# Solving Problems in Lead Optimization

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## Isosteric Replacement of Atoms and Groups

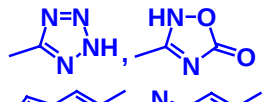
**Substituents: F, Cl, Br, I, $CF_3$ , $NO_2$**
**Methyl, Ethyl, Isopropyl, Cyclopropyl, t.-Butyl,**
**-OH, -SH, $-NH_2$ , -OMe, $-N(Me)_2$**

**Linkers: $-CH_2-$, -NH-, -O-**
**$-COCH_2-$, -CONH-, -COO-**
**>C=O, >C=S, >C=NH, >C=NOH, >C=NOAlkyl**

**Atoms and Groups in Rings: -CH=, -N=**
**$-CH_2-$, -NH-, -O-, -S-,**
**$-CH_2CH_2-$, $-CH_2-O-$, -CH=CH-, -CH=N-**

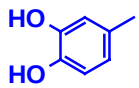
**Large Groups: $-NHCOCH_3$, $-SO_2CH_3$**

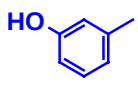
**-COOH, -CONHOH, $-SO_2NH_2$,**

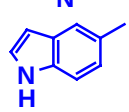


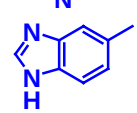




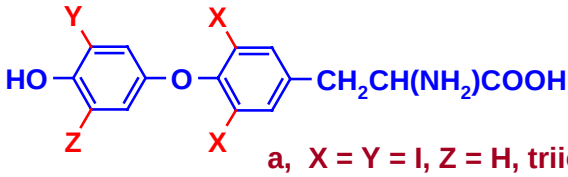


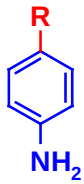



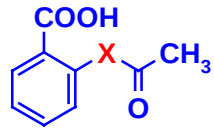
## Consequences of Isosteric Replacement




a, X = Y = I, Z = H, triiodothyronine, T3
b, X = Y = Z = I, thyroxine, T4
c, X = I, Y = i-propyl, Z = H
d, X = $CH_3$, Y = i-propyl, Z = H




p-aminobenzoic acid,
R = COOH
sulfanilamide, R = $SO_2NH_2$




X = -O-
acetylsalicylic acid

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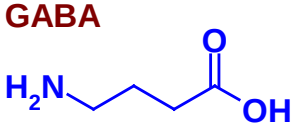
## Consequences of Isosteric Replacement

### Inhibition of Carbonic Anhydrase by Sulfonamides

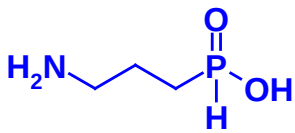
$CH_3SO_2NH_2$, $K_i$ = 100 µM, $pK_a$ = 10.5
$CF_3SO_2NH_2$, $K_i$ = 2 nM, $pK_a$ = 5.8

### Specificity of GABA Receptor Ligands

GABA

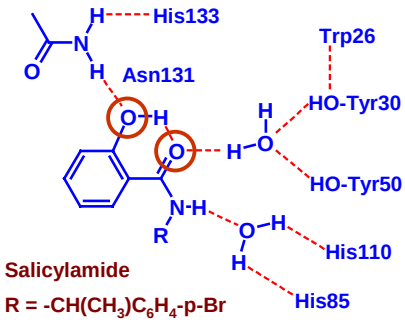



| | $GABA_A$ receptor affinity | $GABA_B$ receptor affinity |
|---|---|---|
| $IC_{50}$ = | 20 nM | 20 nM |




| | | |
|---|---|---|
| $IC_{50}$ = | 4,500 nM | 1 nM |

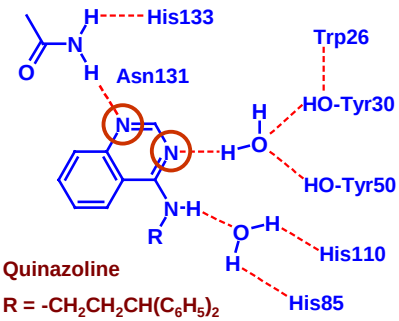
# Receptors Just Recognize Properties




Salicylamide

R = -CH(CH$_3$)C$_6$H$_4$-p-Br

$K_i$ = 0.14 nM




Quinazoline

R = -CH$_2$CH$_2$CH(C$_6$H$_5$)$_2$

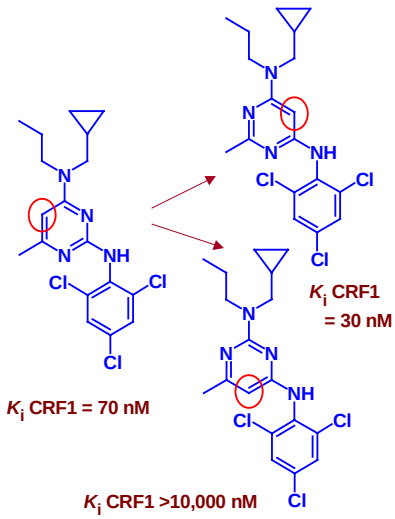
$K_i$ = 0.15 nM

**A pharmacophore is the ensemble of steric and electronic features that is necessary to ensure the optimal supramolecular interactions with a specific biological target and to trigger its biological response.**

C. G. Wermuth et al., Pure Appl. Chem. 70, 1129-1143 (1998)



# Smooth and Rough Structure-Activity Landscapes



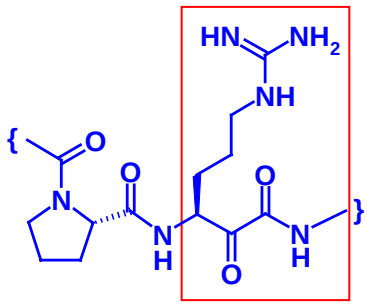
$K_i$ CRF1 = 70 nM

$K_i$ CRF1 = 30 nM

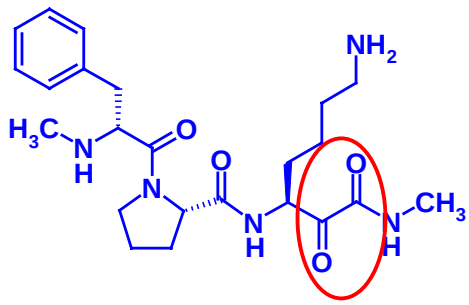
$K_i$ CRF1 >10,000 nM

C. Chen et al., J. Med. Chem. 39, 4358-4360 (1996)

## Merck Thrombin Inhibitors: First lead derived from a natural product



Cyclotheonamide
(partial structure)

