Medicinal Chemistry/ CHEM 458/658

Chapter 3- SAR and QSAR

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Introduction

- Structure-Activity Relationship (SAR)

  - similar structures –similar effects

  - more potency or improved side effects

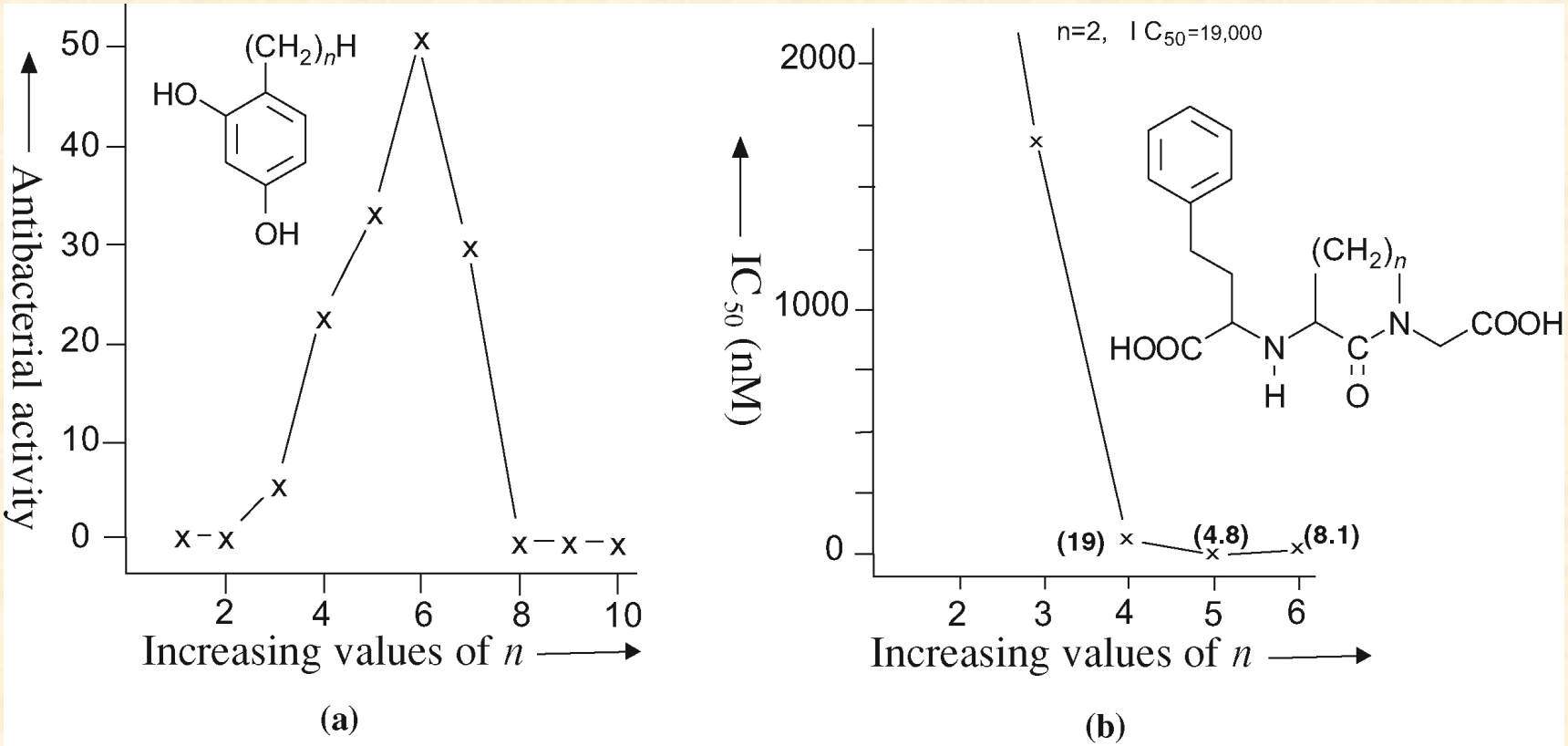
- Quantitative Structure-Activity Relationship (QSAR)

  - similar structures –similar effects but uses parameters to describe the potency

  - parameters – anything (related to drug action) that can be represented by a numerical values

Structure-Activity Relationship (SAR)

- Usually go through minor changes on the lead structure
  - the and shape of the carbon skeleton
  - the nature and degree of substitution
  - stereochemistry



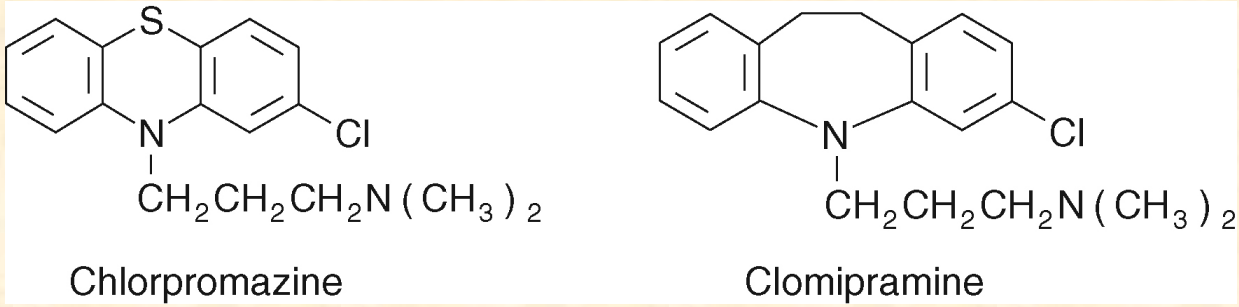
Structure-Activity Relationship (SAR)

- Changing size and shape
  - number of methylene groups in chains and rings
  - increasing or decreasing the degree of unsaturation
  - introducing or removing a ring system

Structure-Activity Relationship (SAR)

