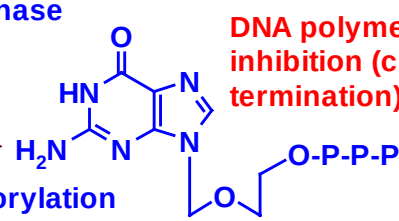


valaciclovir,
a pro-prodrug

1) monophosphorylation by viral thymidine kinase

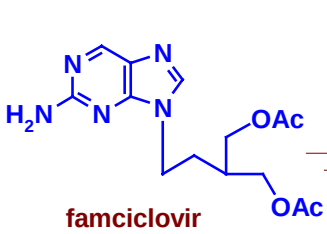
DNA polymerase inhibition (chain termination)



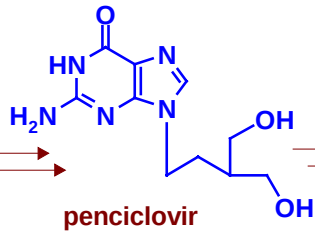


2) phosphorylation by cellular kinase

Antiviral Prodrugs are Trojan Horses



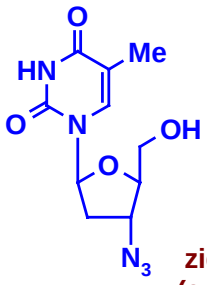
famciclovir



penciclovir

triphosphate

(active form; DNA chain termination)



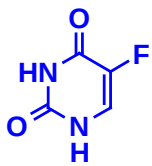
zidovudine (azidothymidine, AZT)

intracellular phosphorylation

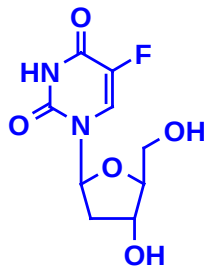
triphosphate

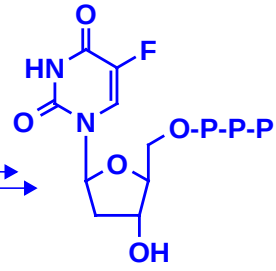
(inhibits reverse transcriptase; inactive against incorporated viruses)

Prodrugs of Site-Specific Trojan Horses



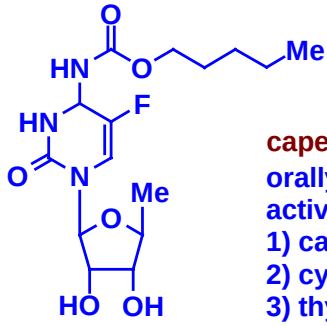
5-fluorouracil





5-F-uridylate

(a thymidylate synthase inhibitor)



capecitabine

orally active prodrug, tumour-specific activation by a cascade of enzymes:

1) carboxypeptidase cleavage (liver)
2) cytidine deaminase (liver, tumours)
3) thymidine phosphorylase (tumours)