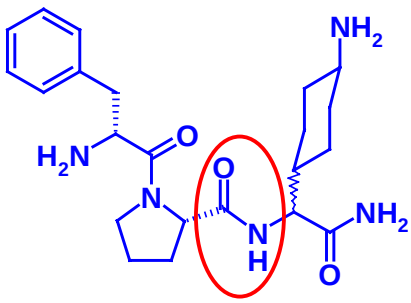


$K_i$ (thrombin) = 2.8 nM
$K_i$ (trypsin) = 7.8 nM

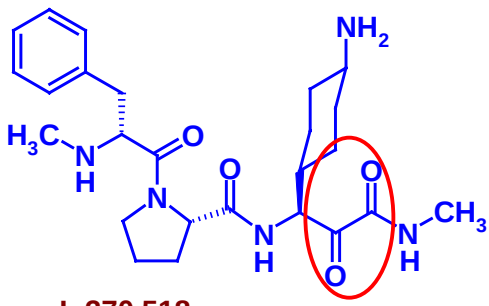


## Merck Thrombin Inhibitors: Model Compounds for Optimization of the P1 residue

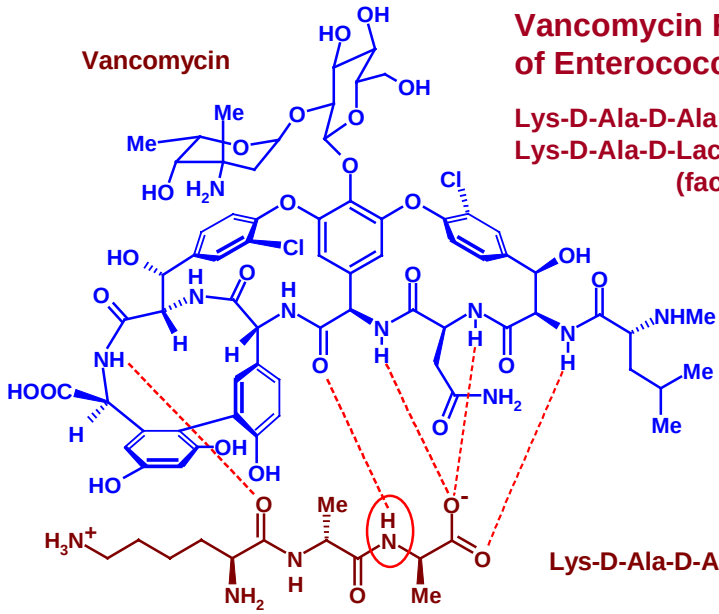
D,L-trans



$K_i$ (thrombin) = 5 300 nM
$K_i$ (trypsin) = 855 000 nM



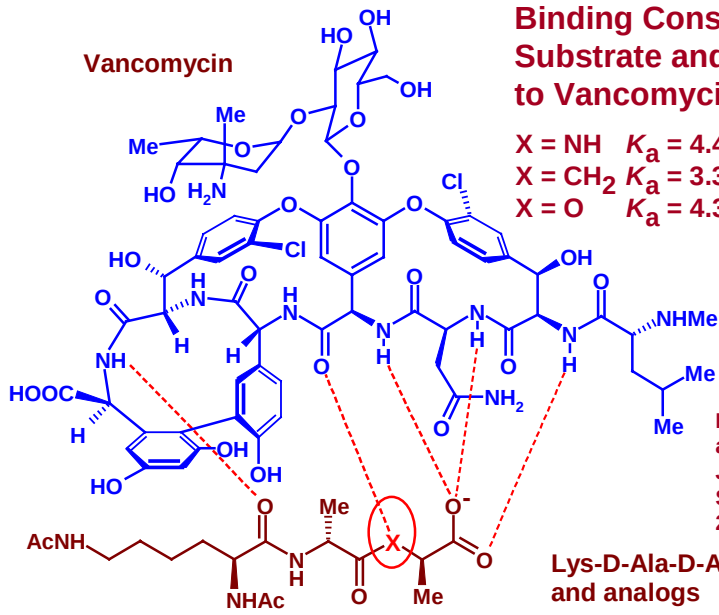
L 370 518
$K_i$ (thrombin) = 0.09 nM
$K_i$ (trypsin) = 1 150 nM




## Vancomycin Resistance of Enterococci

**Lys-D-Ala-D-Ala: sensitive**
**Lys-D-Ala-D-Lac: resistant**
**(factor 1,000)**





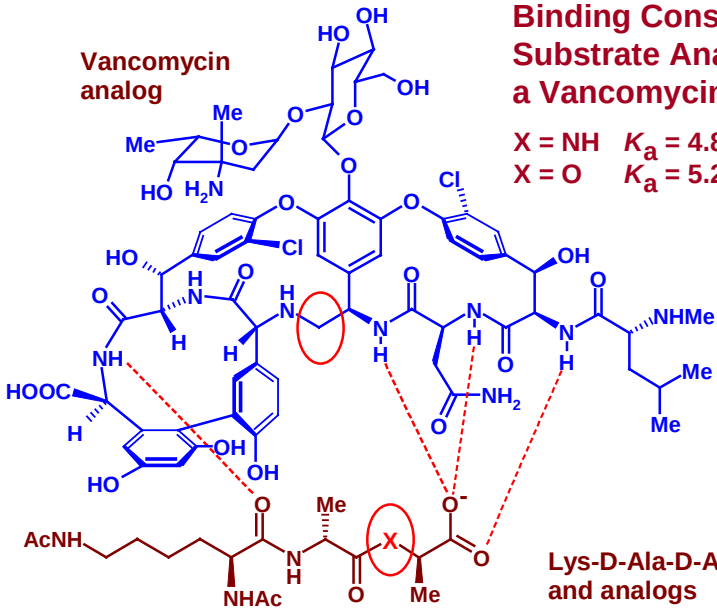

## Binding Constants of Substrate and Analogs to Vancomycin

X = NH $K_a = 4.4 \times 10^5\ M^{-1}$
X = $CH_2$ $K_a = 3.3 \times 10^4\ M^{-1}$
X = O $K_a = 4.3 \times 10^2\ M^{-1}$