- Changing the number of methylene groups

  - increases lipophilicity (increased activity)
  - decreases water solubility (decreased activity)
  - aliphatic compounds – micelle formation – no selective binding



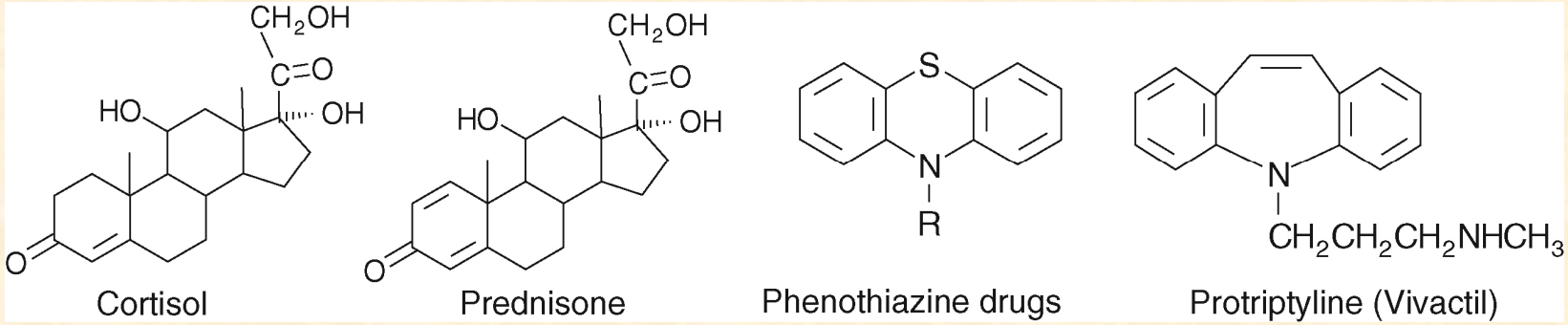
Chlorpromazine — antipsychotic

Clomipramine — antidepressant

Structure-Activity Relationship (SAR)

- Changing the degree of unsaturation

  - increasing – rigidity
  - *E-Z* isomers might complicate the picture
  - more sensitivity
  - increased toxicity



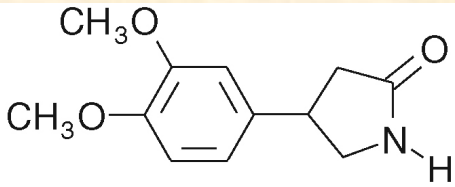
Cortisol | Prednisone | Phenothiazine drugs | Protriptyline (Vivactil)

1 : 30 | antipsychotic | antidepressant

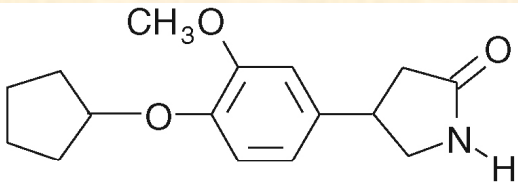
Structure-Activity Relationship (SAR)

- Introduction or removal of a ring system

  - addition – size increase, shape changes (effect mostly unpredictable
  - increasing size – better fills the hydrophobic pocket

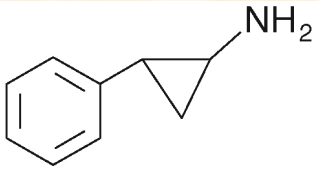


3-(3,4-Dimethoxyphenyl)-butyrolactam

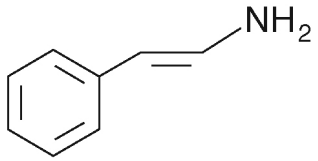


Rolipram, an antidepressant, is ten times more active than 3-(3,4-dimethoxyphenyl)-butyrolactam.

  - small ring to substitute C=C double bonds - stability



Tranylcypromine



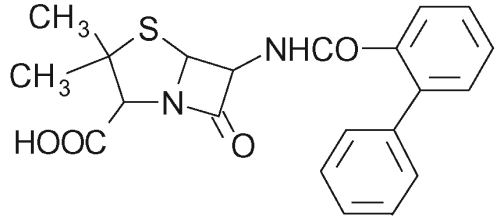
1-Amino-2-phenylethene

antidepressant

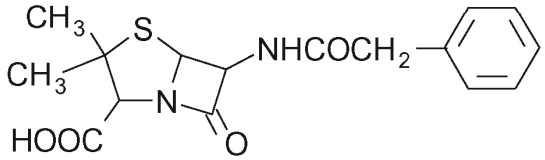
Structure-Activity Relationship (SAR)

- Introduction of an aromatic ring

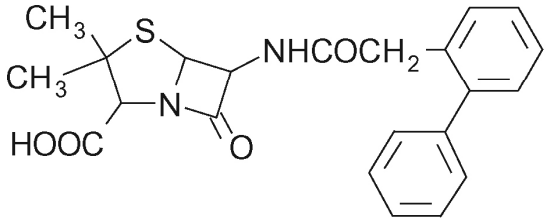
  - increases rigidity, shape changes resistance toward metabolism might improve



Diphenicillin (β-lactamase resistant)



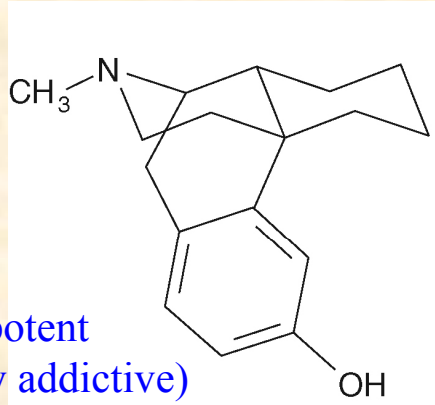
Benzylpenicillin (not β-lactamase resistant)



2-Phenylbenzylpenicillim (not β-lactamase resistant)

