Physicochemical properties

8.3.2018

LIPOPHILICITY

LogP depends on:

Molecular volume

Dipolarity

Hydrogen bond acidity

Hydrogen bond basicity

LIPOPHILICITY

LogP depends on:

Molecular volume

-related to molecular weight and affects the overall size of the cavity that must be formed in the solvent

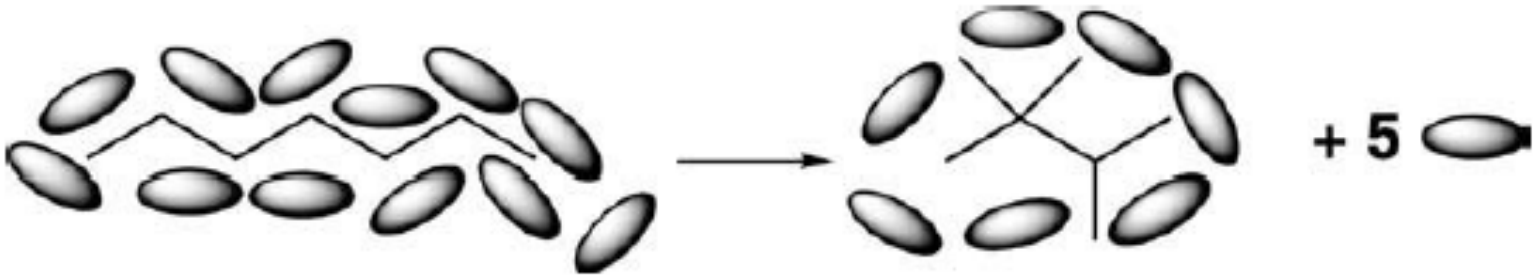


Fig. 19.2 Fewer structured water molecules are needed to wrap a compact molecule (2,2,3-trimethylbutane) than to wrap an extended one (*n*-heptane).

LIPOPHILICITY

LogP depends on:

Molecular volume

Dipolarity

-affects the polar alignment of the molecule with polar solvent (dipole-dipole interaction with molecules of water)

Hydrogen bond acidity

Hydrogen bond basicity

LIPOPHILICITY

LogP depends on:

Molecular volume

Dipolarity

Hydrogen bond acidity

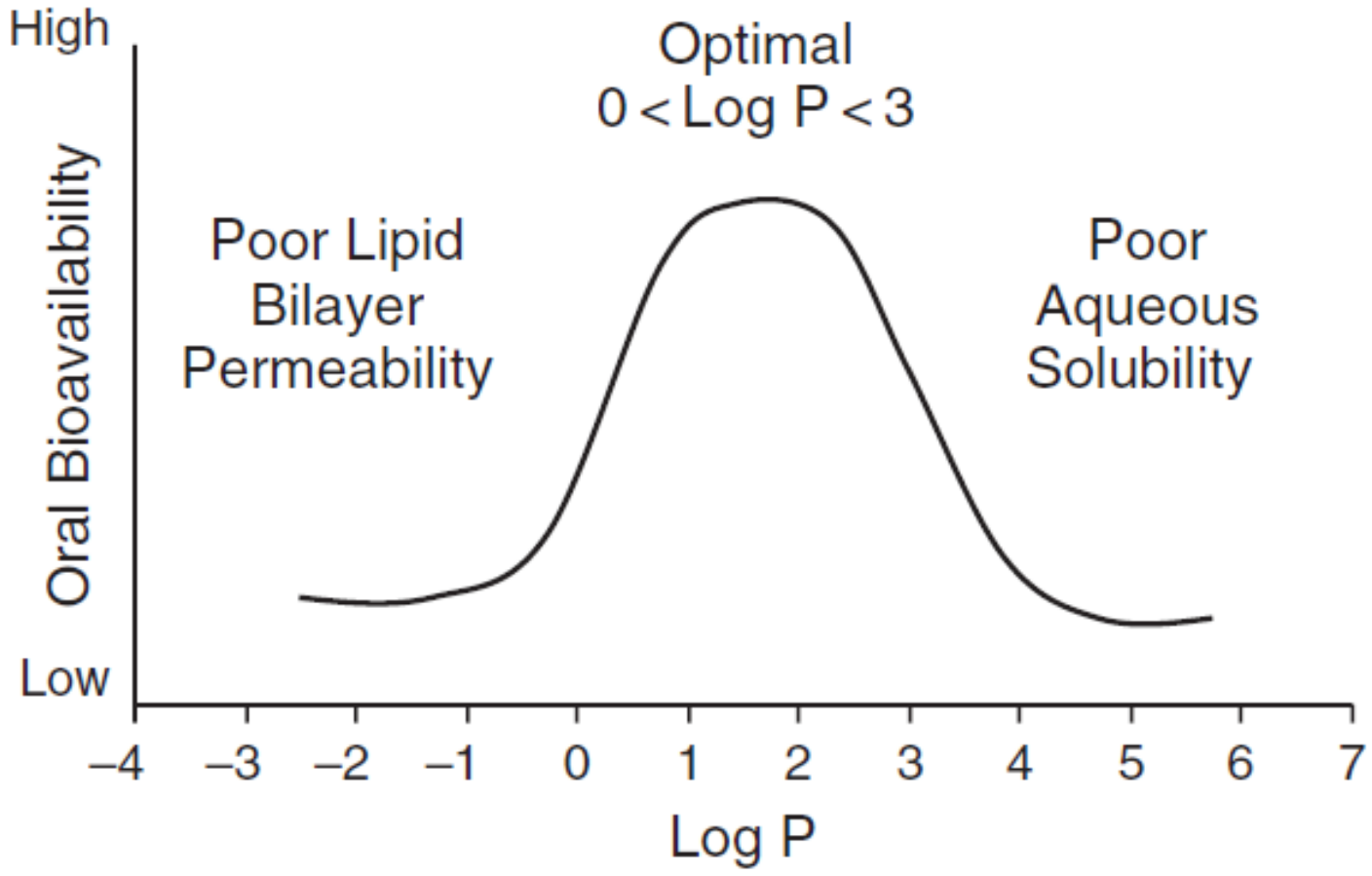
-hydrogen bond donation – hyrogens with polar bonds (OH, NH_2, NH)

Hydrogen bond basicity

-hydrogen bond acceptance (O, N, F atoms)

Both affects the hydrogen bonding rate with environment

LIPOPHILICITY



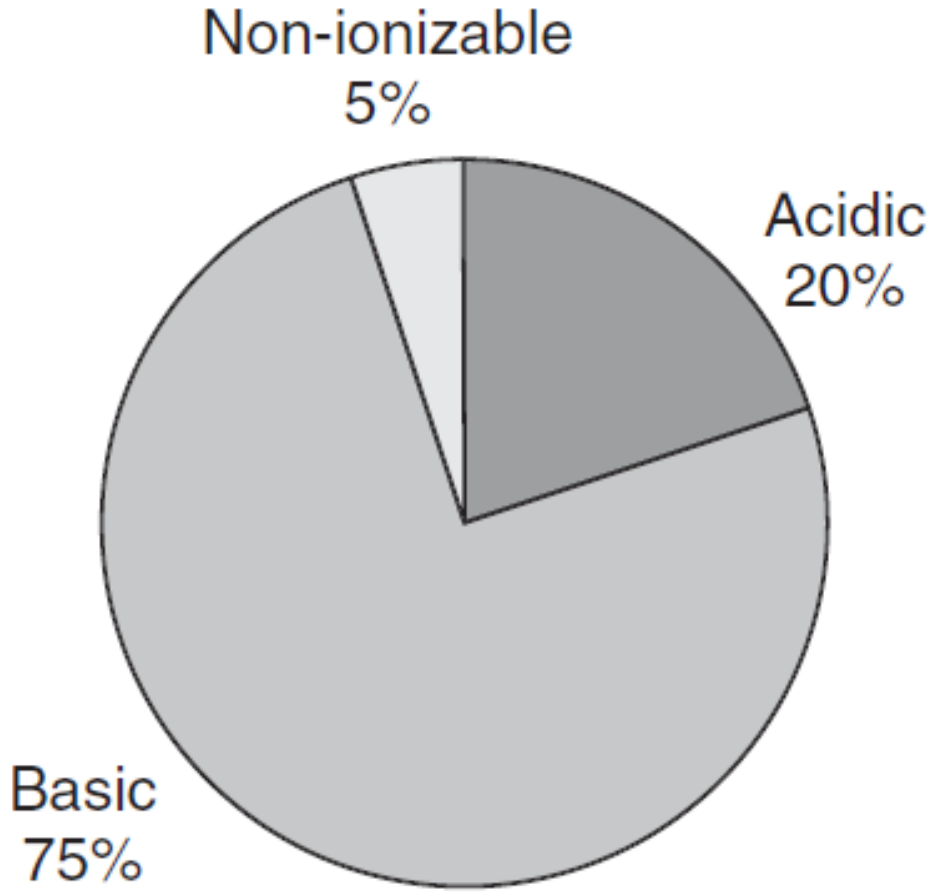
LIPOPHILICITY

Log $D_{7.4}$	Common Impact on Drug-like Properties	Common Impact *In Vivo*
< 1	Solubility high Permeability low by passive transcellular diffusion Permeability possible via paracellular if MW < 200 Metabolism low	Volume of distribution low Oral absorption and BBB penetration unfavorable Renal clearance may be high
1 to 3	Solubility moderate Permeability moderate Metabolism low	Balanced volume of distribution Oral absorption and BBB penetration favorable
3 to 5	Solubility low Permeability high Metabolism moderate to high	Oral bioavailability moderate to low Oral absorption variable
> 5	Solubility low Permeability high Metabolism high	High volume of distribution (especially amines) Oral absorption unfavorable and variable

pK_A

Most of drugs are **ionizable**

Most of drugs are **basic**



pK_A

pKa determines the degree of ionization and affects both solubility and permeability, but in opposite way

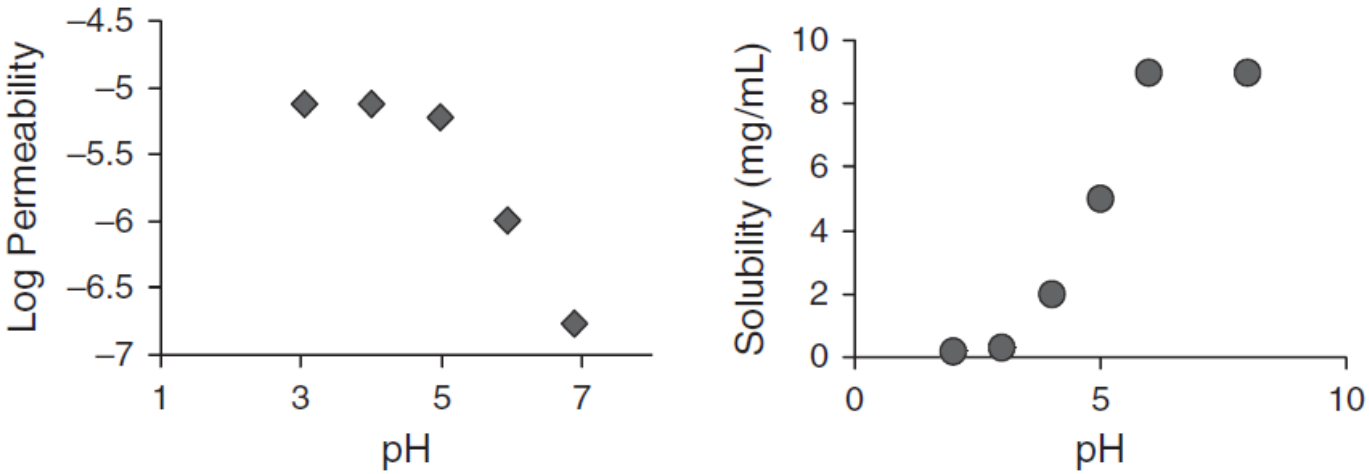


Figure 6.3 ► Permeability and solubility profiles for an acidic compound with a pK_a of 5. Permeability and solubility are pH dependent for ionizable compounds. The properties exhibit opposite effects with pH because of the effects of ionization.

pK_A

Acids	pK_a
Penicillin V	2.7
Salicylic acid	3.0, 13.8
Acetylsalicylic acid	3.5
Diclofenac	4.1
Sulfathiazole	7.1
Phenobarbital	7.4, 11.8
Phenytoin	8.3
Acetaminophen	9.9
Caffeine	14

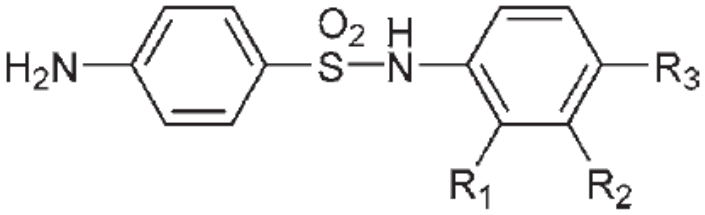
pK_A

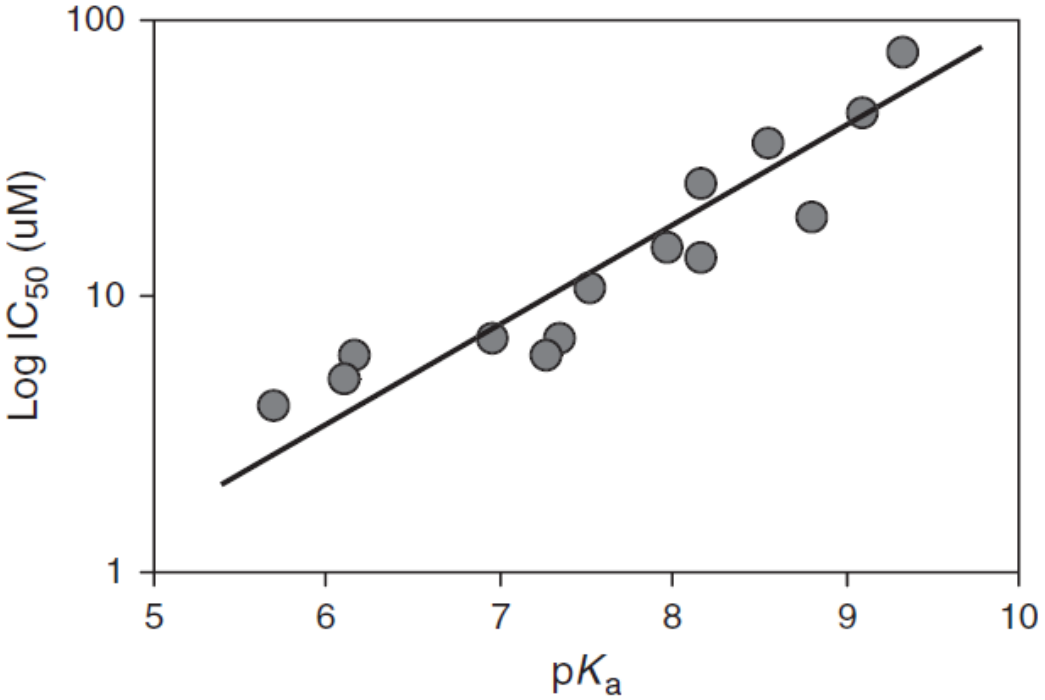
Bases	pK_a
Caffeine	0.6
Quinidine	4.1, 8.0
Tolbutamide	5.3
Cocaine	8.4
Ephedrine	9.4
Imipramine	9.5
Atropine	9.7