B. M. Crowley and D. Boger, J. Am. Chem. Soc. 128, 2885-2892 (2006)

## Binding Constants of Substrate Analogs to a Vancomycin Analog

Vancomycin analog



X = NH $K_a = 4.8 \times 10^3\ M^{-1}$
X = O $K_a = 5.2 \times 10^3\ M^{-1}$

B. M. Crowley and D. L. Boger, J. Am. Chem. Soc. 128, 2885-2892 (2006)



Lys-D-Ala-D-Ala and analogs

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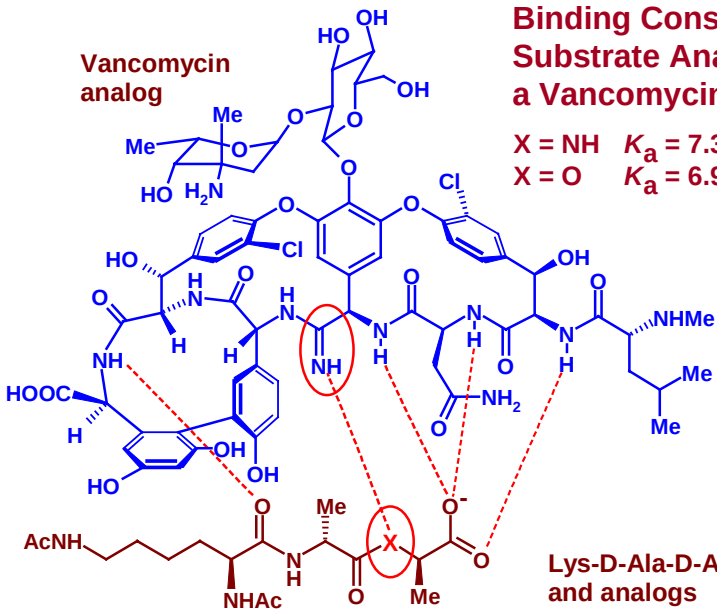
## Binding Constants of Substrate Analogs to a Vancomycin Analog

Vancomycin analog



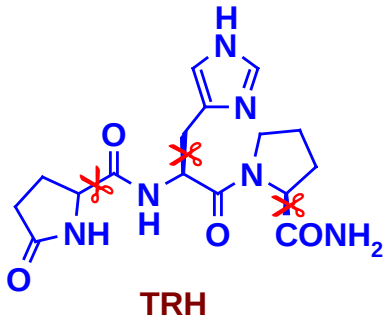
X = NH $K_a = 7.3 \times 10^4\ M^{-1}$
X = O $K_a = 6.9 \times 10^4\ M^{-1}$

J. Xie, A.Okano et al., J. Am. Chem. Soc. 14, 1284-1297 (2012)

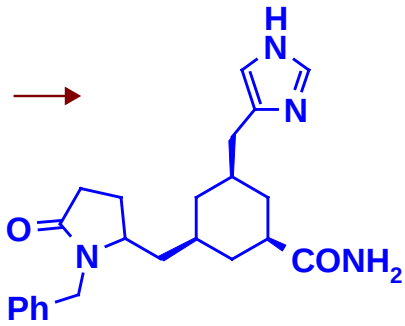


Lys-D-Ala-D-Ala and analogs

# Design of an Orally Active TRH Mimetic




TRH



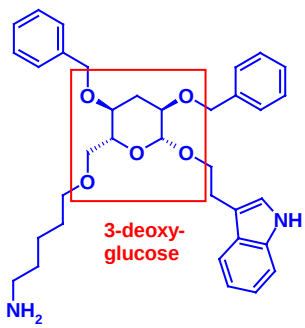

**metabolically not stable, no oral bioavailability**

**peptidomimetic, orally bioavailable, sufficient half-life time**

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

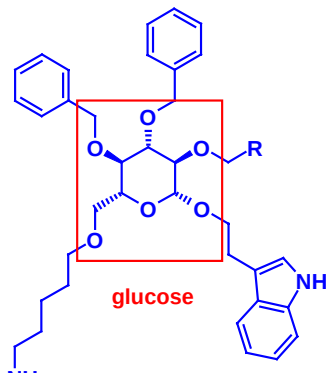


# Scaffold Hopping to Somatostatin Mimics




mimic of the receptor-recognizing ß-turn Phe7-Trp8-Lys9-Thr10 of somatostatin; agonist activity at 3 µM

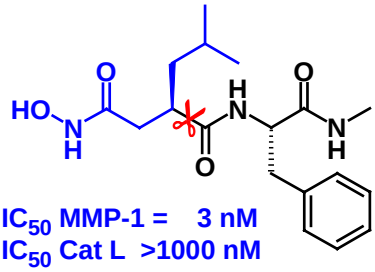
K. C. Nicolaou et al., Peptide Chem. Struct. Biol., Proceedings of the 11th Am. Peptide Symp., 1990, pp. 881-884



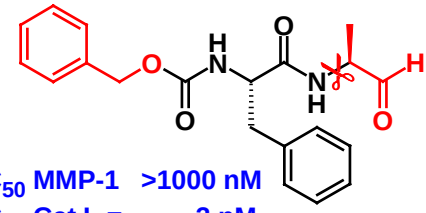

R = phenyl: non-selective, weak sst-receptor partial agonist
R = imidazol-4-yl: selective sst4-receptor agonist, 100 nM

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

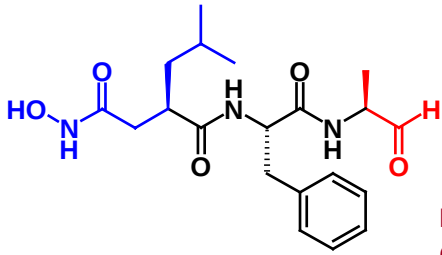
# Design of Dual $Zn^{++}$/Cysteine Protease Inhibitors



$IC_{50}$ MMP-1 = 3 nM
$IC_{50}$ Cat L >1000 nM



$IC_{50}$ MMP-1 >1000 nM
$IC_{50}$ Cat L = 3 nM

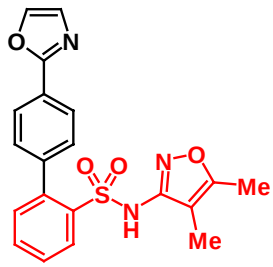


$IC_{50}$ MMP-1 = 25 nM
$IC_{50}$ Cat L = 15 nM

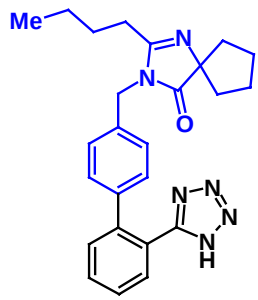
M. Yamamote et al., Bioorg. Med. Chem. Lett. 12, 375-378 (2002)



# Design of a Dual $AT_1$ and $ET_A$ Antagonist



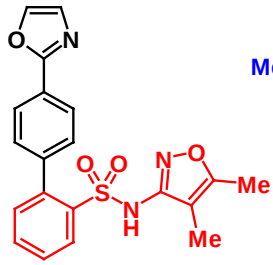
$AT_1$ $K_i$ > 10,000 nM
$ET_A$ $K_i$ = 1.4 nM



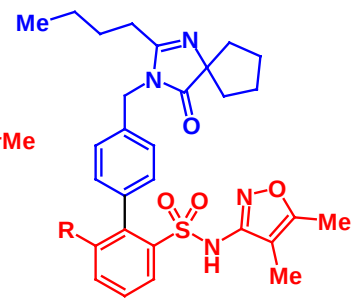
$AT_1$ $K_i$ > 0.8 nM
$ET_A$ $K_i$ >10,000 nM