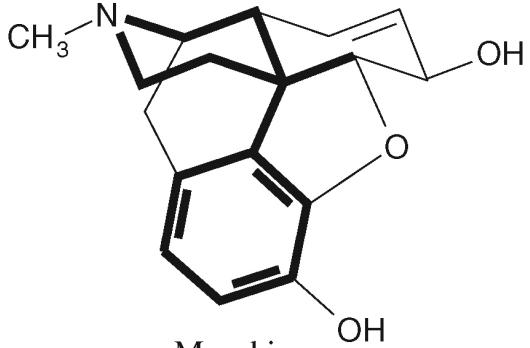
Structure-Activity Relationship (SAR)

- Modifying the ring system of drugs of natural origin
  - fine tuning of effect and side effects

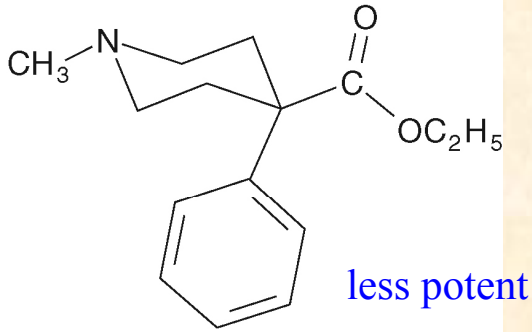


more potent
(highly addictive)

Levorphanol

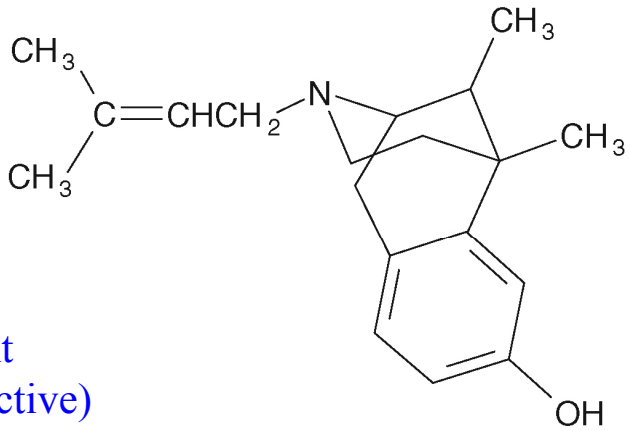


Morphine



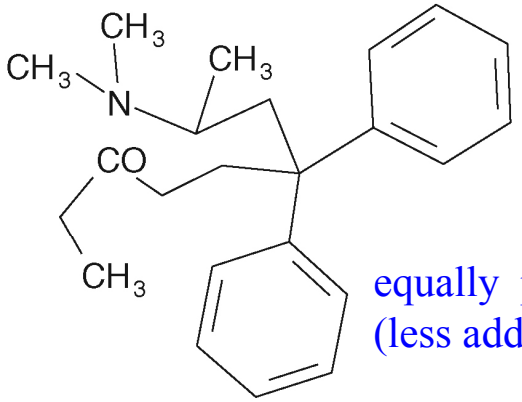
less potent

Pethidine



less potent
(less addictive)

Pentazocine



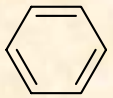
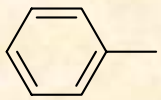
equally potent
(less addictive)

Methadone

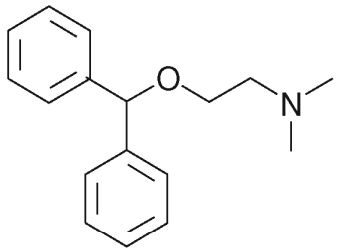
Structure-Activity Relationship (SAR)

- Introduction of new substituents

methyl groups ⟹ increases lipophilicity

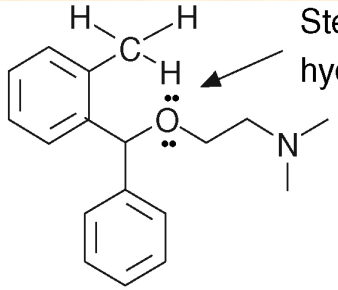
Compound	Structure	P	Analogue	Structure	P
benzene		135	toluene		490
acetamide	CH_3CONH_2	83	propionamide	$CH_3CH_2CONH_2$	360
urea	NH_2CONH_2	15	N-methylurea	$CH_3NHCONH_2$	44

steric hindrance – might block activity



Diphenhydramine

1

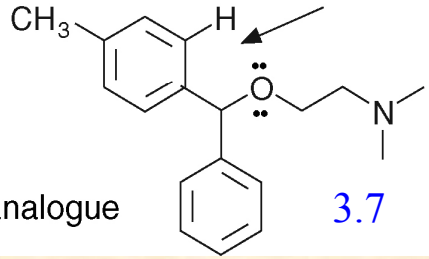


Steric hindrance between the hydrogen atom and the lone pairs.

0-Methyl analogue

0

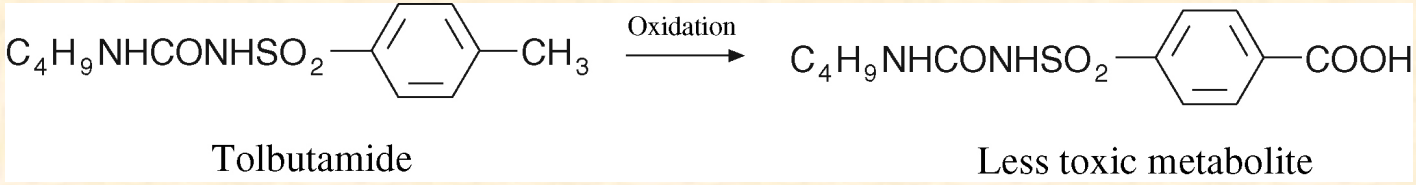
No steric hindrance between the hydrogen atom and the lone pairs.



p-Methyl analogue 3.7

Structure-Activity Relationship (SAR)