pK_A

Effect of mesomeric effect on sulfonamide activity :
most acidic compounds are most potent
almost linear dependence

pK_A

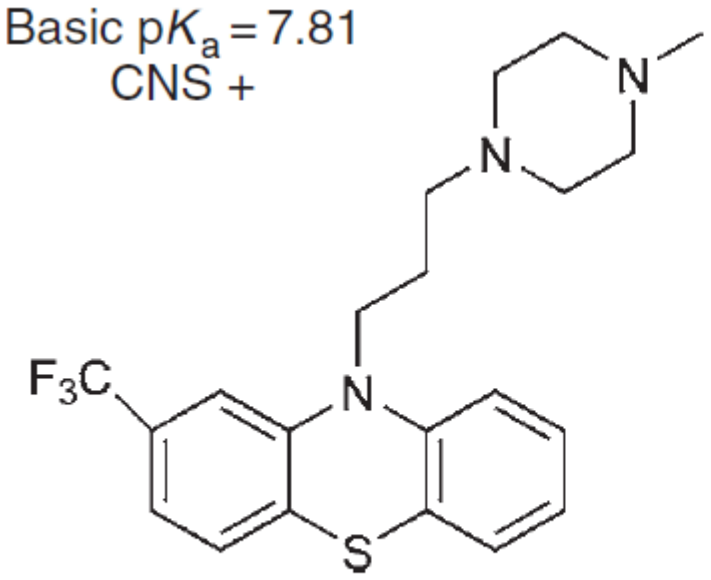




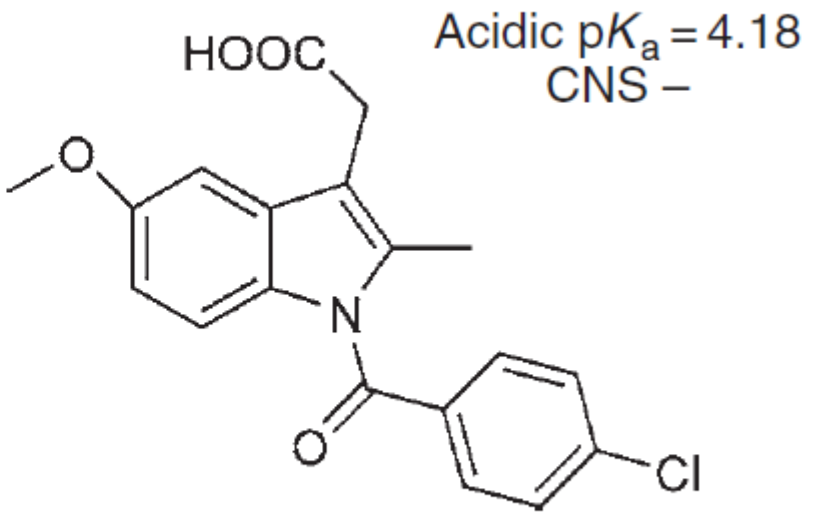
Compounds	IC_{50} (uM)	pK_a
4-OCH_3	75	9.34
H	45	9.10
4-Cl	35	8.56
4-I	25	8.17
2-Cl, 4-OCH_3	19	8.81
3-CF_3	15	7.98
2-Cl	14	8.18
4-$COCH_3$	11	7.52
4-CN	7	7.36
4-NO_2	7	6.97
2-OCH_3, 4-NO_2	6	7.27
2-Cl, 4-NO_2	6	6.17
2-NO_2, 4-CF_3	5	6.10
2-Br, 4-NO_2	4	5.70

pK_A

basic drugs permeates blood-brain barrier, acidic do not so



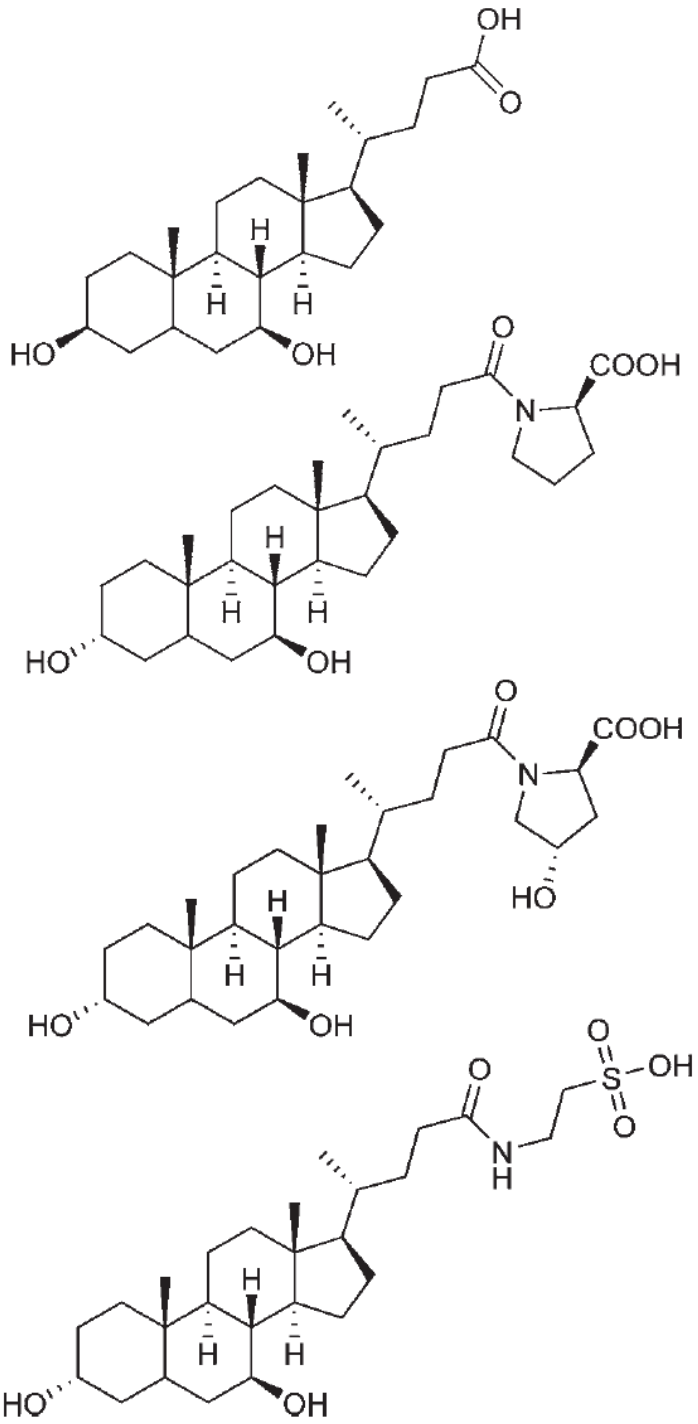
Trifluoroperazine



Indomethacin

pK_A

pKa effect on water solubility of bile acids:



$pK_a = 5.0$, Solubility = 8 μM

$pK_a = 3.9$, Solubility = 113 μM

$pK_a = 3.1$, Solubility = 250 μM

$pK_a = 1\text{-}2$, Solubility = 450 μM

pK_A

The strenght of acid can be increased by electron withdrowing group on α carbon (halogen, carboxy, cyano, nitro...)

The strenght of base can be decreased by adding conjugated double bond system close to nitrogen (nitrogen lone electron pair is delocalized)

Basicity of aniline can be increased by $-OCH_3$ and decreased by $-NO_2$ substitution

SOLUBILITY

Solubility is a determinant of intestinal absorption and oral bioavailability

Solubility is increased by adding ionizable groups or reducing logP and MW

Salt formation increse dissolution rate

SOLUBILITY

Problems of low-soluble compounds:

- Poor absorption and bioavailability after oral dosing
- Insufficient solubility for IV dosing
- Artificially low activity values from bioassays
- Erratic assay results (biological and property methods)
- Development challenges (expensive formulations and increased development time)
- Burden shifted to patient (frequent high-dose administrations)

design problem:

-lipophillic groups are often added to enhance target binding

-most active compounds are often poor soluble

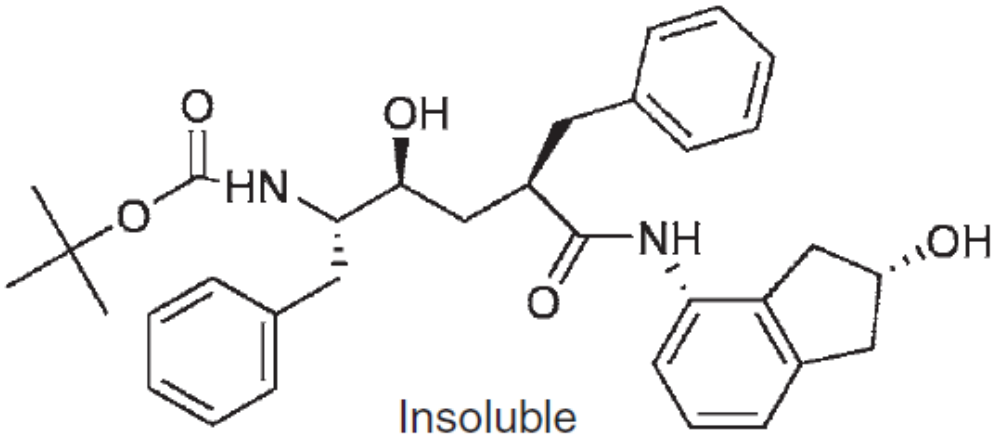
SOLUBILITY

Structural properties affecting solubility:

- Lipophilicity: Determined by van der Waals, dipolar, hydrogen bonds, ionic interactions
- Size: Molecular weight, shape
- pK_a: Determined by functional group ionizability
- Crystal lattice energy: Determined by crystal stacking, melting point

SOLUBILITY

Effect of solubility on oral bioavailability:



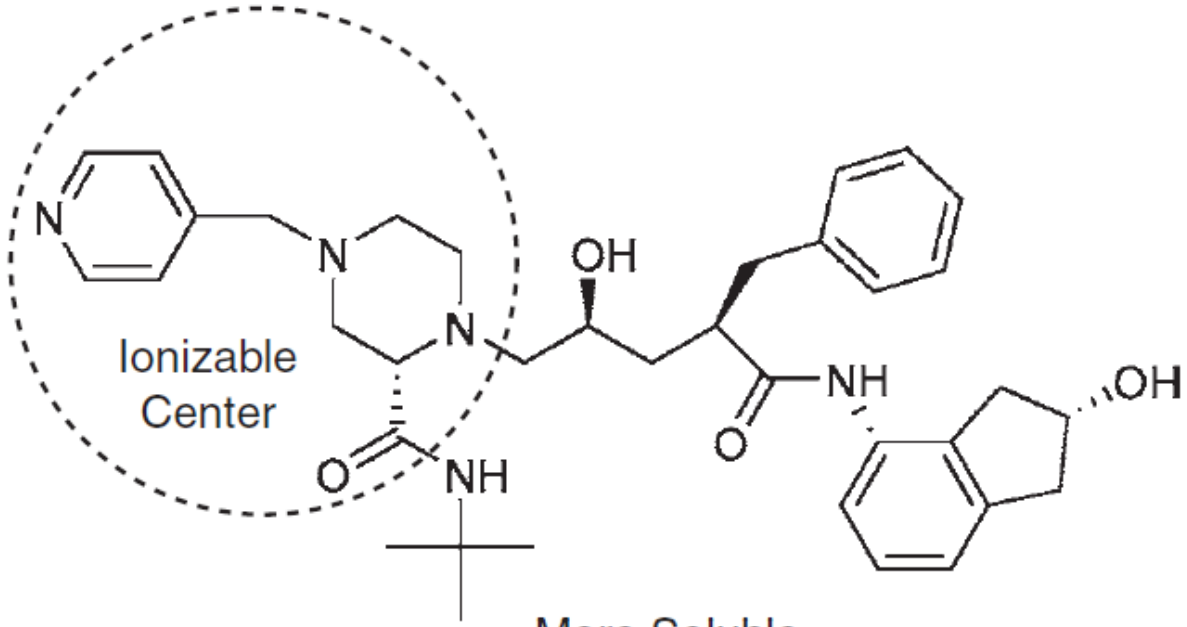
Insoluble

L-685,434

IC_{50} = 0.3 nM

CIC_{95} = 400 nM

No Oral Bioavailability



More Soluble

Indinavir

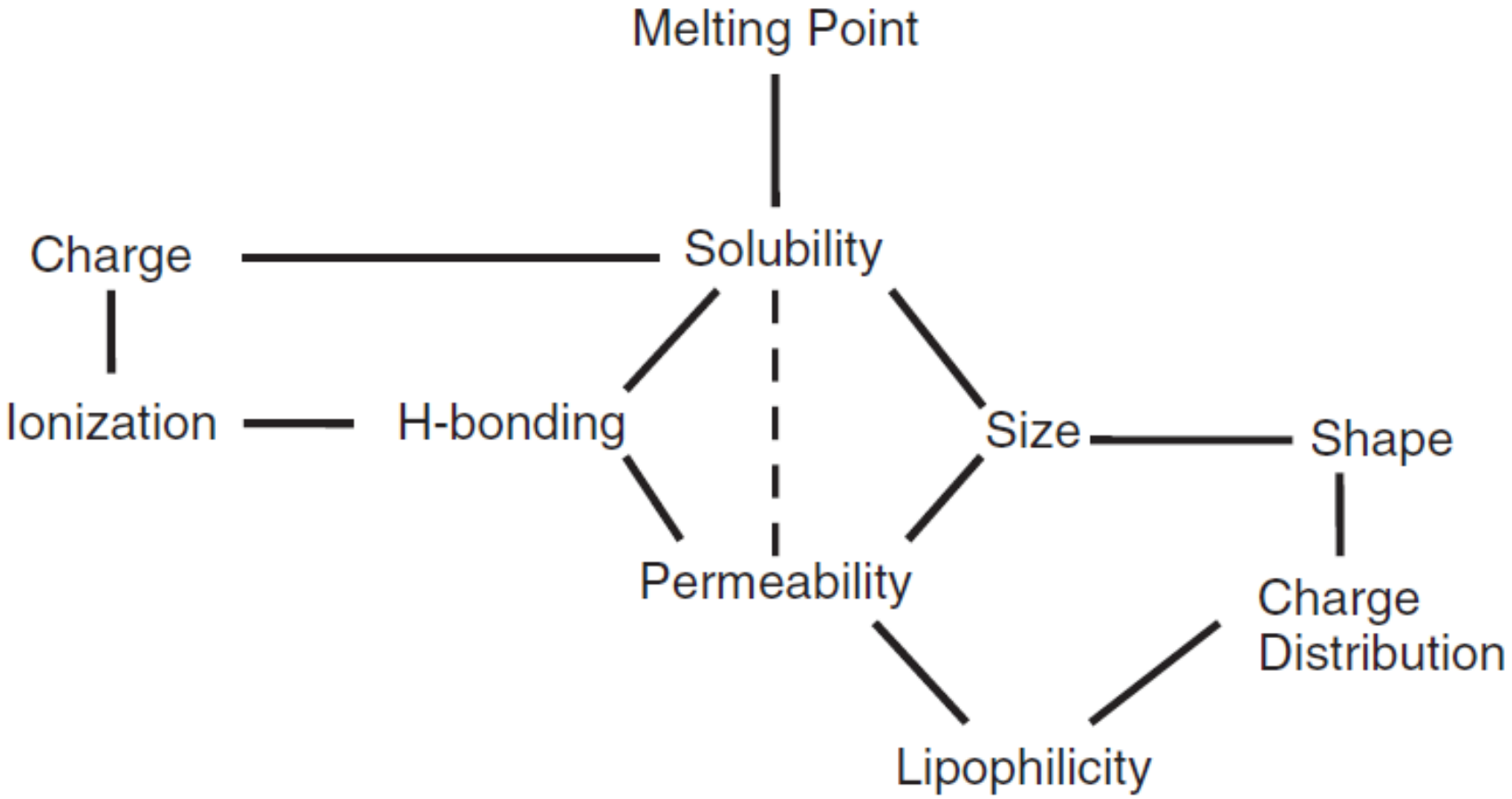
IC_{50} = 0.41 nM

CIC_{96} = 24–100 nM

Oral Bioavailability = 60% Human

SOLUBILITY

Changing one property affest other properties:



SOLUBILITY

Permeability tends to vary over a more narrow range than does solubility.