N. Murugesan et al., J. Med. Chem. 45, 3829-3835 (2002);
N. Murugesan et al., J. Med. Chem. 48, 171-179 (2005)

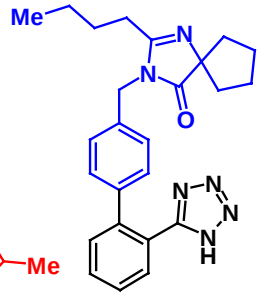
# Design of a Dual $AT_1$ and $ET_A$ Antagonist



$AT_1$ $K_i$ > 10,000 nM
$ET_A$ $K_i$ = 1.4 nM



R = $CH_2OEt$
$AT_1$ $K_i$ = 0.8 nM
$ET_A$ $K_i$ = 9.3 nM



$AT_1$ $K_i$ > 0.8 nM
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N. Murugesan et al., J. Med. Chem. 45, 3829-3835 (2002);
N. Murugesan et al., J. Med. Chem. 48, 171-179 (2005)

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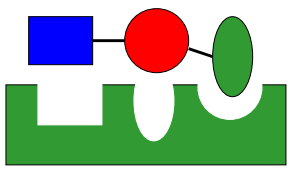
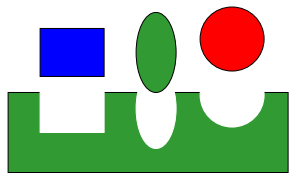
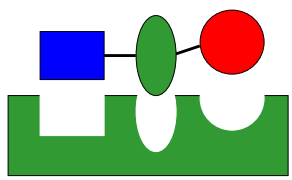
# To Fit or Not to Fit a Binding Site



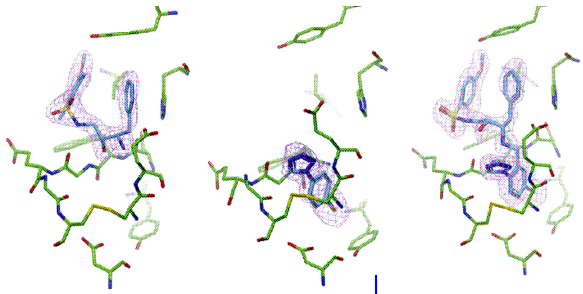
a common situation
in screening or docking:
the ligand does not
fit the binding site



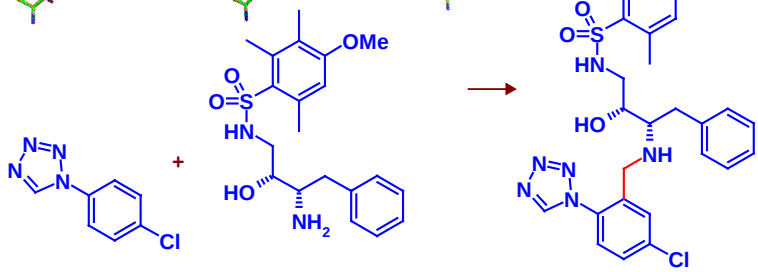
fragments fit the pockets
of the binding site



ligand fits the binding site



## Fragment-based Design of a Thrombin Inhibitor




$IC_{50}$ = 330 µM $IC_{50}$ = 12 µM $IC_{50}$ = 1.4 nM

N. Howard et al., J. Med. Chem. 49, 1346-1355 (2006)

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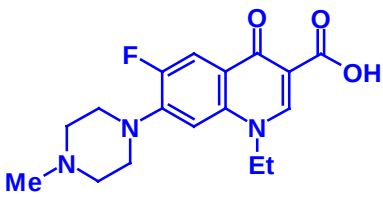
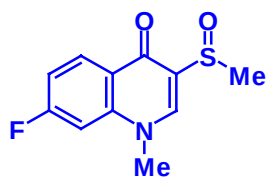
## The SOSA Approach - Selective Optimization of Side Activities

„The most fruitful basis for the discovery of a new drug is to start with an old drug“

Sir James Black, Nobel Prize 1988




norfloxazin, an antibiotic

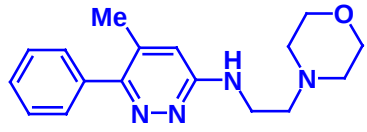



flosequinan, a mixed arterial and venous vasodilator

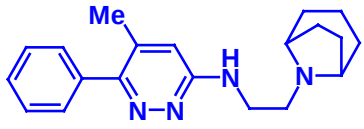
C. G. Wermuth, Med. Chem. Res. 10, 431-439 (2001); C. G. Wermuth, J. Med. Chem. 47, 1303-1314 (2004); H. Kubinyi, in H. Kubinyi, G. Müller, Chemogenomics in Drug Discovery, Wiley-VCH, 2004, pp. 43-67

# „Selective Optimization of Side Activities“

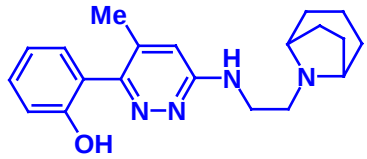

minaprine, an antidepressant
$K_i$ musc $M_1$ = 17,000 nM




5-methyl isomer of minaprine
$K_i$ musc $M_1$ = 550 nM




tropane analog
$K_i$ musc $M_1$ = 60 nM



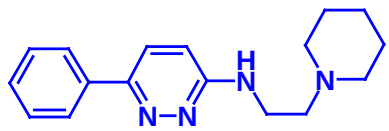

ortho-hydroxy substitution
$K_i$ musc $M_1$ = 3 nM

C. Wermuth, The „SOSA“ Approach, Med. Chem. Res. 10, 431-439 (2001)

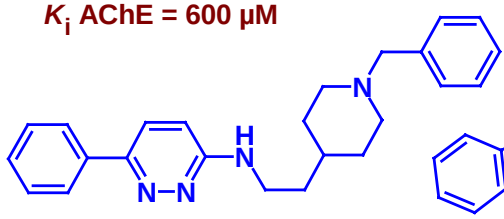
Hugo Kubinyi, www.kubinyi.de

# „Selective Optimization of Side Activities“

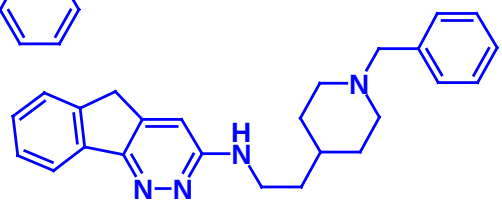

minaprine, an antidepressant
$K_i$ AChE = 600 µM




desoxo,desmethyl-minaprine
$K_i$ AChE = 13 µM




N-benzyl analog
$K_i$ AChE = 120 nM

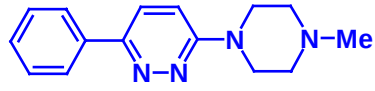



rigid analog
$K_i$ AChE = 10 nM

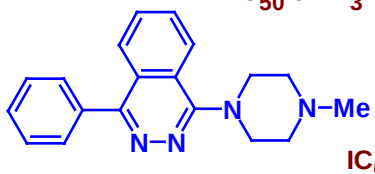
C. Wermuth, The „SOSA“ Approach, Med. Chem. Res. 10, 431-439 (2001)