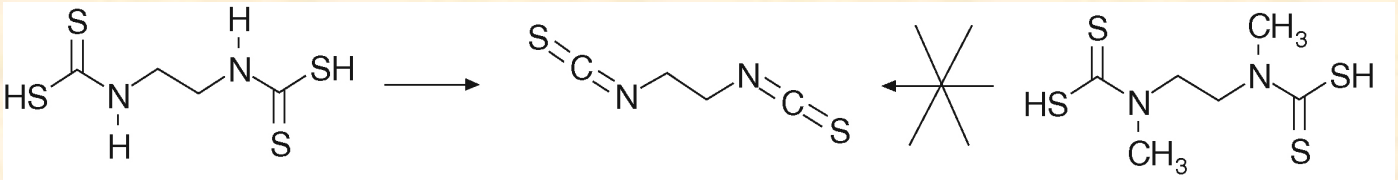
- Introduction of methyl group
  - methyl group on aromatic rings – increased rate of metabolism



Tolbutamide — Less toxic metabolite

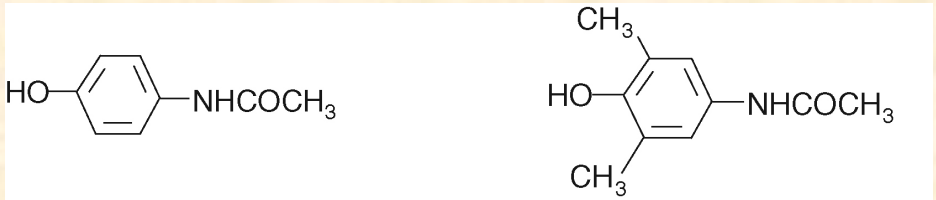
  - demethylation – easy on heteroatoms, especially on N^+, S^+

  - reduce the rate of metabolism



Nabam — 1,2-Diisothiocyanoethane — Dimethyl analogue of nabam

  - reduce unwanted side effects



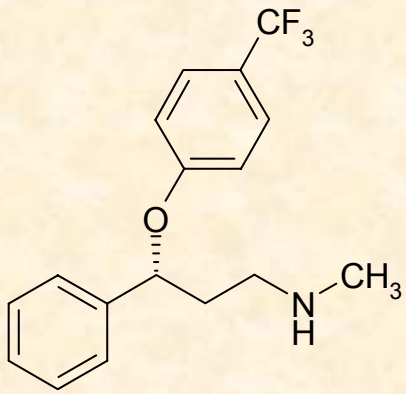
Paracetamol — *o,o'*-Dimethyl analogue of paracetamol

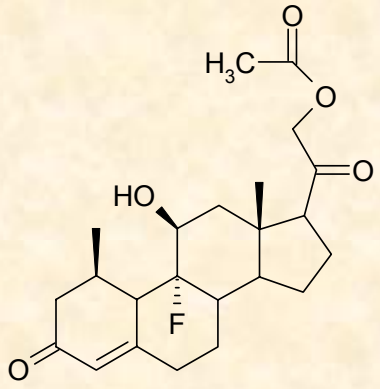
Structure-Activity Relationship (SAR)

- Introduction of halogens

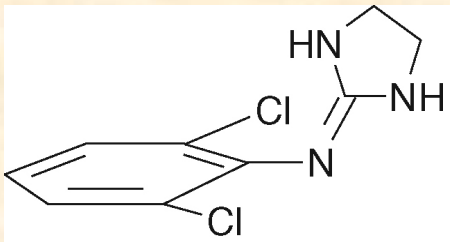
Mostly F and Cl - C-X bond stability - reactivity

CF_3 is also very popular

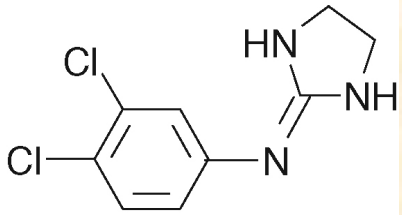




location



Clonidine ED_{50} 0.01 mg kg^{-1}



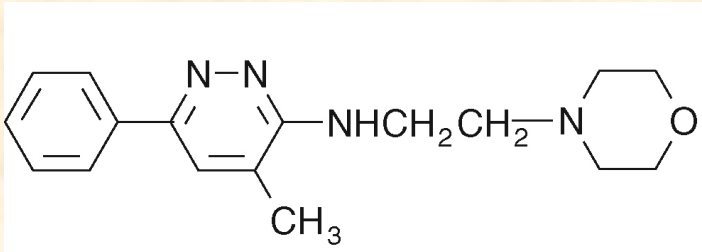
ED_{50} 3.00 mg kg^{-1}

Structure-Activity Relationship (SAR)

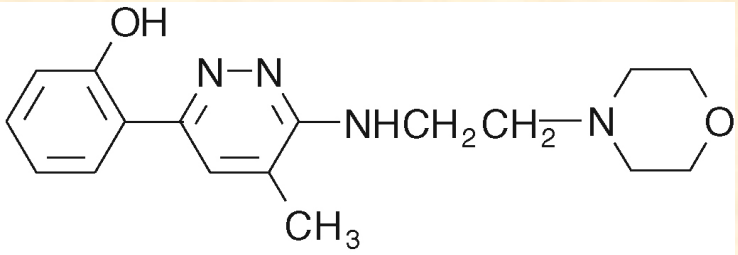
- Introduction of hydroxyl groups

  Mostly to increase hydrophilic character

  Phenolic OH is special



Minaprine

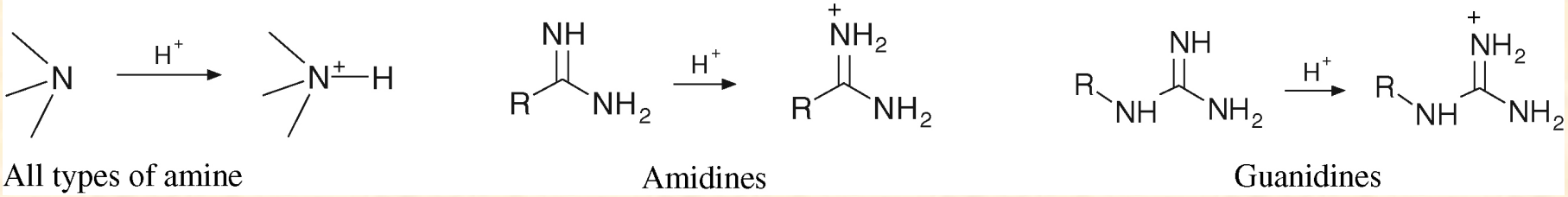


The *ortho*-hydroxylated analogue

Structure-Activity Relationship (SAR)