The difference between a high-permeability and low-permeability compound can be 50-fold (0.001-0.05 min^{-1})

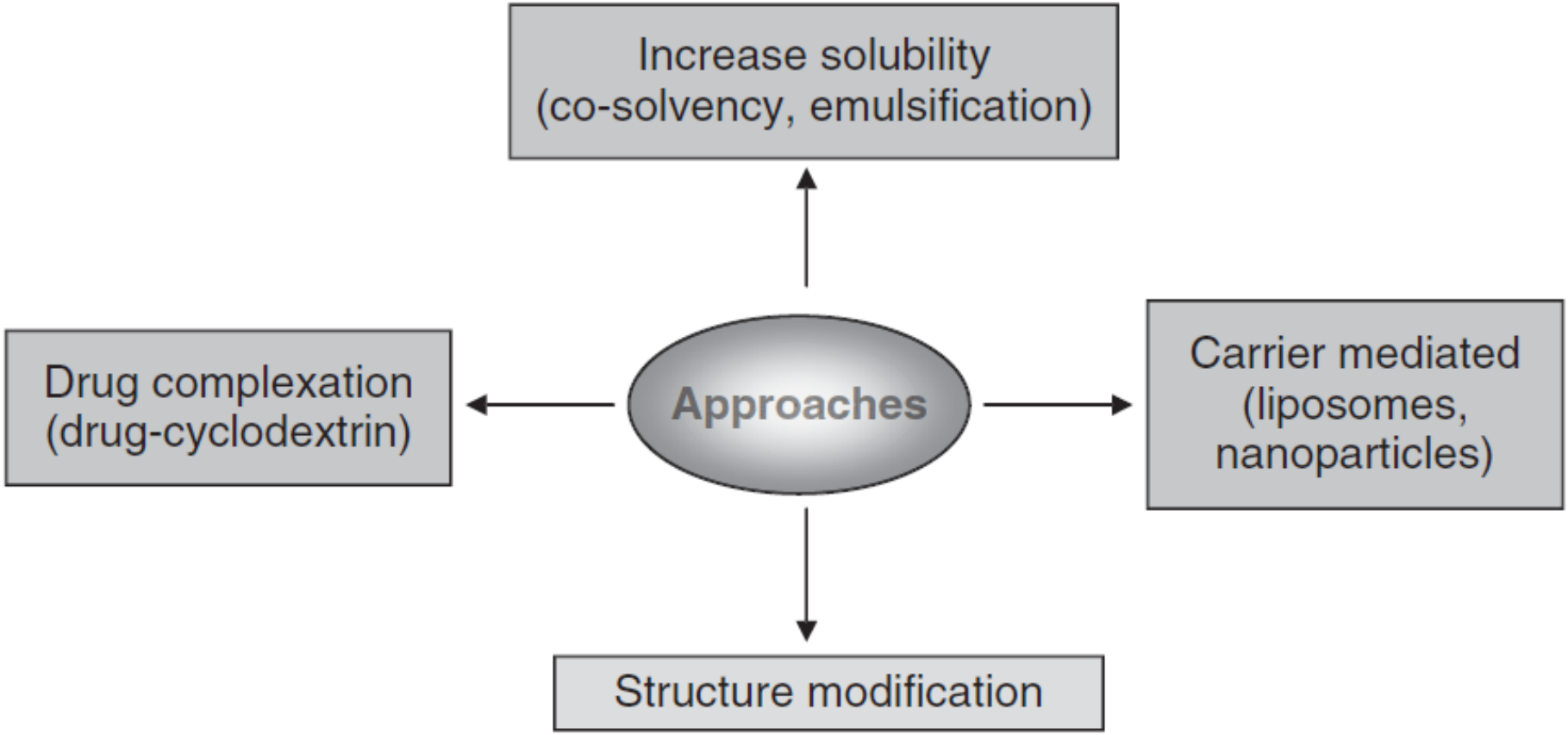
The difference between a high-solubility and low-solubility compound can be million-fold (0.1 µg/mL-100mg/mL)

Therefore, if a structural modification improves solubility by 1000-fold while reduces permeability by 10-fold, there will be still 100-fold improvement of absorption

SOLUBILITY

Approaches to improve solubility

– structure modification is the first choice



SOLUBILITY

Structure modification strategies for solubility improvement:

Structure modification
Add ionizable group
Reduce Log P
Add hydrogen bonding
Add polar group
Reduce molecular weight
Out-of-plane substitution to reduce crystal packing
Construct a prodrug

SOLUBILITY

1. Addition of ionizable groups

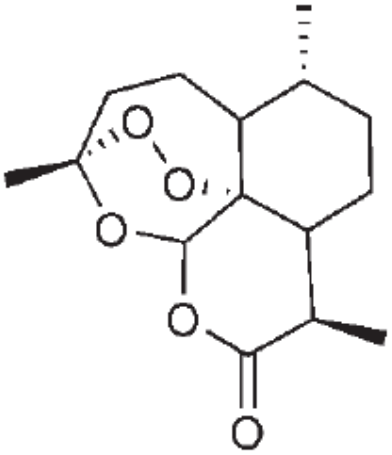
typically basic amine or carboxylic group is added

Small groups or simple functionalities	Larger solubilizing moieties
—CO_2H	R—OH → R—O—CH_2—CH_2—CO_2H
—SO_3H, —OSO_3H	R—NH_2 → R—NH—CH_2—CH_2—CH_2—SO_3H
—PO_3H_2, —OPO_3H_2	$(R)_2C=O$ → $(R)_2C=N$—O—CH_2—CO_2H
—NH_2, —NHR, —NR_2	R—OH → O-morpholinylethyl
N-oxides	R—OH → O-glucoside
S-oxides	R—OH → O—CO—CH_2—CH_2—CO_2H
Sulfones	R—OH → *m*-O—C_6H_4—SO_3H

SOLUBILITY

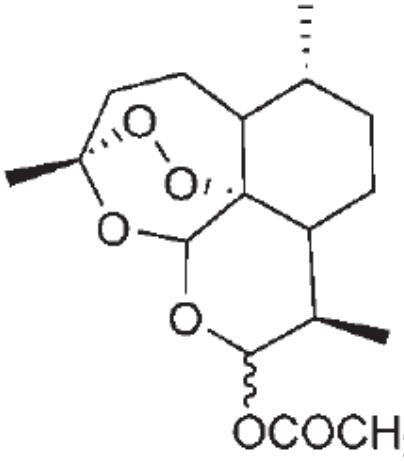
1. Addition of ionizable groups

typically basic amine or carboxylic group is added



Artemisinin

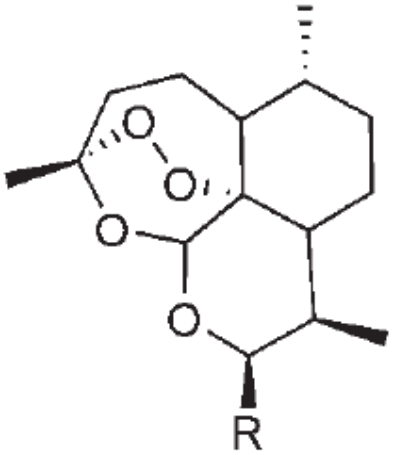
- Low aq sol.
- Low oil sol.



Na-Salt

- Good aq sol.
- Unstable

$OCOCH_2CH_2COONa$



R = $O(CH_2)nNR_1R_2$

$OCH_2CH(OH)NR_1R_2$

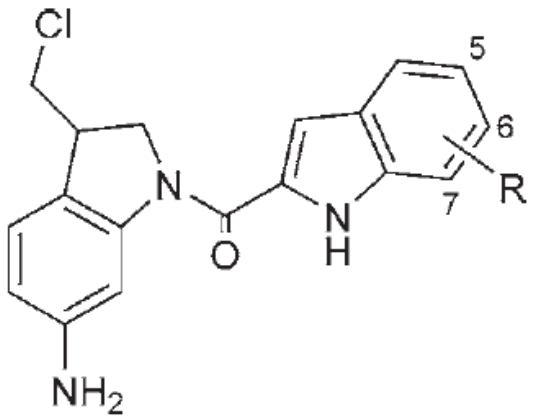
$O(CH_2)_2NR_1R_2$

Amine Maleates or Oxlates

- Better aq sol.
- Good stability
- Active P.O.

SOLUBILITY

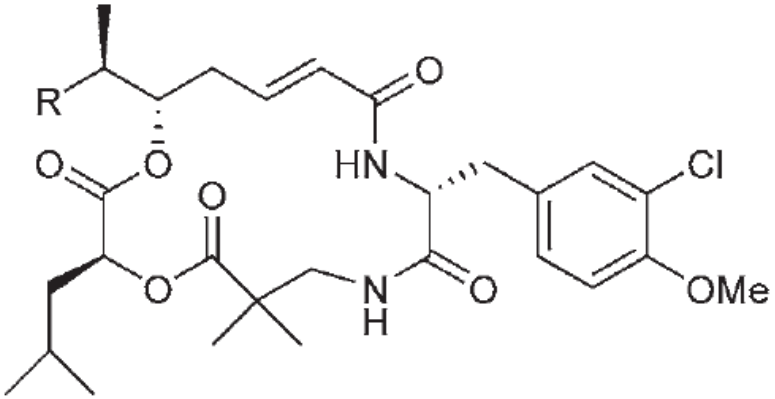
1. Addition of ionizable groups

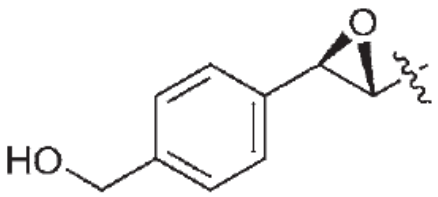


R	Solubility (μM)	IC50 (μM) AA8	UV4	EMT6	SKOV3
5,6,7-triOMe	32	0.35	0.055	0.27	0.63
5-OMe	23	0.31	0.047	0.23	0.67
5-O$(CH_2)_2NMe_2$	700	0.16	0.044	0.12	0.26
5-OMe, 6-O$(CH_2)_2NMe_2$	>1200	0.22	0.039	0.11	0.15
5-OMe, 7-O$(CH_2)_2NMe_2$	47	0.14	0.029	0.09	0.16

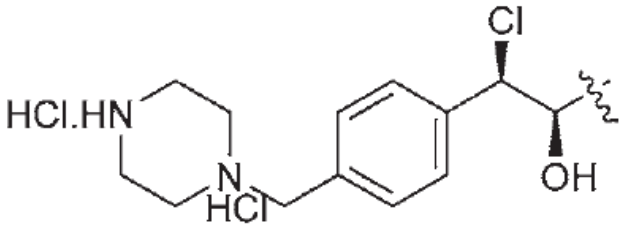
SOLUBILITY

1. Addition of ionizable groups





$IC_{50} = 0.004$ nM, Low solubility
Weak activity *in vivo*

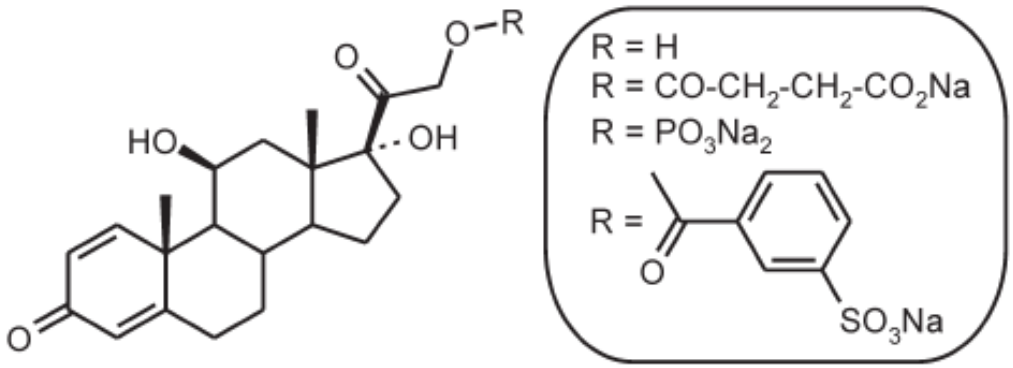


$IC_{50} = 0.021$ nM, Soluble
Very active *in vivo*

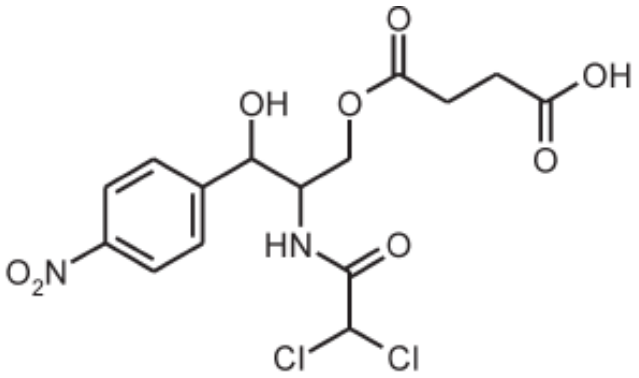
Figure 7.17 ► Series compounds that are more active in vitro and have low solubility may not be as active in vivo as series analogs that have lower in vitro activity but are soluble and, thus, better absorbed.