# 3-Aminopyridazines as 5-HT$_3$ Antagonists

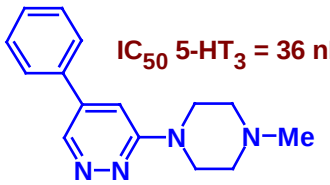

minaprine, an antidepressant



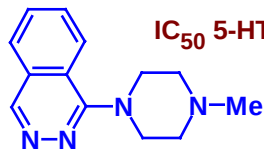

$IC_{50}$ 5-HT$_3$ = 425 nM




$IC_{50}$ 5-HT$_3$ = 370 nM




$IC_{50}$ 5-HT$_3$ = 36 nM




$IC_{50}$ 5-HT$_3$ = 10 nM

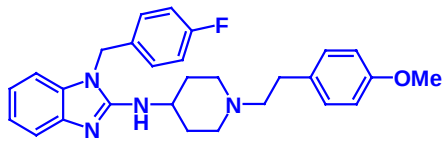
Y. Rival et al., J. Med. Chem. 41, 311-317 (1998)



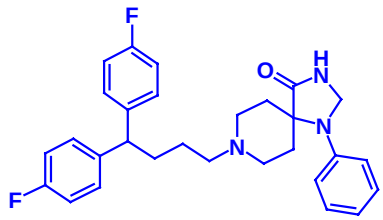
# Design of Selective sst5 Receptor Ligands

opioid, histamine, dopamine and serotonin receptors have high amino acid homology to sst5

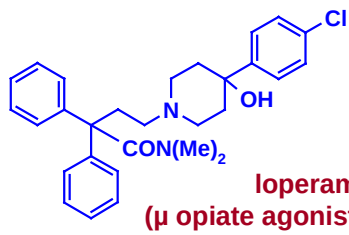
➔ ligand screening results:




astemizole (H1 antagonist)
$K_i$ hSST5R = 4.07 µM



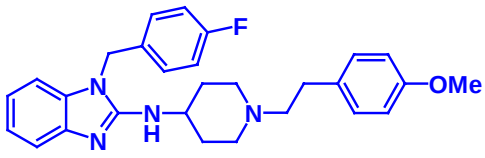

fluspirilene (D2 antagonist)
$K_i$ hSST5R = 4.51 µM



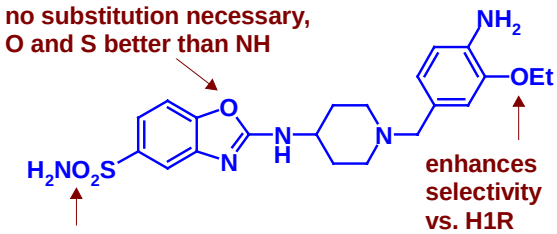

loperamide
(µ opiate agonist)
$K_i$ hSST5R = 4.52 µM

R. E. Martin et al., J. Med. Chem. 50, 6291-6294 (2007)

# Design of Selective sst5 Receptor Ligands




astemizole (H1 antagonist)
$K_i$ hSST5R = 4.07 µM
$IC_{50}$ H1R = 3 nM
$IC_{50}$ hERG = 0.9 nM



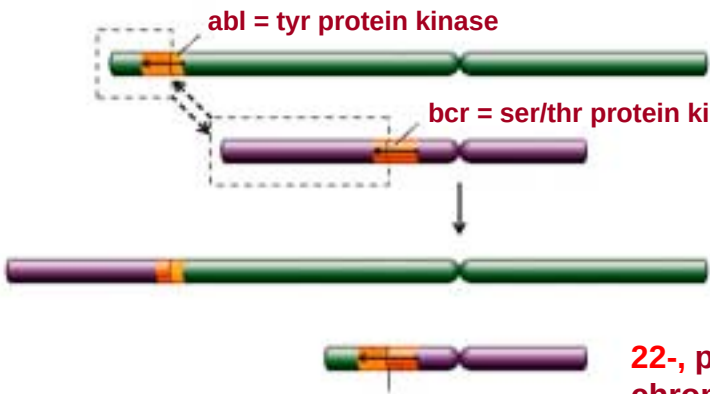

$K_i$ hSST5R = 13 nM

$K_i$ hH1R = 2.6 µM
$K_i$ hSST1R = 1.75 µM
$K_i$ hSST2,3,4R > 10 µM
no significant hERG activity

R. E. Martin et al., J. Med. Chem. 50, 6291-6294 (2007)



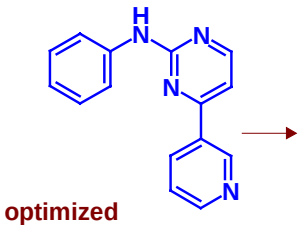
# Chromosome Translocation in CML



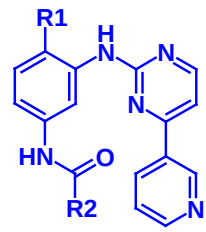

bcr-abl fusion protein, a hybrid with constitutionally enhanced tyrosine protein kinase activity

22-, philadelphia chromosome, present in 90+% of all cases of chronic mye-logenous leukemia

# Development of Imatinib (STI 571, Gleevec®)

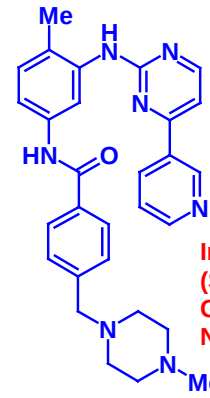


optimized lead, strong PKC inhibition



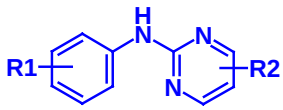
amides inhibit also tyrosine kinases, such as bcr-abl

R1 = Me (instead H) abolishes undesired PKC affinity



Imatinib (STI571, Gleevec, Novartis)