- Introduction of basic groups

Mostly to increase binding via H-bonding/acid base interactions

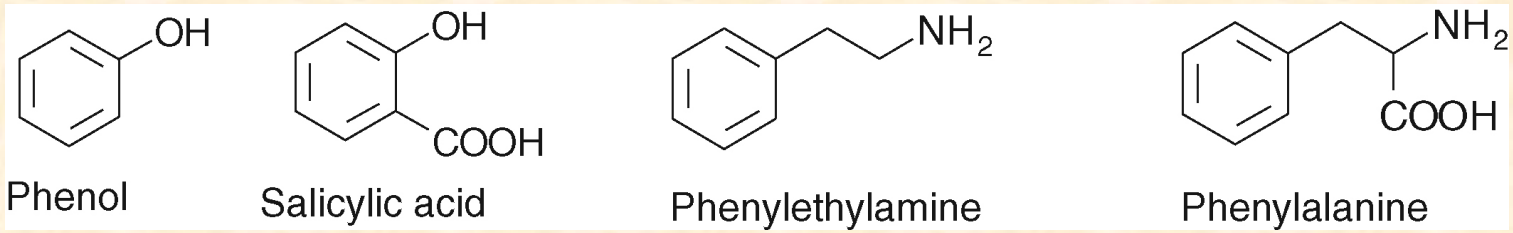


All types of amine | Amidines | Guanidines

Structure-Activity Relationship (SAR)

- Introduction of COOH and SO_3H groups

Mostly to increase binding via H-bonding/acid base interactions – in vivo salt formation
introduction to small leads – usually changes the activity



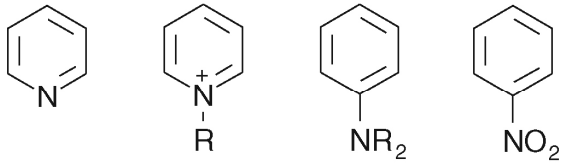
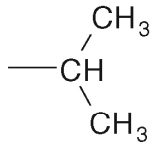
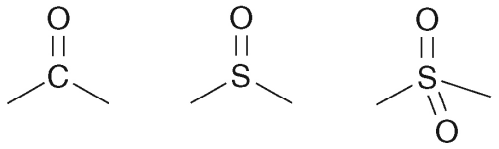
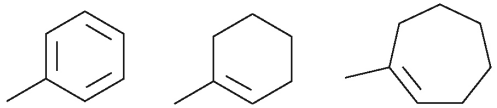
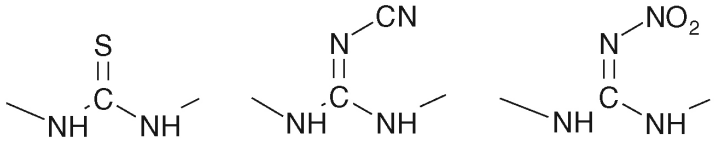
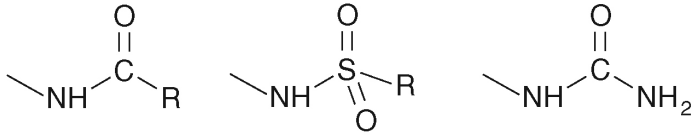
SO_3H – no significant effect except faster excretion

Other S groups are rare - metabolism

Structure-Activity Relationship (SAR)