SOLUBILITY

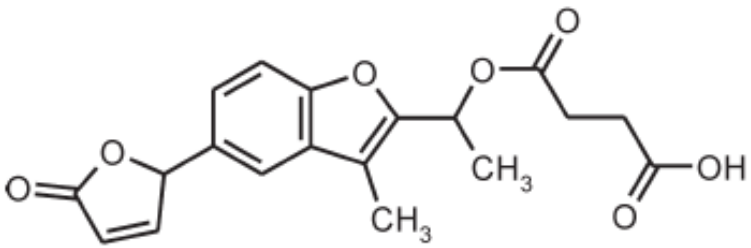
1. **Addition of ionizable groups** - acids



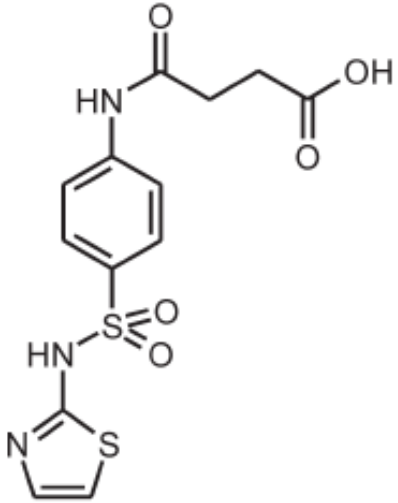
prednisolone derivatives



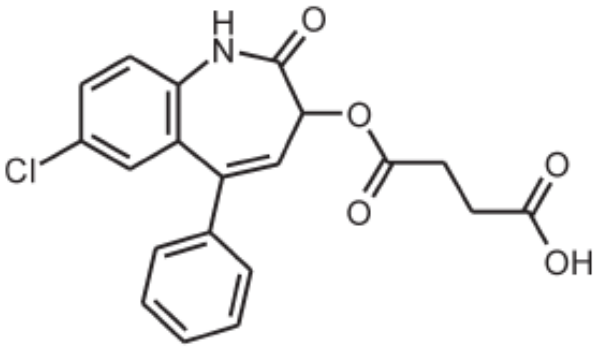
chloramphenicol hemisuccinate



benfurodil hemisuccinate



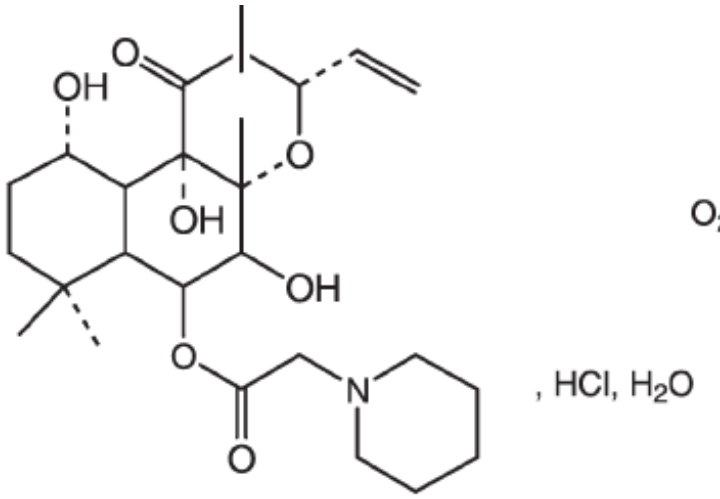
succinylsulfathiazole



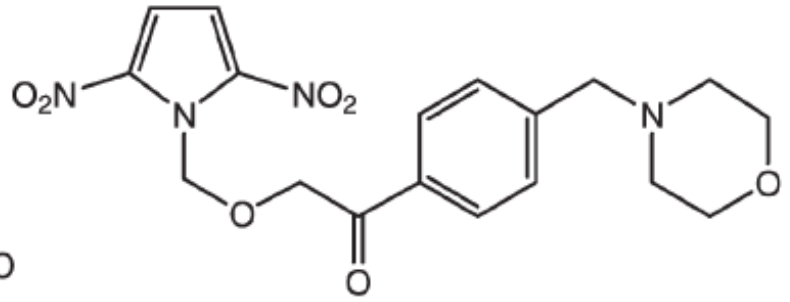
oxazepam hemisuccinate

SOLUBILITY

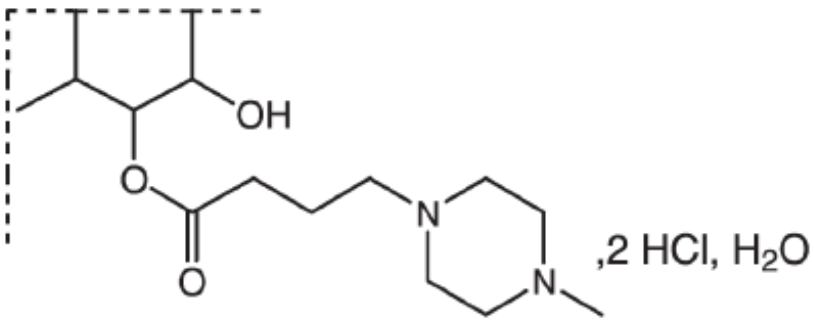
1. **Addition of ionizable groups** - base



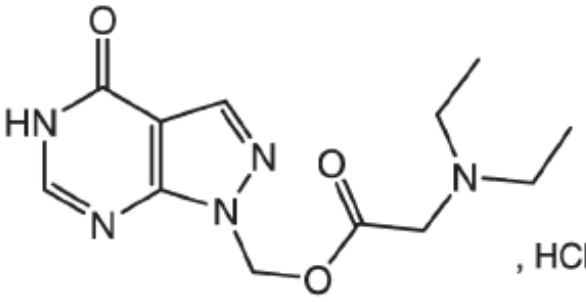
6-(piperidinoacetyl)-
7-deacetylforskolin hydrochloride



(4-morpholinylmethyl)-benzoate
of metronidazole



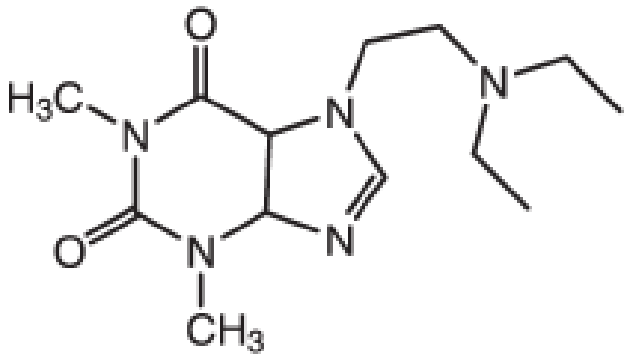
6-(4-methylpiperazinobutyryl)-
7-deacetylforskolin dihydrochloride



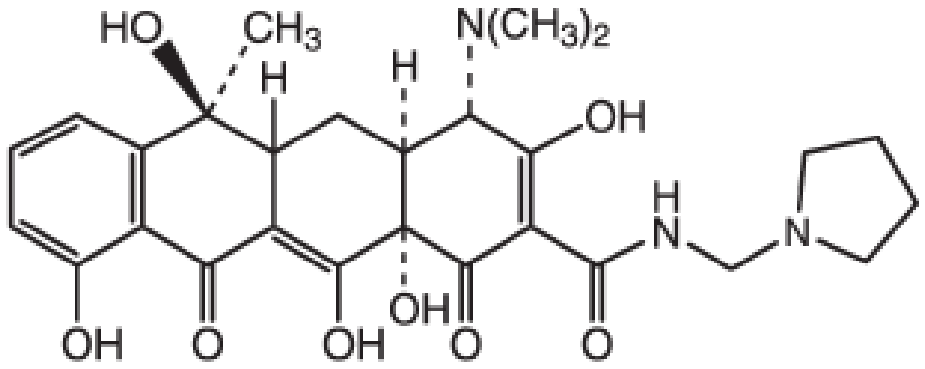
1-(N,N-diethylglycyloxymethyl)allopurinol
hydrochloride

SOLUBILITY

1. **Addition of ionizable groups** - base



etamphyllin



rolitetracycline

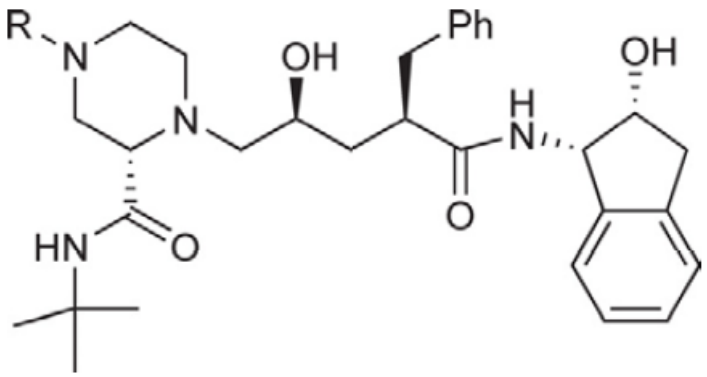
SOLUBILITY

The most active compound in vitro is not necessarily the most active in vivo

A succesfull drug candidate posesses balanced potency and suitable physico-chemical properties

SOLUBILITY

2. Reduction of logP



#	R	Cmax (uM)	Solubility (mg/mL) at pH 7.4	Log P
1	benzyloxycarbonyl	<0.10	<0.001	4.67
2	8-quinolinylsulfonyl	<0.10	<0.001	3.7
3	2,4-difluorophenylmethyl	0.73	0.0012	3.69
4	3-pyridylmethyl	11.4	0.07	2.92

Figure 7.18 ▶ For a series of protease inhibitors, absorption increased (as indicated by C_{max}) as solubility increased. Compound 4 in the chart was developed into the commercial drug indinavir.

SOLUBILITY

3. Increasing hydrogen bonding properties

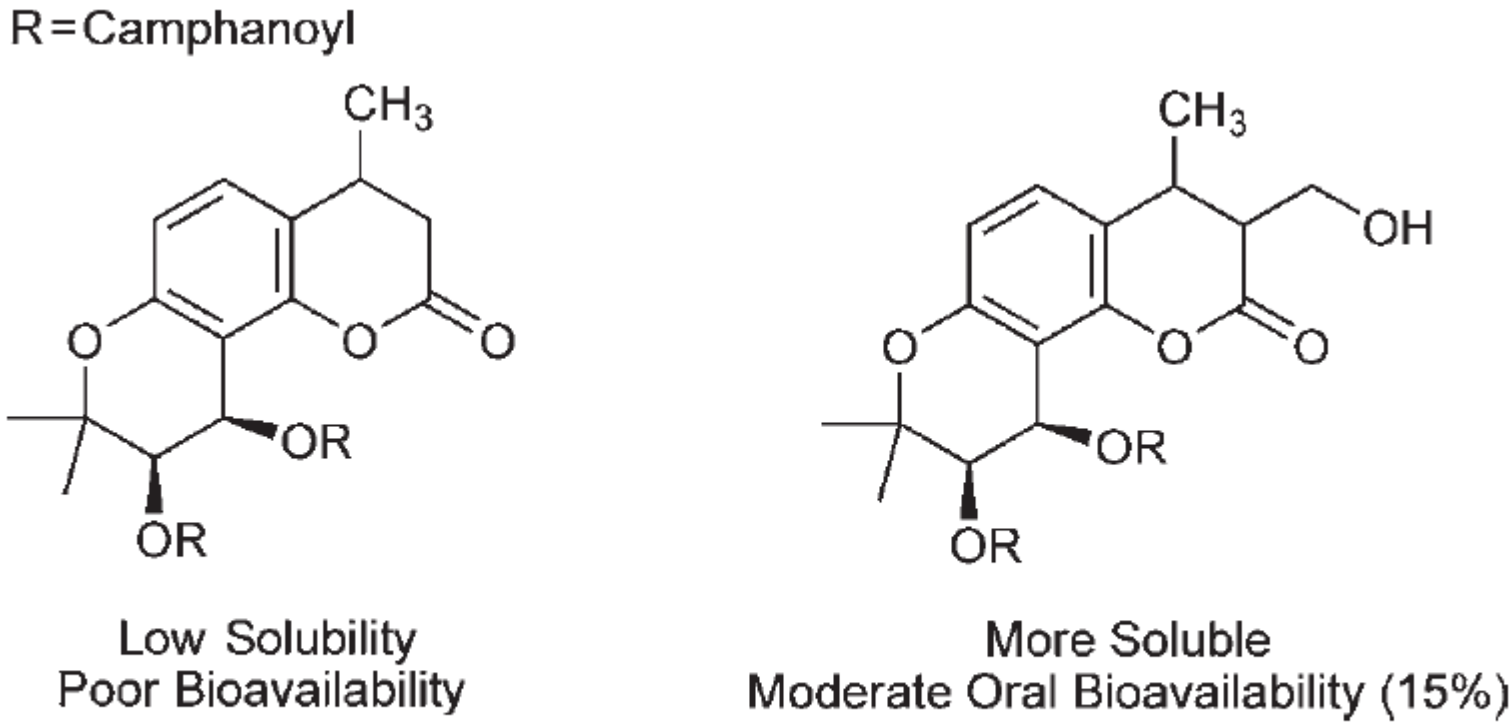
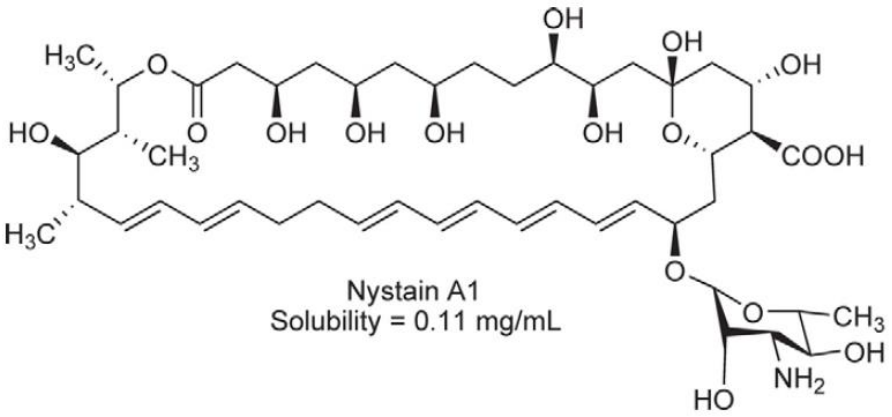


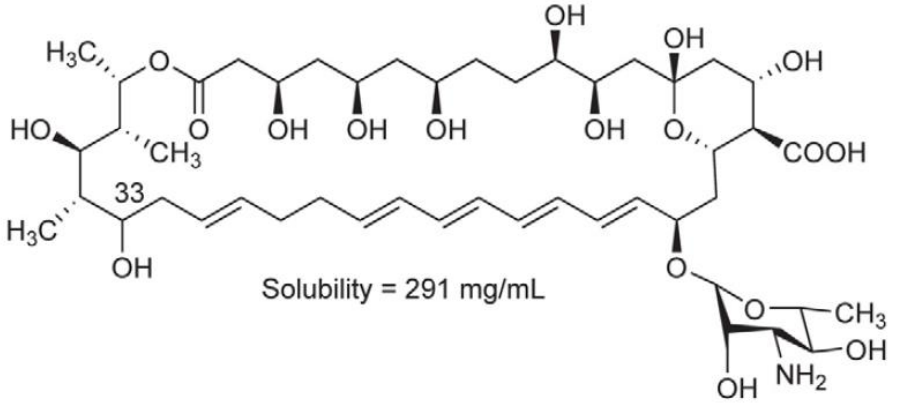
Figure 7.19 ► Effects of H-bonds on solubility for anti-AIDS agents.