N-Me-piperazine increases solubility

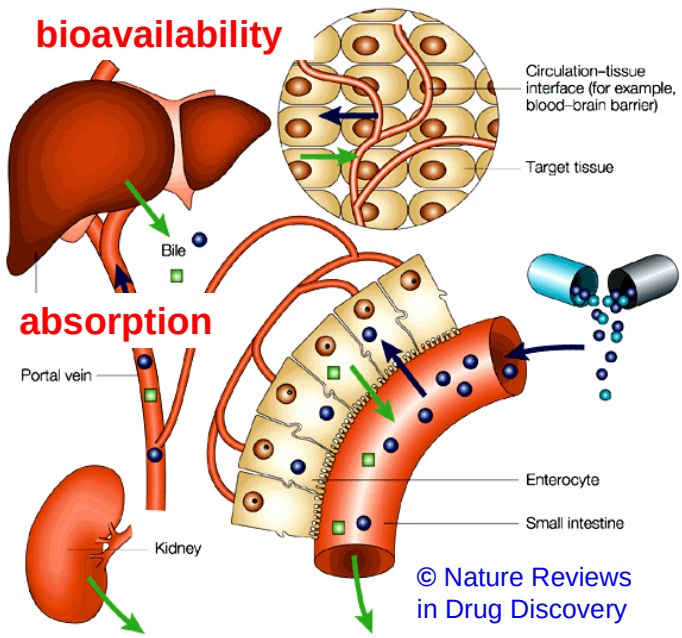


lead structure, active against PKC

R. Capdeville et al., Nature Rev. Drug Discov. 1, 493-502 (2002)



## bioavailability



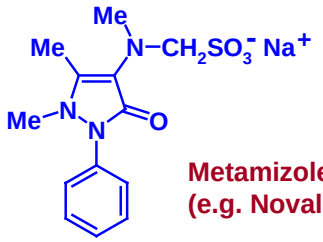

## Sites of Drug Metabolism:

(intestinal wall), liver, (organs)

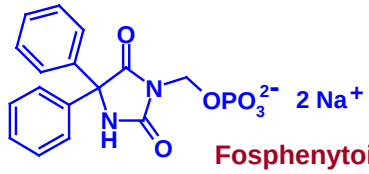
## Sites of Drug Elimination:

kidneys (polar compounds), bile, feces (lipophilic analogs), lung

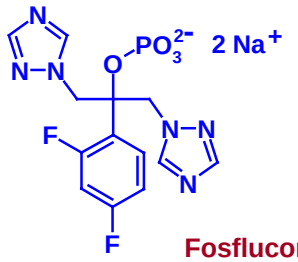
# Liberation: Better Soluble Drug Derivatives



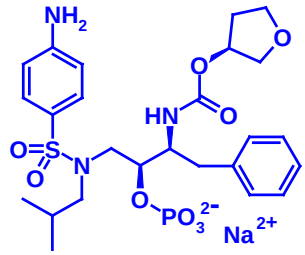

Metamizole
(e.g. Novalgin®)




Fosphenytoin




Fosfluconazole

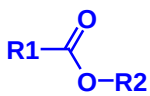


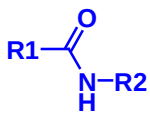

Fosamprenavir

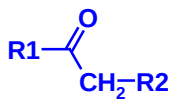


# Modulation of Biological Halflife Time

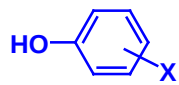
**Metabolism by**
**a) hydrolysis**

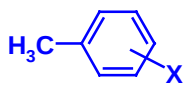


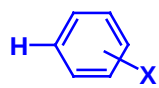



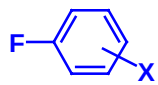




**b) oxidation**



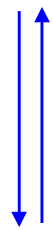



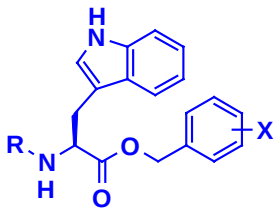

**Metabolic degradation**

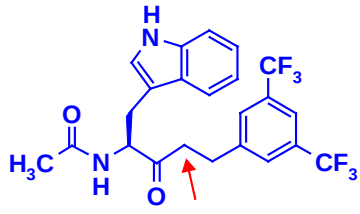
**fast**



**slow**

# Optimization of an NK1 Receptor Antagonist





orally available analog

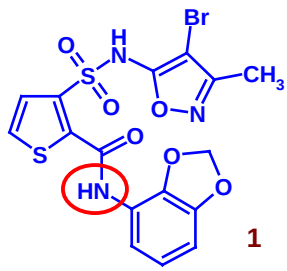
$IC_{50}$ = 3 nM

| | |
|---|---|
| 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 |

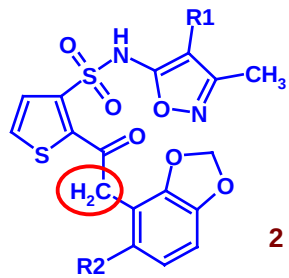
A. M. MacLeod et al., J. Med. Chem. 37, 1269-1274 (1994);
A. M. MacLeod et al., J. Med. Chem. 38, 934-941 (1995)

Hugo Kubinyi, www.kubinyi.de

# Optimization of an $ET_A$ Receptor Antagonist



1



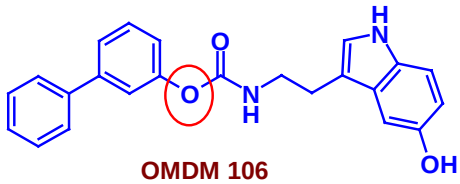
2

| Compound | oral bioavailability, % | $t_{1/2}$, h |
|---|---|---|
| 1 | 0 | < 0.5 |
| 2a, R1 = Cl, R2 = H | 30 | 1.5 |
| 2b, R1 = $CH_3$, R2 = $CH_3$ | 100 | 7 |

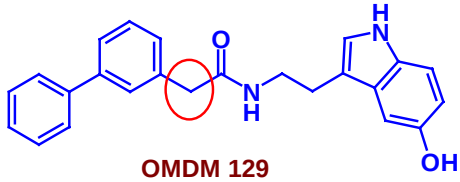
C. Wu et al., J. Med. Chem. 40, 1690-1697 (1997)

# Isosteric Replacement: A Rule with Exceptions

## Structure and Pharmacology of AA-5-HAT Analogs




OMDM 106



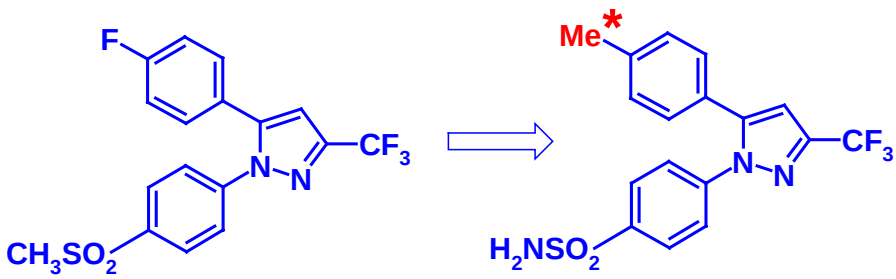

OMDM 129

| | FAAH | TRPV1 |
|---|---|---|
| | $IC_{50}$ in µMol | |
| OMDM 106 | 0.5 | >10 |
| OMDM 129 | >50 | 0.43 |