- Changes the existing substituents of a lead

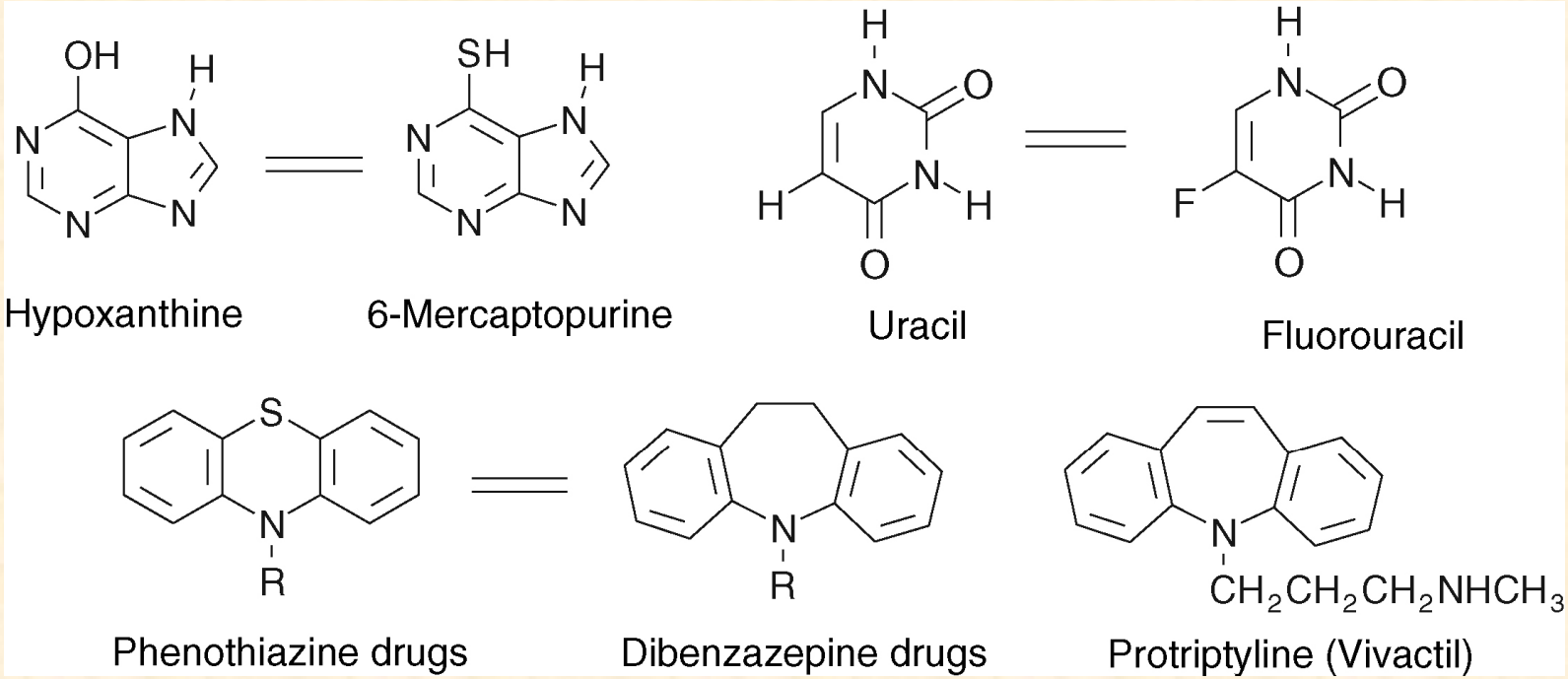
  isosteres - bioisosteres

Classical Isosteres	Bioisosteres
$-CH_3$, $-NH_2$, $-OH$, $-F$, $-Cl$.	
$-Cl$, $-SH$ $-PH_2$	
$-Br$, Isopropyl 	
$-CH_2-$, $-NH-$, $-O-$, $-S-$	
$-COCH_2R$, $-CONHR$, $-COOR$, $-COSR$	
$-HC=$, $-N=$	
In rings: $-CH=CH-$, $-S-$	
$-O-$, $-S-$, $-CH_2-$, $-NH-$	
$-CH=$, $-N-$	

Structure-Activity Relationship (SAR)

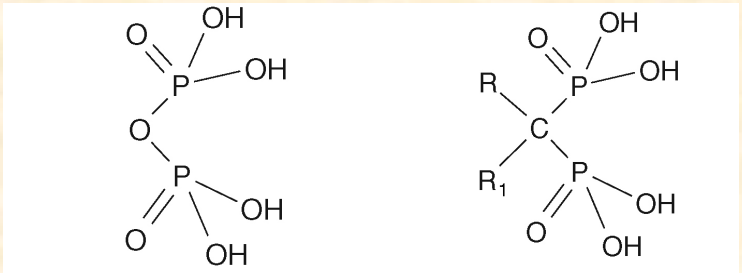
- Changes the existing substituents of a lead

  isosteres - bioisosteres



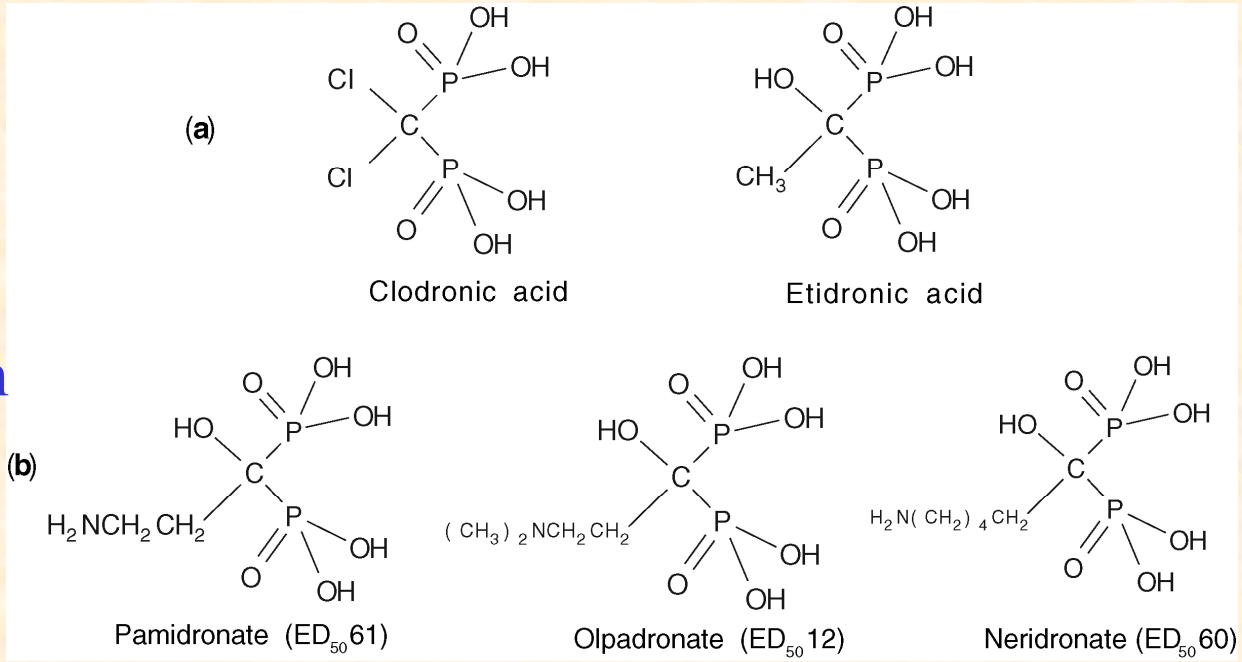
Structure-Activity Relationship (SAR)