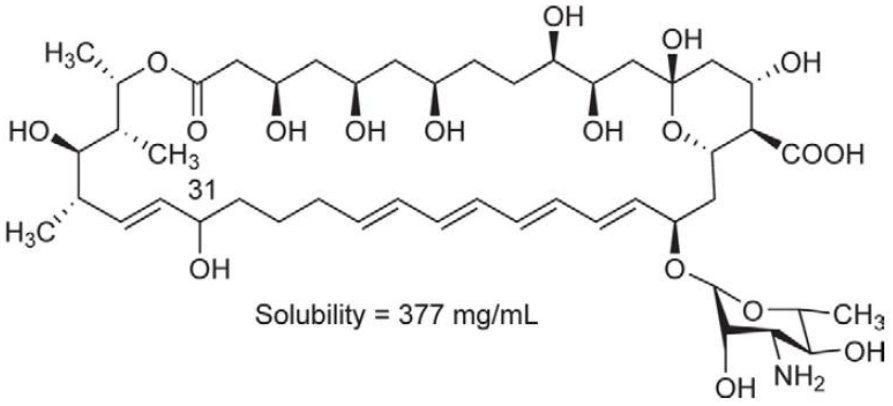
SOLUBILITY

3. Increasing hydrogen bonding properties

rapid increase
of solubility due to
disruption of aggregate
formation



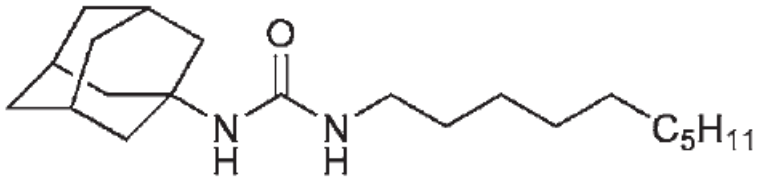


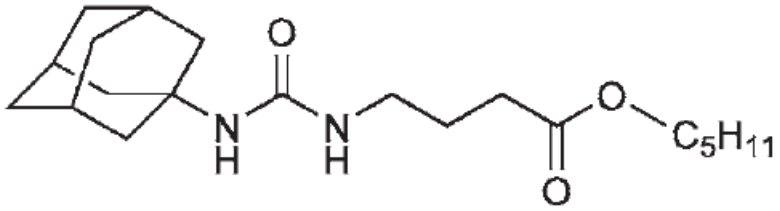


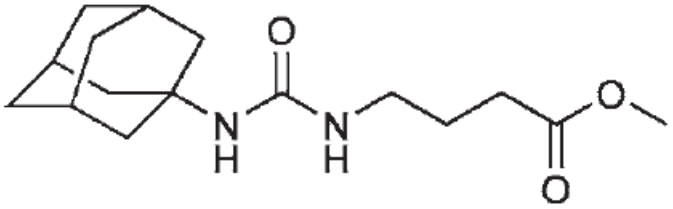
SOLUBILITY

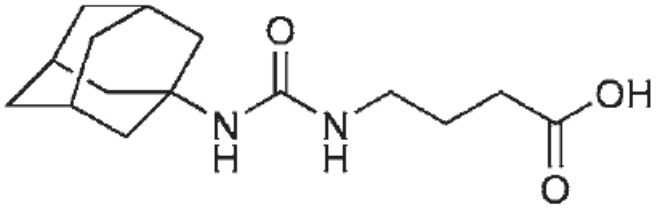
4. Addition of polar group

ester or carboxylic group (epoxide hydrolase inhibitors)









IC_{50}	Solubility
0.10 μM	0.62 mg/mL
0.17 μM	1.69 mg/mL
1.6 μM	1.66 mg/mL
37 μM	7.06 mg/mL

SOLUBILITY

4. Addition of polar group

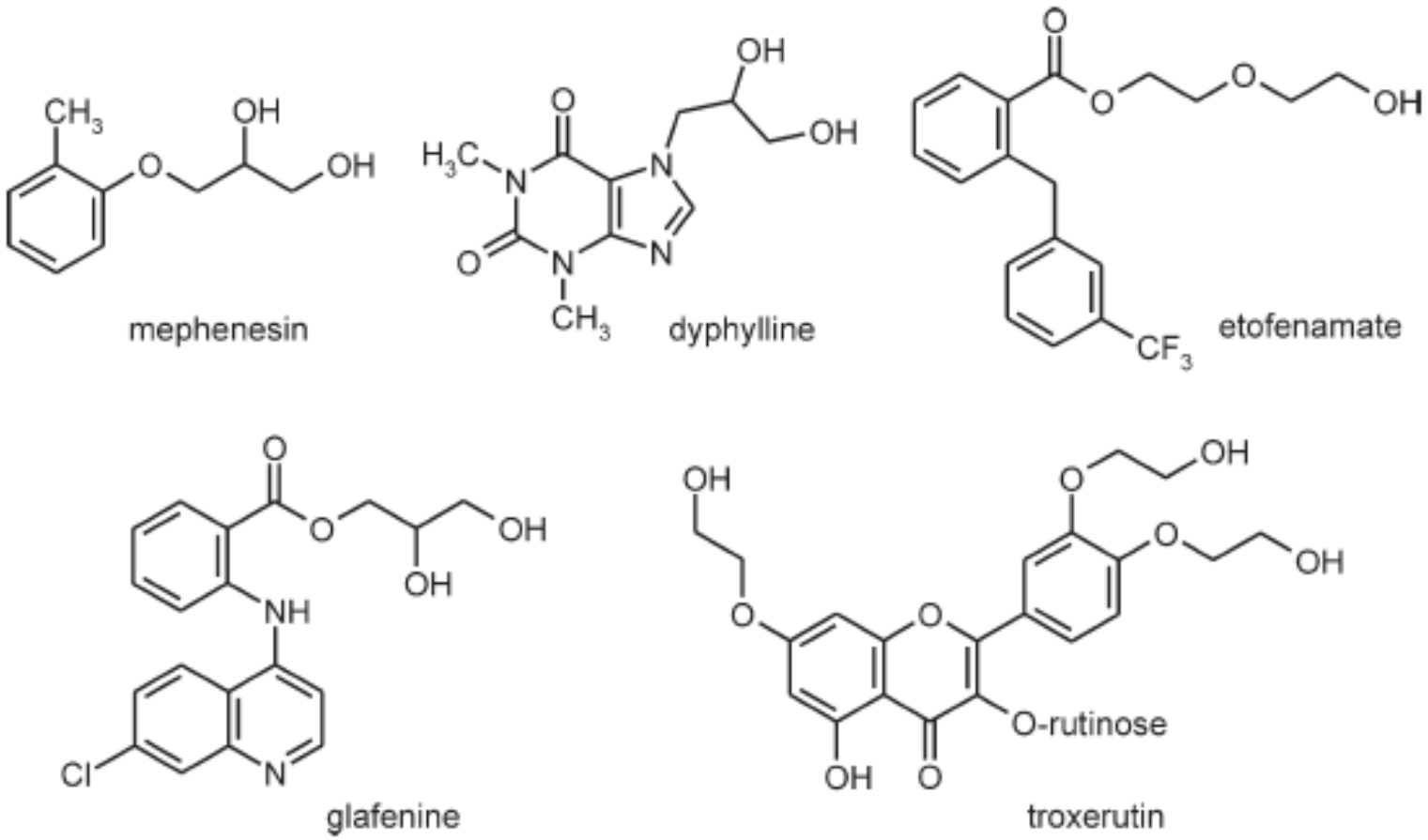
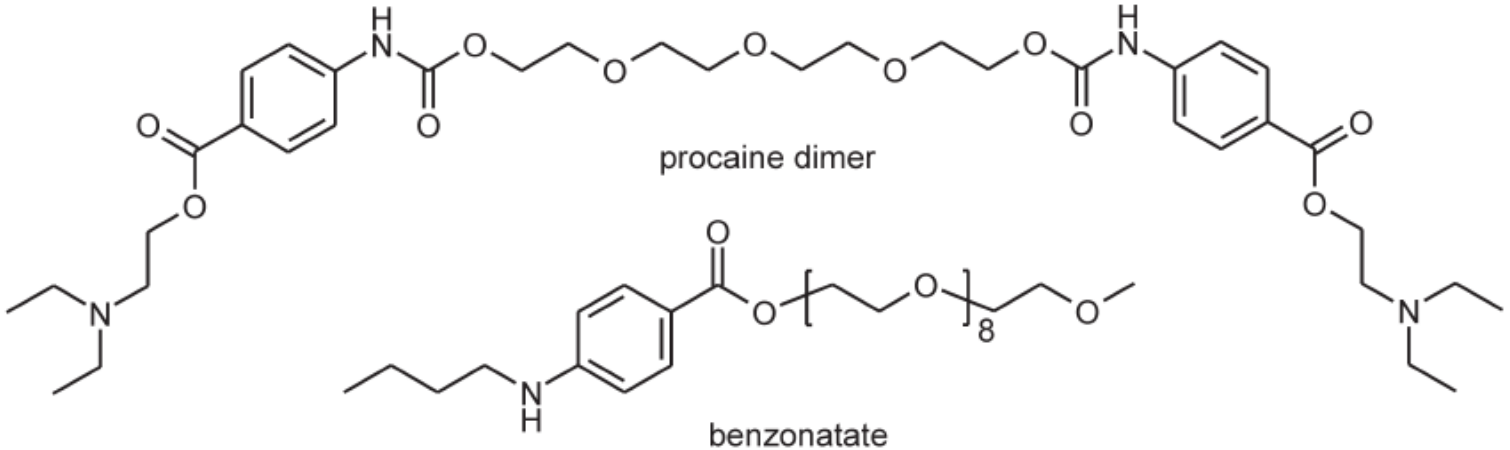


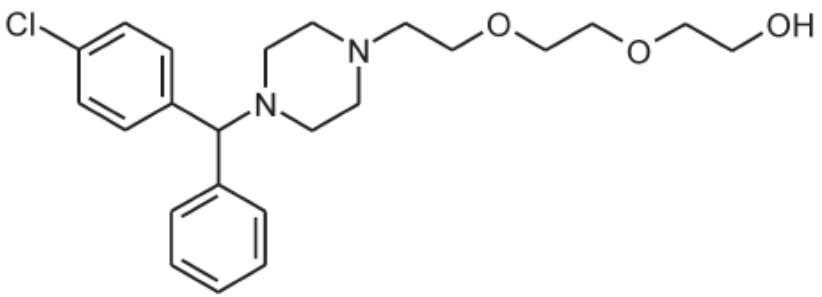
Fig. 36.19 Glycolyl and glyceryl side chains.

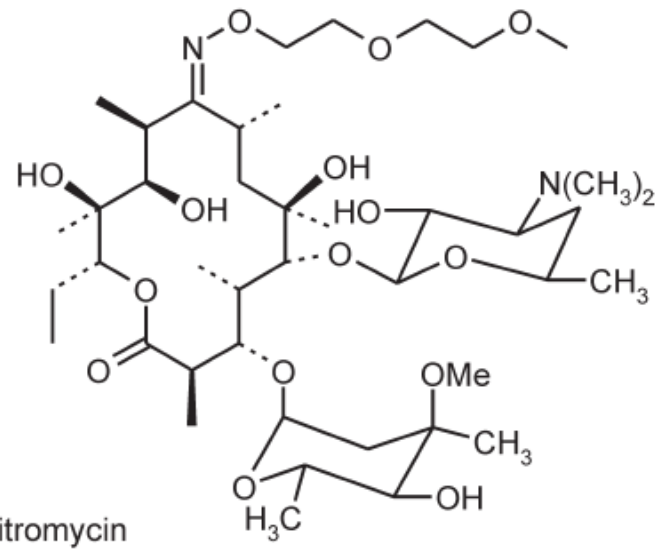
SOLUBILITY

4. Addition of polar group

polyethylene glycol

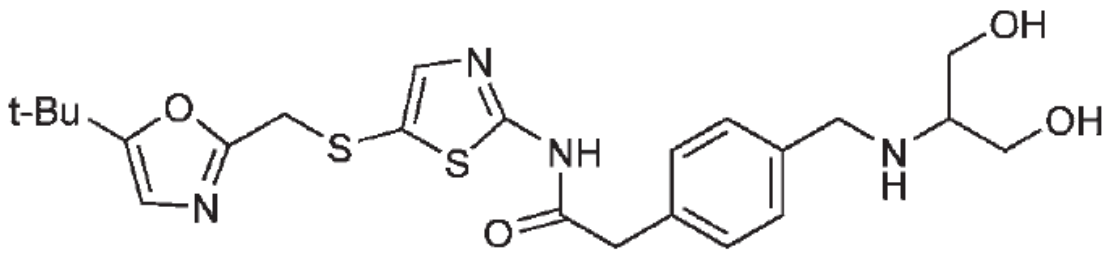






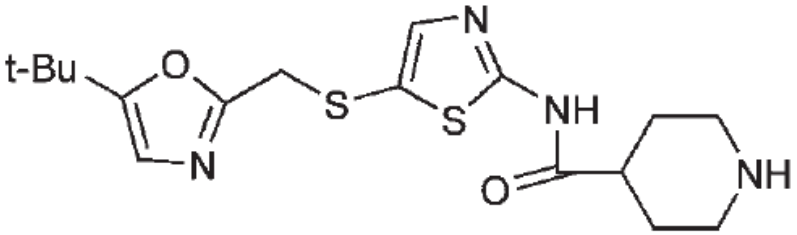
SOLUBILITY

5. Reduction of the molecular weight



CL = 0.22 nmol/min/mg % TIC (P388) = 140 LCK (A2789) = 3.3

- Low MW
- More soluble
- Low CL
- More potent *in vivo*



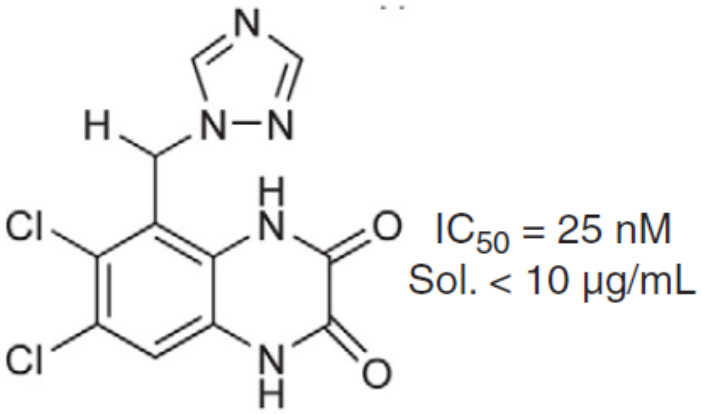
CL = 0.05 nmol/min/mg % TIC (P388) = 140 LCK (A2789) = 3.6–5.0

Figure 7.22 ► Reduction in molecular weight for these CDK2 inhibitors resulted in increased solubility, improved metabolic stability, and increased in vivo potency.