G. Ortar et al., J.Med. Chem. 50, 6554-6569 (2007)



# Oxidative Metabolism and Drug Design

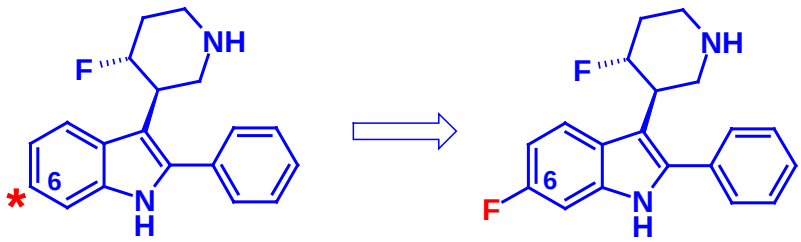



early COX2 inhibitor
$t_{1/2}$ (rat) up to 220 h

celecoxib
$t_{1/2}$ (rat) = 3.5 h

T. D. Penning et al., J. Med. Chem. 40, 1347-1365 (1997);
D. A. Smith, H. van de Waterbeemd and D. K. Walker, Pharmacokinetics and Metabolism in Drug Design, Wiley-VCH, 2001, p. 83

## Oxidative Metabolism and Drug Design




$K_i$ h5-HT$_{2A}$ = 0.43 nM

rat:
bioavailability = 18%
$t_{1/2}$ = 1.4 h

major metabolite: 6-OH

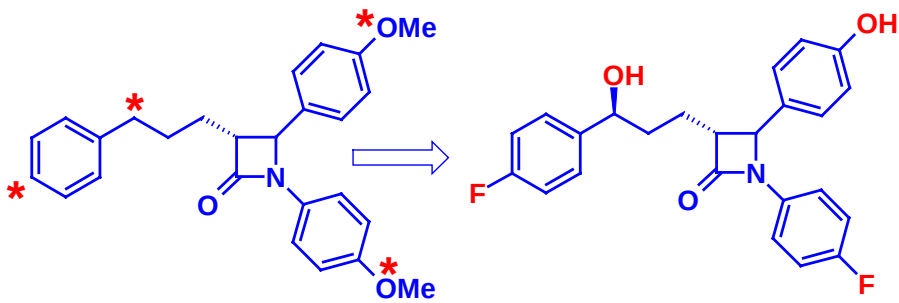
$K_i$ h5-HT$_{2A}$ = 0.06 nM

rat:
bioavailability = 80%
$t_{1/2}$ = 12 h

M. Rowley et al., J. Med. Chem. 44, 1603-1614 (2001)

Hugo Kubinyi, www.kubinyi.de

## Oxidative Metabolism and Drug Design




SCH 48461
$ED_{50}$ (hamster) = 2.2 mg/kg

Ezetimib (SCH 58235, oral cholesterol absorption inhibitor)
$ED_{50}$ (hamster) = 0.04 mg/kg

M. van Heek et al., J. Pharmacol. Exp. Ther. 283, 157-163 (1997);
D. A. Smith, H. van de Waterbeemd and D. K. Walker, Pharmacokinetics and Metabolism in Drug Design, Wiley-VCH, 2001, p. 85

# 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 activation

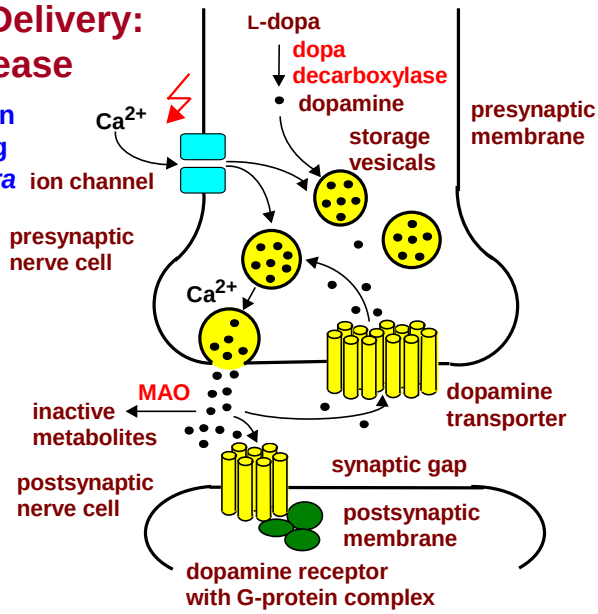
**Other mechanisms of organ-specific action**

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



# 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**

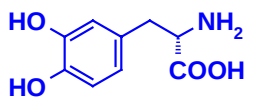
dopamine is not bio-available, peripheral side effects, MAO

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



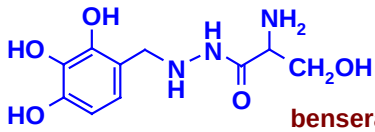
# Integrated Optimisation of Drug Therapy

## Dopamine Substitution in Parkinson‘s Disease



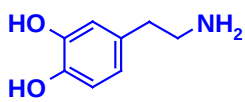

L-dopa as dopamine prodrug

periphery ⇢ dopamine



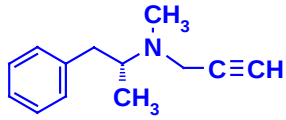

benserazide

brain ↓




dopamine

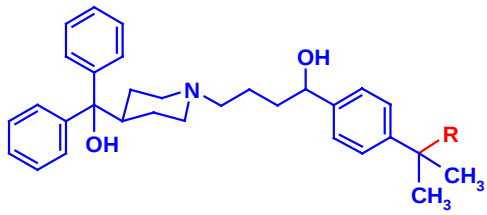
inactive metabolites ⇢




(R)-(-)-selegiline

## Avoidance of CNS Side Effects by Active Efflux

**Terfenadine, R = $CH_3$**
**lipophilic $H_1$ antagonist (no sedative side effect, due to active elimination by a drug transporter; cardiotoxic, due to hERG inhibition)**

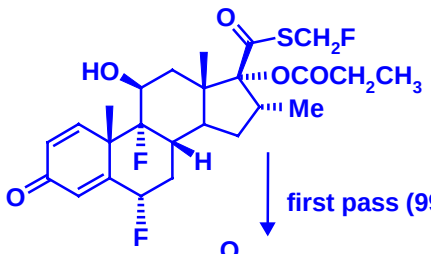



| | | |
|---|---|---|
| R = $CH_3$ | $IC_{50}$ = | 56 nM |
| R = OH | $IC_{50}$ = | 460 nM |
| R = COOH | $IC_{50}$ = | 23,000 nM |