- Case Study: SAR investigation to discover potent geminal bisphosphonates



first generation

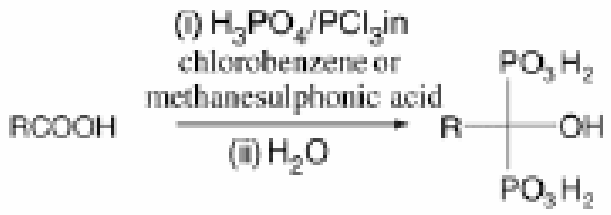
second generation



Structure-Activity Relationship (SAR)

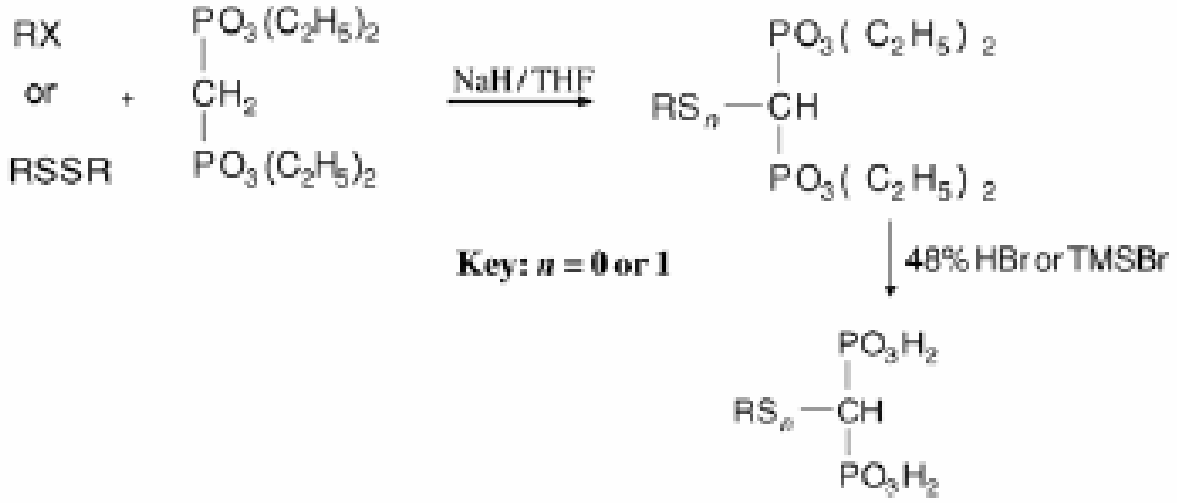
- Case Study: SAR investigation to discover potent geminal bisphosphonates

Method 1



Method 2

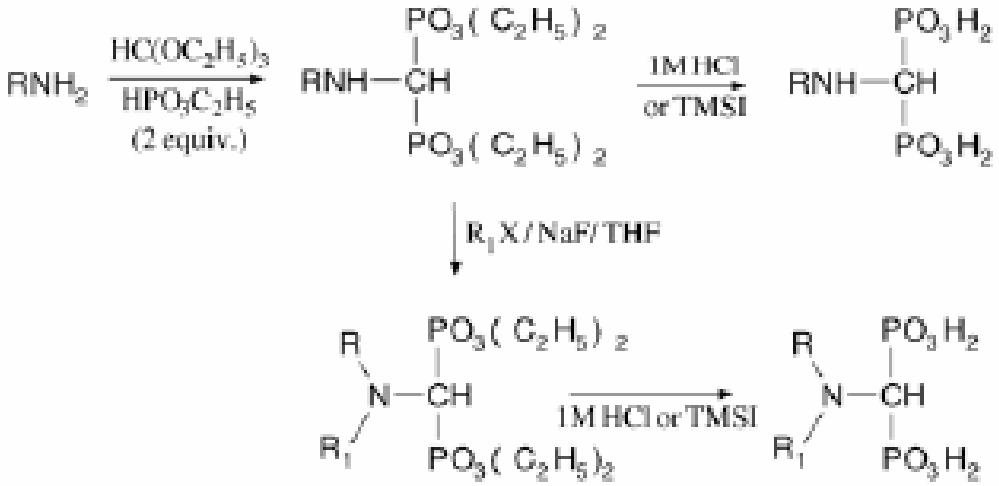
Method 3



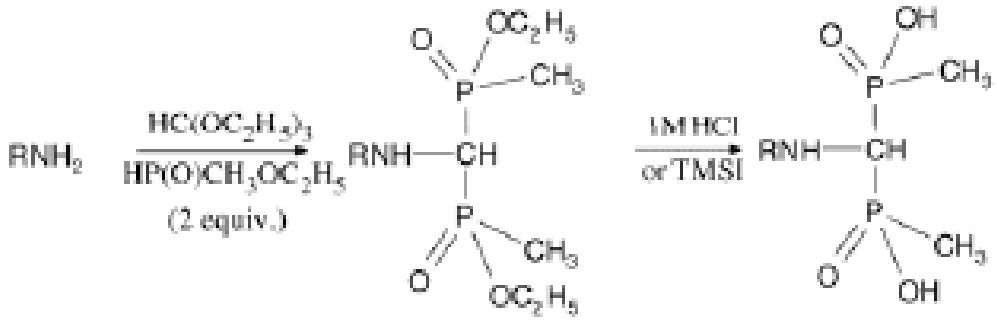
Structure-Activity Relationship (SAR)

- Case Study: SAR investigation to discover potent geminal bisphosphonates

Method 4



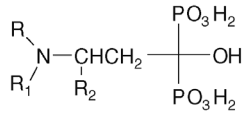
Method 5



Structure-Activity Relationship (SAR)

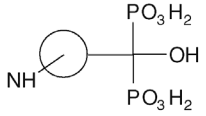
- Case Study:
  SAR investigation
  to discover potent geminal
  bisphosphonates

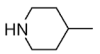
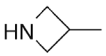
General structural formulae



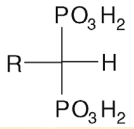
Compound	R	R_1	R_2	ED_{50}
1 Pamidronate	H	H	H	61
2	H	H	CH_3	3.4
3 Olapadronate	CH_3	CH_3	H	12
4	CH_3	CH_3	CH_3	18
5 Ibandronate	C_5H_{11}	CH_3	H	1.2
6	C_5H_{11}	CH_3	CH_3	65