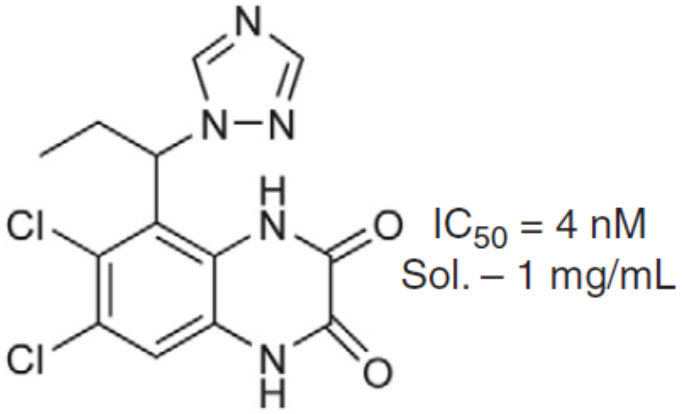
SOLUBILITY

6. Out-of-plane substitution

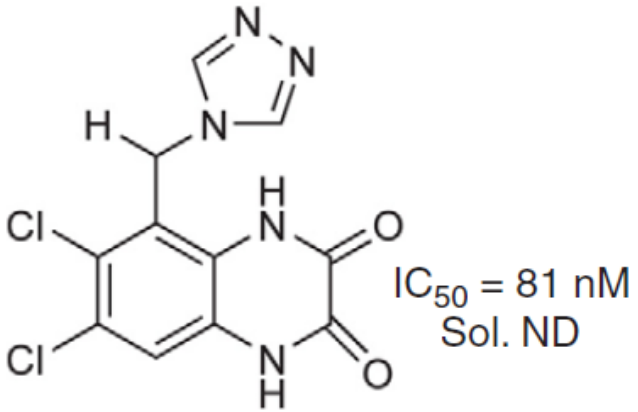
planar molecules forms tight crystall lettice and aggregates in water solutions



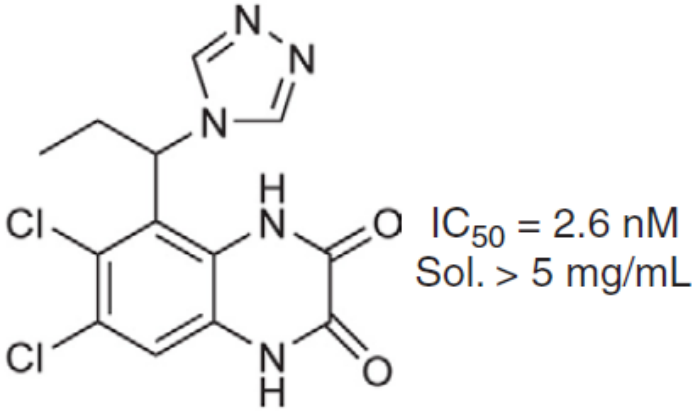
IC_{50} = 25 nM
Sol. < 10 µg/mL



IC_{50} = 4 nM
Sol. – 1 mg/mL



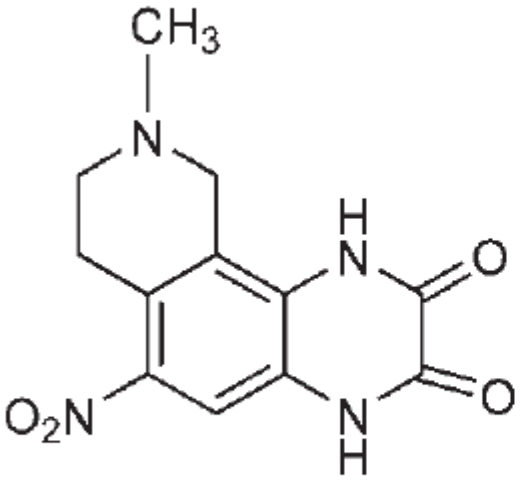
IC_{50} = 81 nM
Sol. ND



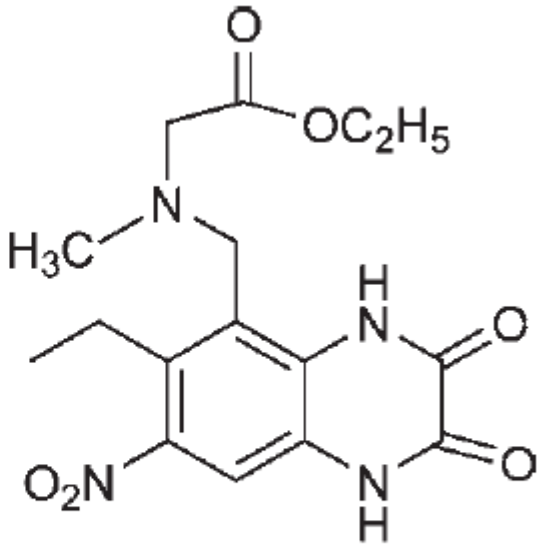
IC_{50} = 2.6 nM
Sol. > 5 mg/mL

SOLUBILITY

6. Out-of-plane substitution



PNQX
Solubility 8.6 µg/mL

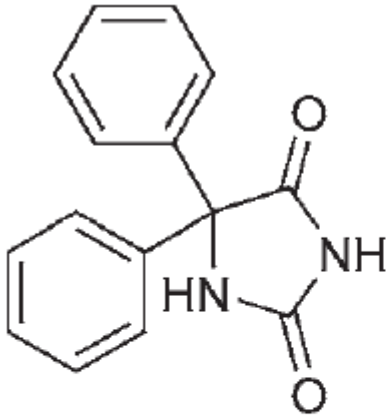


Solubility 150 µg/mL

SOLUBILITY

7. Prodrug construction

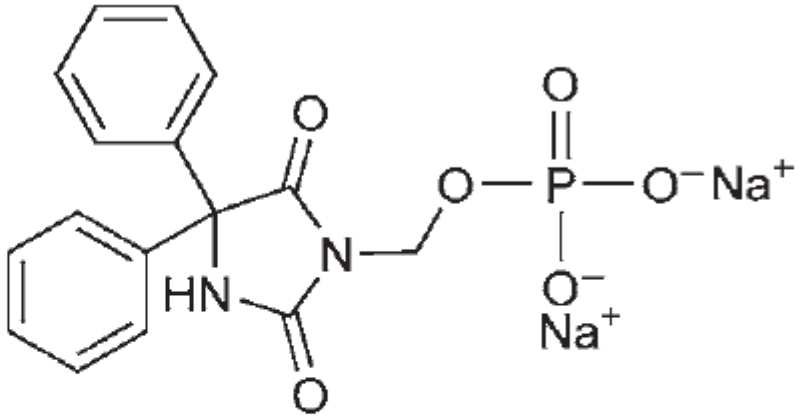
addition of carged or polar groups



Phenytoin

Solubility 20–25 µg/mL

Problematic Formulation



Fosphenytoin

Solubility 142 mg/mL

4400 fold increase!

Cerebyx™

SOLUBILITY

8. Salt formation

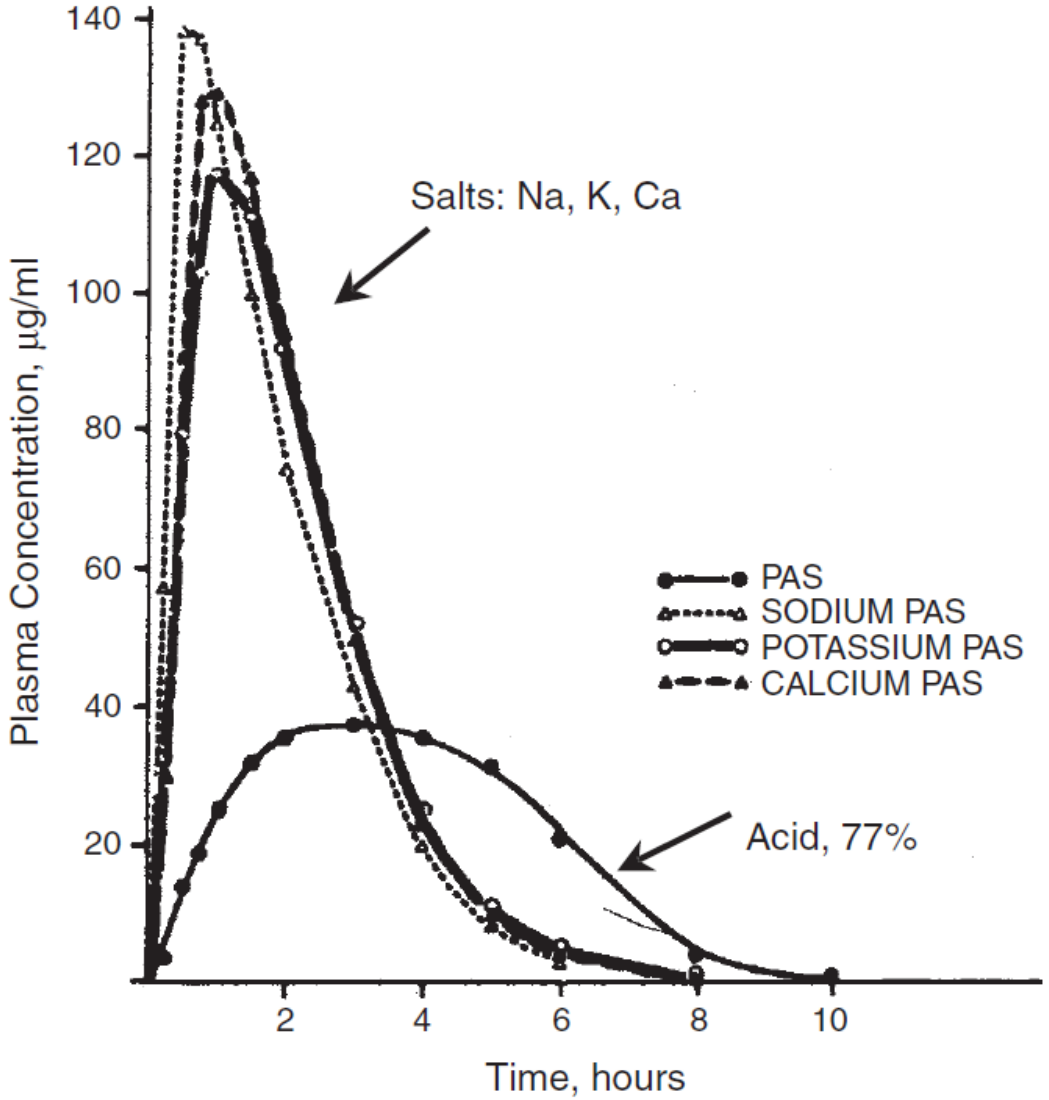
Solubility of salts are generally higher than of free acid or base

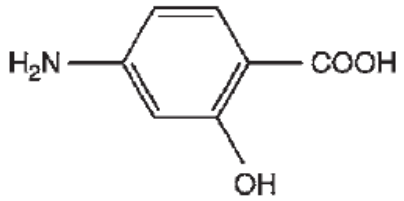
After dissolving, free acid or base may crastallize due to pH of environment. However, compound may stay at supersaturated solution and do not precipitate immediately

Salt increases bioavailability due to increasing dissolution rate

SOLUBILITY

8. Salt formation





Salts

- Increase dissolution rate
- Slow precipitation
- Precipitates as amorphous

SOLUBILITY

8. Salt formation

Counter anions	Percent
Chloride	48
Sulfate	5.8
Bromide	5.2
Mesylate	3.2
Maleate	3.1
Citrate	2.8
Tartrate	2.7
Phosphate	2.5
Acetate	2.1
Iodide	1.2

SOLUBILITY

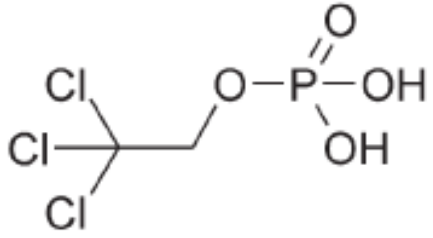
8. Salt formation

Counter cations	Percent
Sodium	58
Calcium	12
Potassium	9.8
Magnesium	4.5
Meglumine	2.4
Ammonium	2.0
Aluminum	1.4
Zinc	1.1
Piperazine	0.90
Tromethamine	0.90

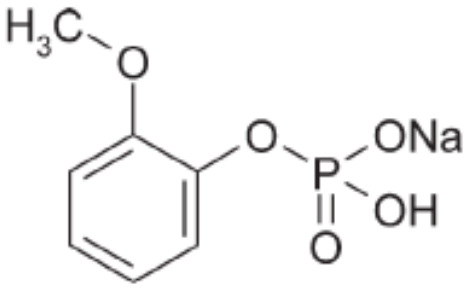
SOLUBILITY

9. Crystalline solid formation

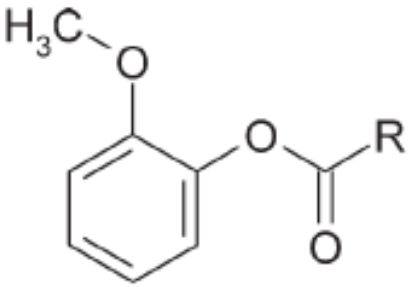
structure modification gains crystalline derivatives of liquid active compounds or increases low m.p.



trichloroethanol monosodium phosphate

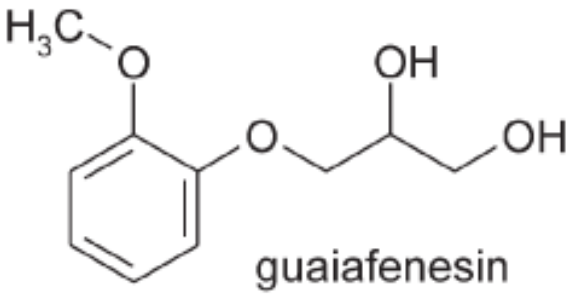


guaiacol monosodium phosphate

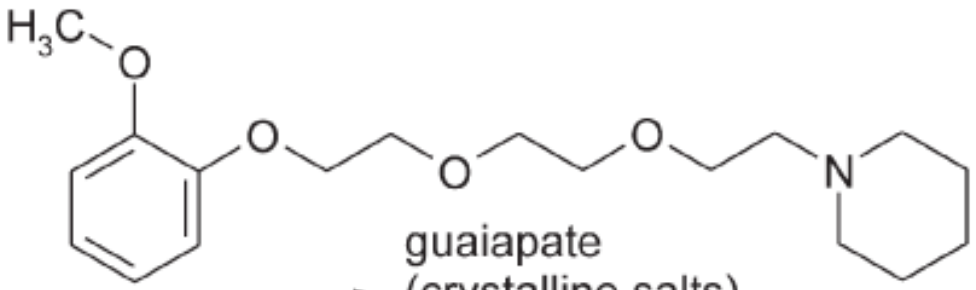


guaiacol esters

R = C_6H_5 -
C_6H_5 - CH_2 -
C_6H_5 -$(CH_2)_2$ -



guaiafenesin



guaiapate
(crystalline salts)