**Fexofenadine, R = COOH**
**active terfenadine metabolite**



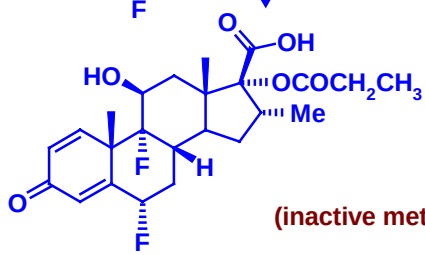
## Soft Drugs: Corticosteroid Esters




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

**(inhalation; topically active in asthma treatment)**

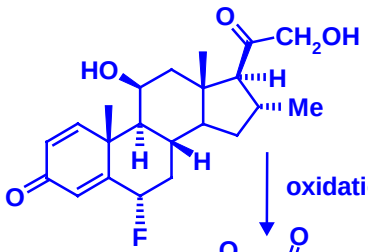
**first pass (99%)**




**(inactive metabolite)**

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

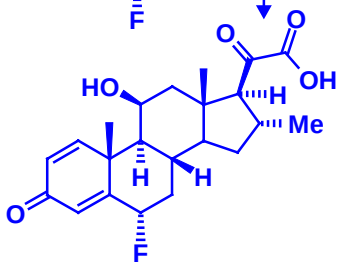
# Soft Drugs: Corticosteroid Esters




fluocortolone

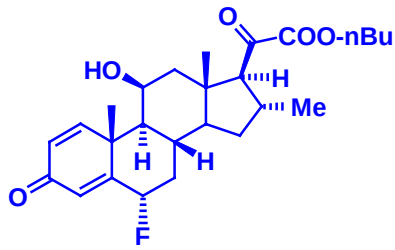
(topically and systemically active)

oxidation




(topically and systemically inactive)

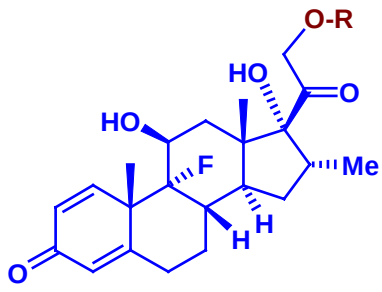
ester formation




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

Hugo Kubinyi, www.kubinyi.de

# Colon-Selective Delivery of Corticosteroids in Inflammatory Bowel Disease

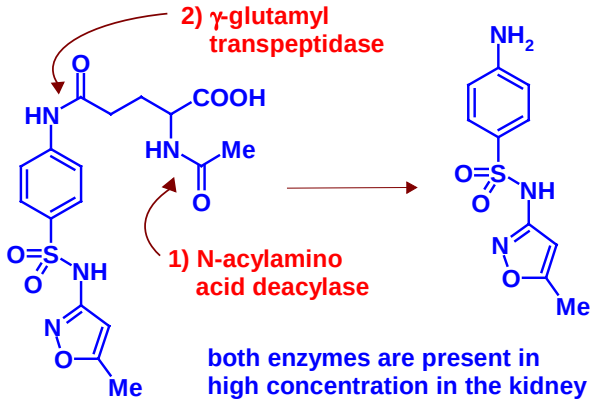



R = H, Dexamethasone
oral dose almost exclusively absorbed in the intestine, only about 1% reach the cecum

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)

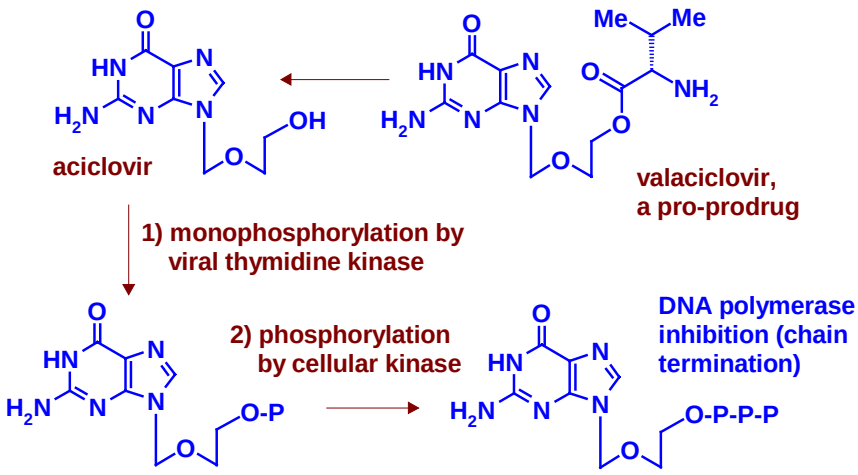
# Kidney-Selective Release of the Antiinfective Sulfonamide Sulfamethoxazole



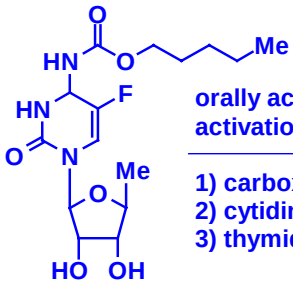

C. G. Wermuth, The Practice of Medicinal Chemistry, 3rd Edition, Elsevier/Academic Press, New York 2008, p. 729-730;
M. Orlowski et al., J. Pharmacol. Exp. Ther. 212, 167-172 (1979)



# Antiviral Prodrugs are Trojan Horses



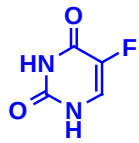
# Tumor Cell-Specific Trojan Horses



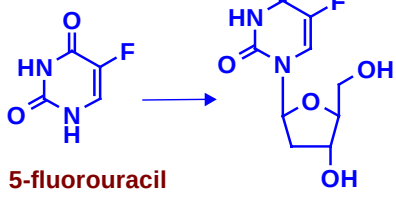
capecitabine

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

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



5-fluorouracil



5-fluorouracil

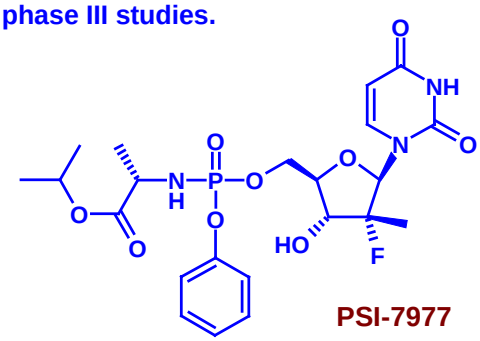
5-F-2'-desoxy-uridylate

(thymidylate synthase inhibitor)

Hugo Kubinyi, www.kubinyi.de

# 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.**



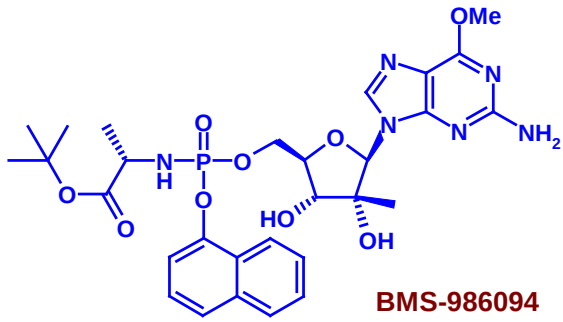
PSI-7977

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.

# 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.**



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