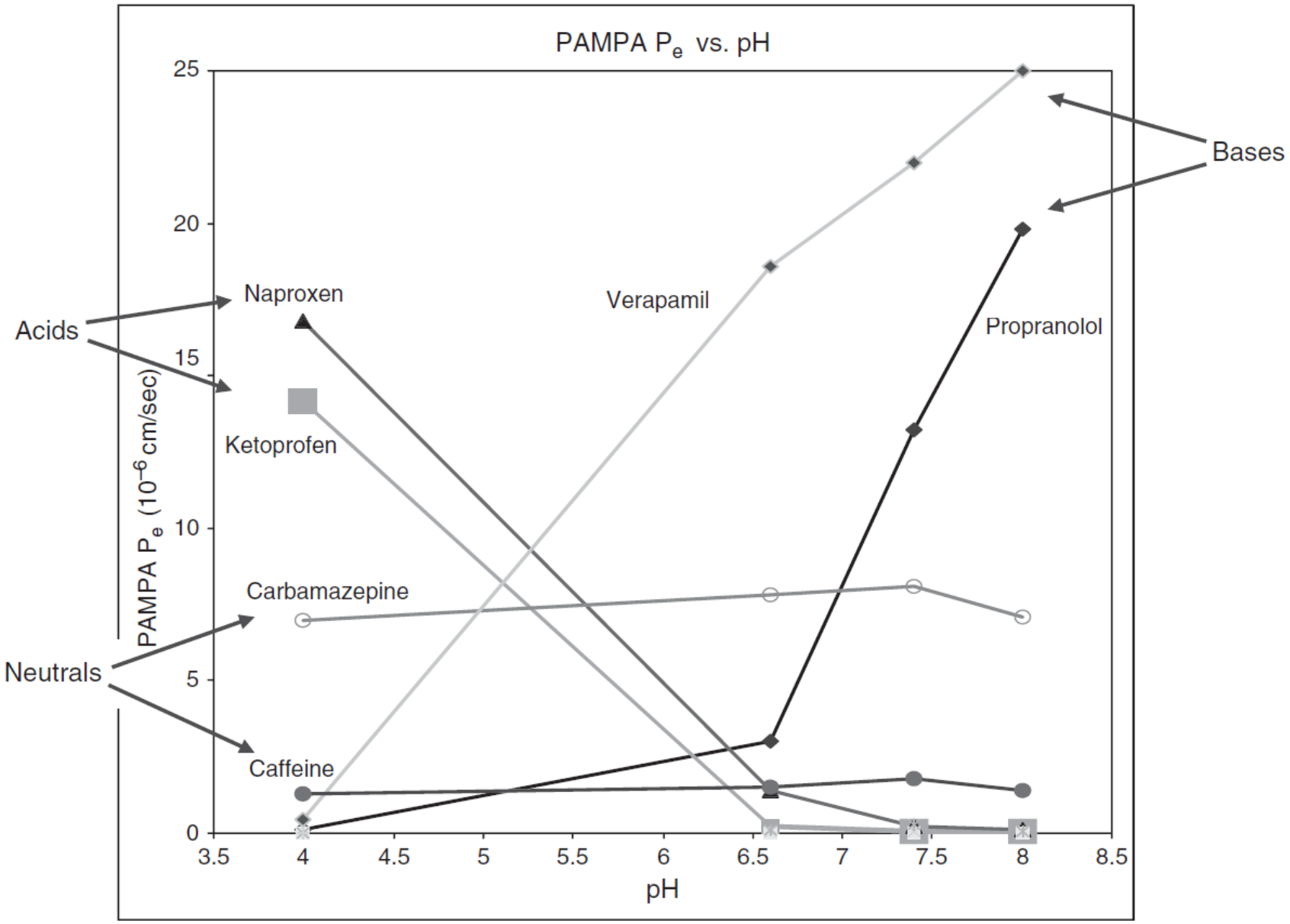
PERMEABILITY

95% of drugs permeates by passive diffusion

generally, uncharged molecules are able to permeate

but small part of ionizated molecules are able to permeate too, while forming neutral pairs with suitable counterions

PERMEABILITY



PERMEABILITY

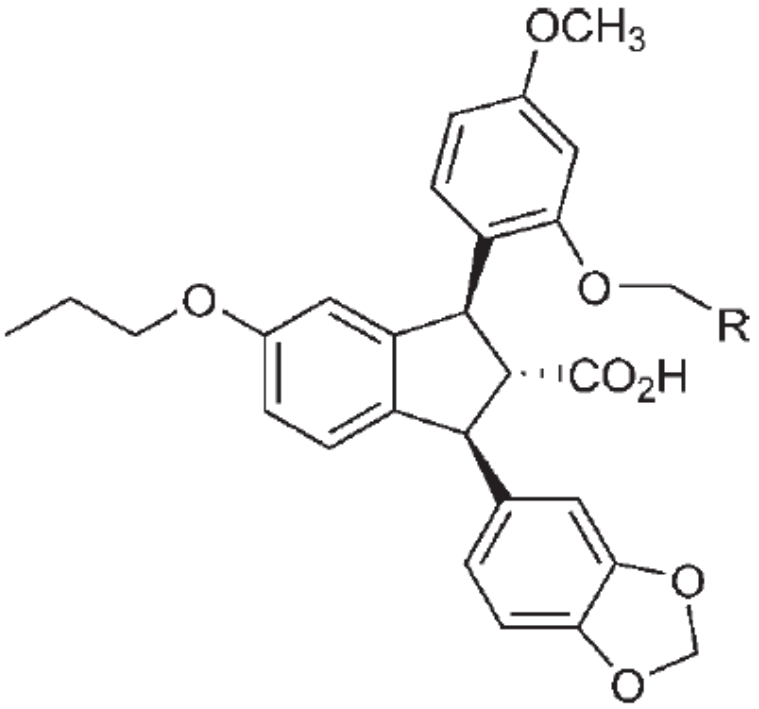
The only way to improve permeability **is structure modification**

Formulations are not effective in fixing poor permeability

Structure modification strategy
Ionizable group to non-ionizable group
Add lipophilicity
Isosteric replacement of polar groups
Esterify carboxylic acid
Reduce hydrogen bonding and polarity
Reduce size
Add nonpolar side chain
Prodrug

PERMEABILITY

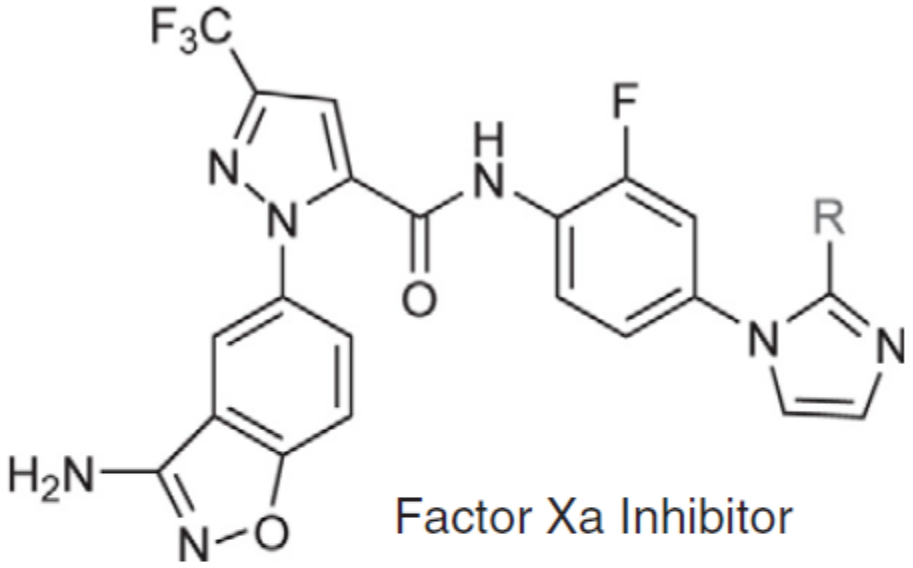
1. Reducing ionizable groups



R	ETA, Ki (nM)	Caco-2 (cm/h)	% F (rat)
CO_2H	0.43	0.0075	4
CH_2OH	1.1	0.2045	66

PERMEABILITY

2. Increasing lipophilicity



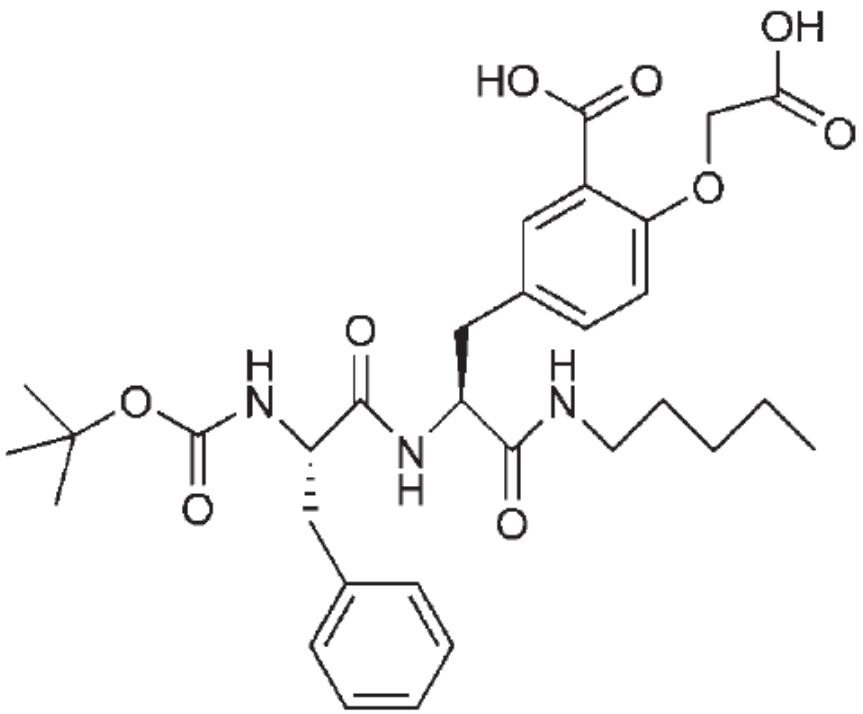
Factor Xa Inhibitor

R	FXa K_i (nM)	Caco-2 P_{app} ($\times 10^{-6}$ cm/s)	CL (L/h/Kg)	$T_{1/2}$ (h)	Vdss (L/Kg)	F (%)
CH_2NHMe	0.12	0.2	1.1	3.7	4.6	24
CH_2NMe_2	0.19	5.6	1.1	3.4	5.3	84

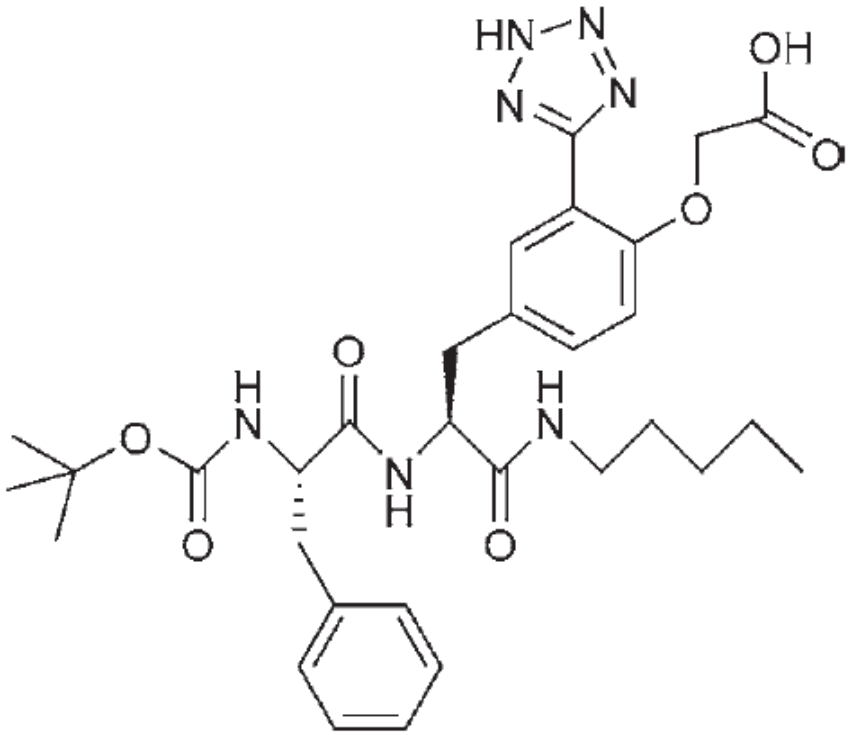
PERMEABILITY

3. Isosteric replacement of polar groups

tetrazole for carboxylic group



K_i (PTP1B) = 2 μM
Caco-2 < 1×10^{-7} cm/s
No Cellular Activity

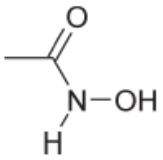
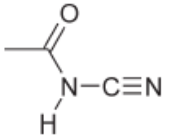
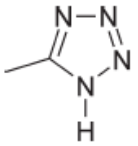
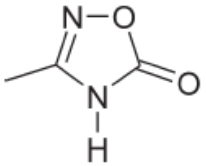
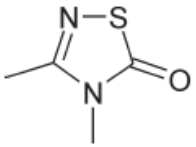
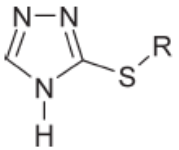


K_i (PTP1B) = 2 μM
Caco-2 = 1.9×10^{-7} cm/s
Positive Cellular Activity

PERMEABILITY

3. Isosteric replacement of polar groups

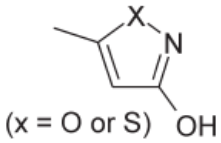
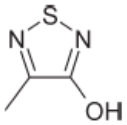
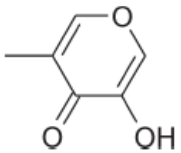
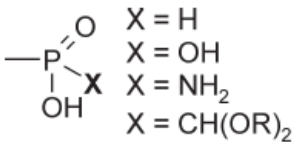
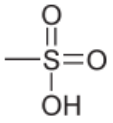
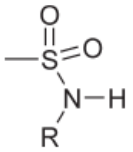
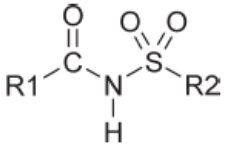
isosteres of carboxylic group

	hydroxamic acids	High chelating power
	acyl-cyanamides	Mainly academic interest
	tetrazoles	Very popular Great number of publications. Recent in use. $pK_a = 6.6$ to 7.2
	oxo-oxadiazoles	Lipophilic bioisosteric replacement for tetrazoles
	oxo-thiadiazole	Lipophilic bioisosteric replacement for tetrazoles
	mercaptoazoles + sulfinylazoles + sulfonylazoles	Phosphonate isosteres pK_a mercapto: 8.2–11.5 pK_a sulfinyl: 5.2–9.8 pK_a sulfonyl: 4.8–8.7

PERMEABILITY

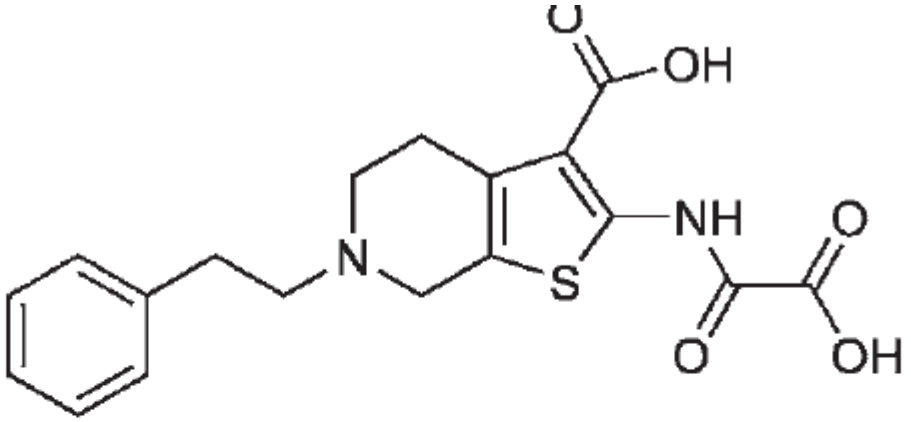
3. Isosteric replacement of polar groups

isosteres of carboxylic group

	isoxazoles isothiazoles	GABA and glutamic acid analogues
	hydroxy-thiadiazole	Isoxazole isostere pK_a # 5
	hydroxy-chromones	Kojic acid derivatives: As GABA agonists
	phosphinates phosphonates phosphonamides	Many examples in the glutamate antagonist series and in the $GABA_B$ antagonists
	sulphonates	Sulphonic analogues of GABA and glutamic acid
	sulphonamides	Weak acids, used rather as equivalents of phenolic hydroxyls: catecholamine analogues
	acyl-sulphonamides	Glycine GABA β-alanine antiatherosclerotics pK_a # 4.5

PERMEABILITY

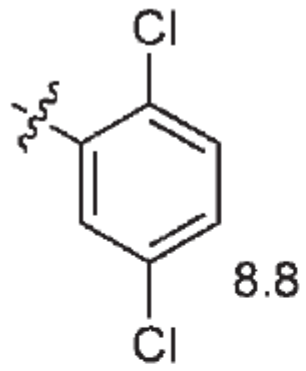
4. Esterification of craboxylic groups



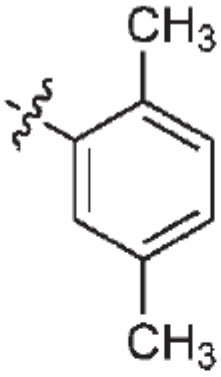
	Diacids	Di-Ethyl Ester Prodrug
In vitro (PTP1B)	Potent & Selective	
Oral Bioavailability (Rat)	13%	Not Determined
Permeability (MDCK)	Low	High
2-DOG Uptake in C2C12 Cell	Inactive	70%

PERMEABILITY

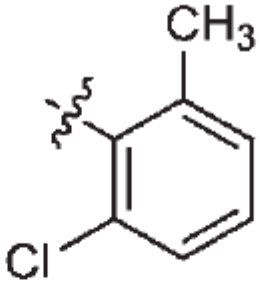
5. Reduction of hydrogen bonding and polarity



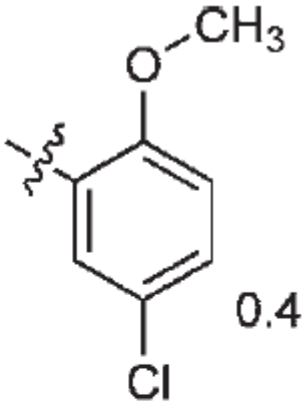
8.8



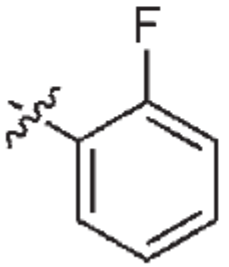
4.8



5.6



0.4



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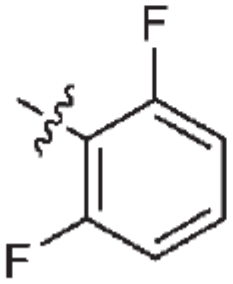

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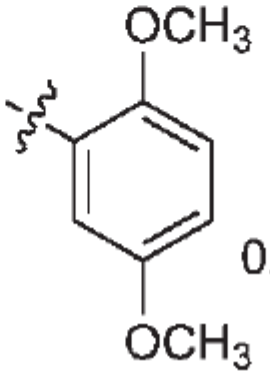

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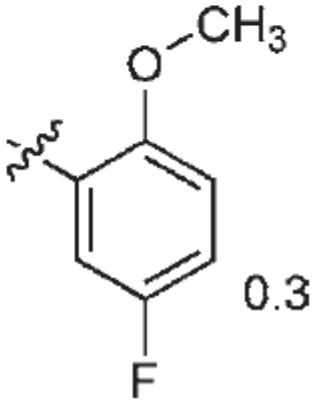
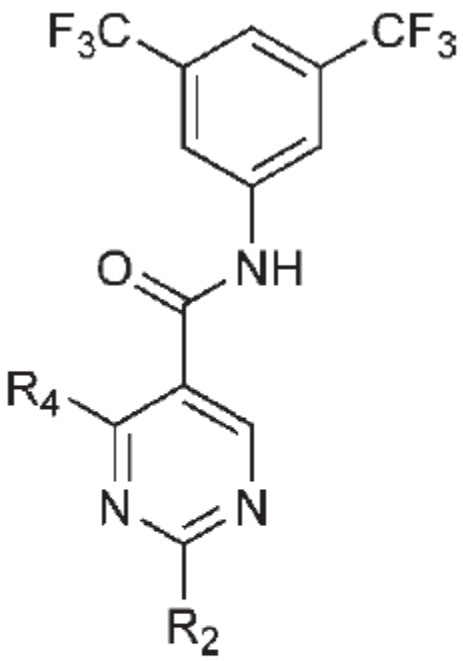


0.3

PERMEABILITY

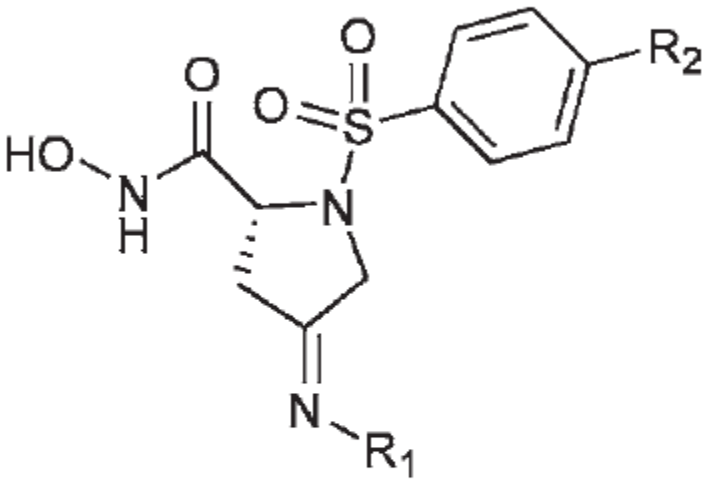
6. Reduction of size



R4	R2	Caco-2 Permeability ($\times 10^{-7}$ cm/s, n = 3, mean ± SD)
CF_3	Cl	11 ± 4
H	Cl	61 ± 7
CH_3	Cl	62 ± 6
CH_2CH_3	Cl	58 ± 9
$CH_2CH_2CH_3$	Cl	31 ± 9
CF_2CF_3	Cl	9 ± 9
Cl	Cl	31 ± 6
Ph	Cl	9 ± 7
CF_3	F	19 ± 6

PERMEABILITY

6. Reduction of size



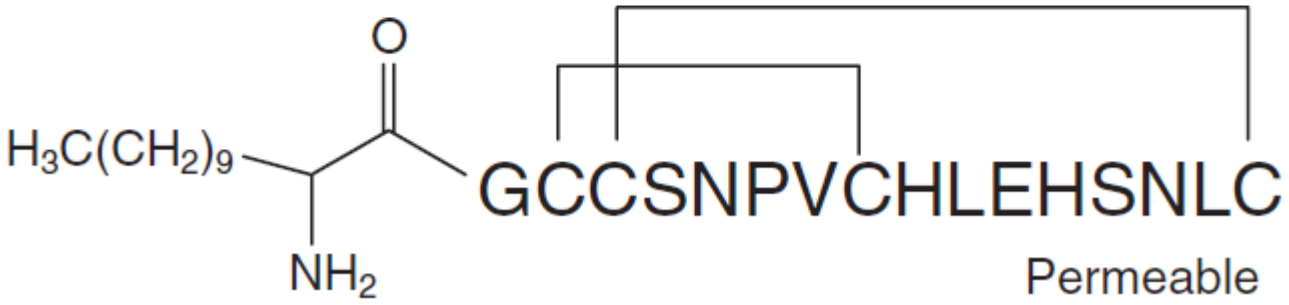
R1	R2	% Dose Absorbed (rat ileum)
OH	OMe	29–35
OH	O^{n}Bu	2–5
OMe	O-4-Pyr	50–68
O^{t}Bu	O-4-Pyr	10–18
OPh	O-4-Pyr	not detected
OMe	OMe	78–81
OMe	OEt	23–42
OMe	O^{n}Bu	28–36
OMe	OPh	15–18

PERMEABILITY

7. Addition of non-polar side chain

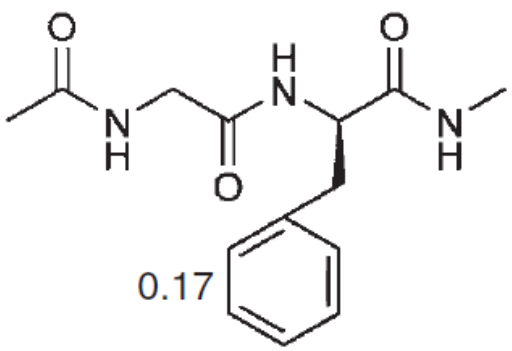
increasing membrane affinity by long saturated chain

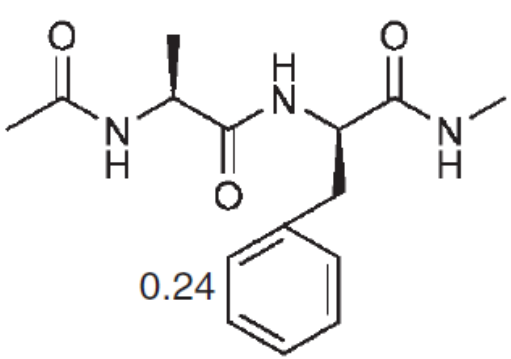
cyclic peptide:

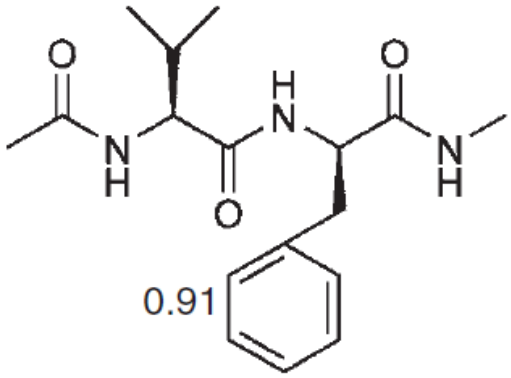


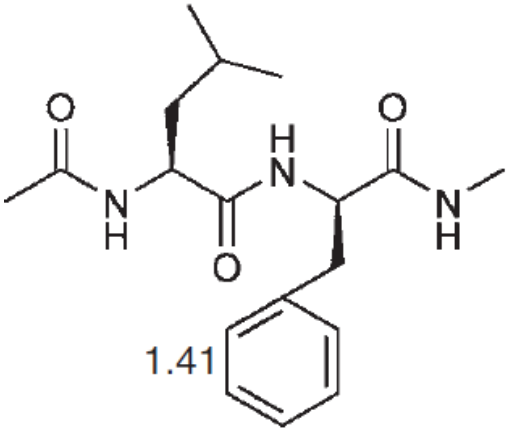
PERMEABILITY

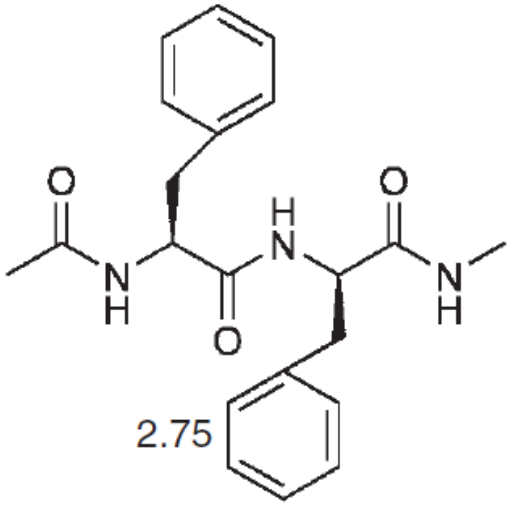
7. Addition of non-polar side chain

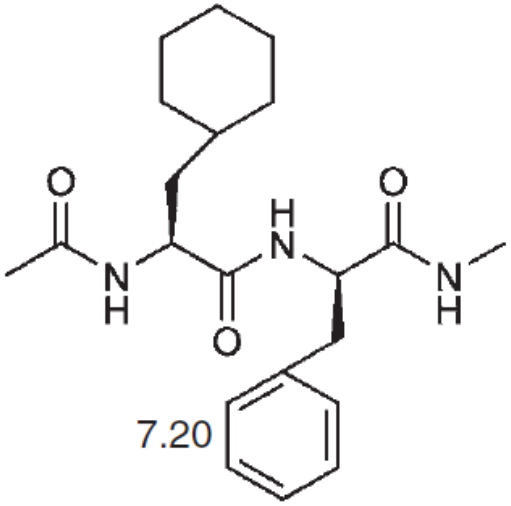












PERMEABILITY

8. Prodrug construction

example of modifications increasing lipohilicity/reducing number of ionizable groups