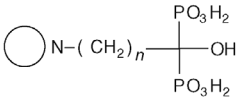
General structural formula

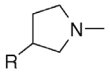
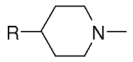
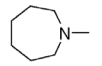
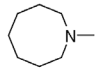
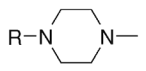


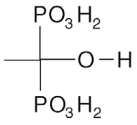
Compound	Ring	ED_{50}
21		50
22		250
23		~2500
24		>3000

General structural formulae



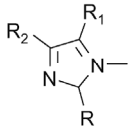
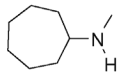
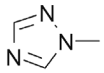


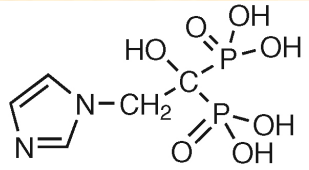
Compound	Ring	R	n	ED_{50}
7		H	2	10
8		H	3	25
9		H	5	250
10		Ph	2	70
11		4-Cl-Ph	2	3.5
12		H	2	5.6
13		Ph	2	~11
14		Ph	3	100
15		Ph	5	>300
16		3-F-Ph	2	30
17			2	25
18			2	>300
19		Me	2	~400
20		Ph	2	>10000

Heterocyclic ring—$(CH_2)_n$— 

Structure-Activity Relationship (SAR)

- Case Study: SAR investigation to discover potent geminal bisphosphonates

Compound	R	ED_{50}	Compound	Ring	R	R_1	R_2	*n*	ED_{50}
25		>2000	29		H	H	H	1	0.07
			30		H	H	H	2	45
26		800	31		Me	H	H	1	3
			32		H	Me	Me	1	1.5
27		40	33						>300
28		7	34						600



Zoledronice acid (Zometa, ED_{50} 0.07 μg/kg^{-1})

Quantitative Structure-Activity Relationship (QSAR)

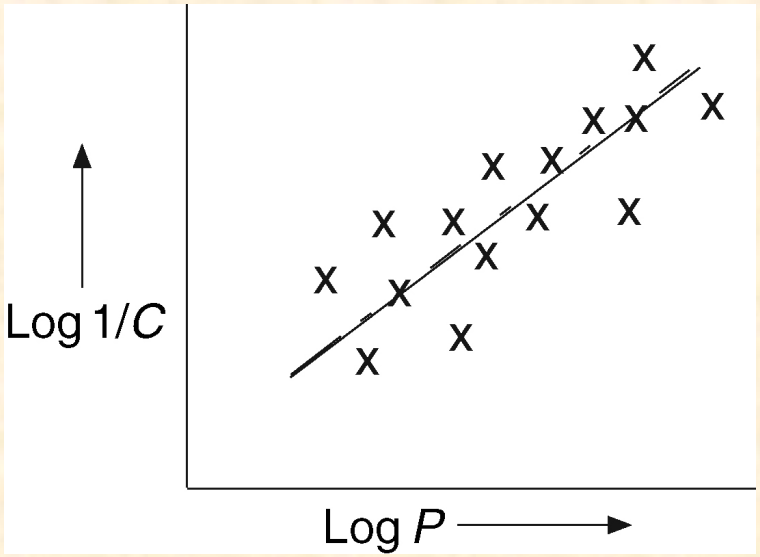
- QSAR – mathematical relationship (equations)
  biological effect vs. physicochemical parameters

  - lipophilicity
  - electron distribution
  - shape
  - size
  - partition coefficients
  - Hammett or Tafts constants

  Biological activity = F {parameters (s)}

Quantitative Structure-Activity Relationship (QSAR)

- Regression Analysis



Quantitative Structure-Activity Relationship (QSAR)

- Lipophilic parameters

  Partition coefficient

$$\log (1/C) = k_1 \log P + k_2$$

---

(1) Toxicity of alcohols to red spiders:
log (1/C) = 0.69 log P + 0.16 r = 0.979, n = 14, s = 0.087

(2) The binding of misc. neutral molecules to bovine serum:
log (1/C) = 0.75 log P +2.30 r = 0.96, n = 42, s = 0.159

(3) The binding of misc. neutral molecules to haemoglobin:
log (1/C) = 0.71 log P +1.51 r = 0.95, n = 17, s = 0.16

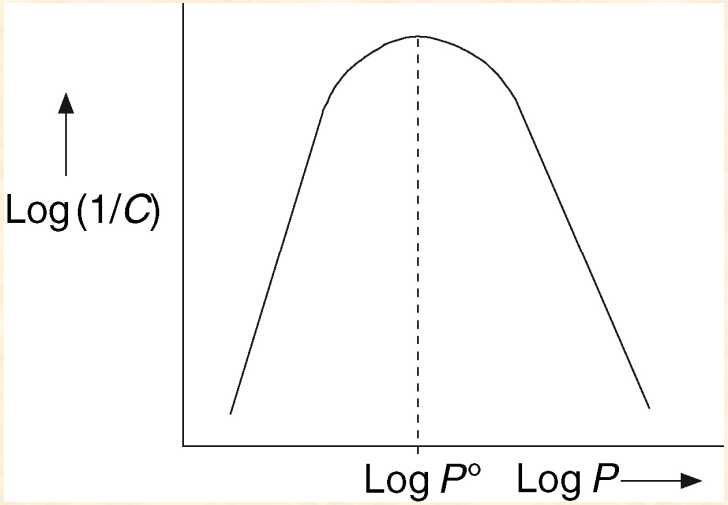
(4) Inhibition of phenols on the conversion of P-450 to P-420 cytochromes:
log (1/C) = 0.57 log P +036 r = 0.979, n = 13, s = 0.132

Quantitative Structure-Activity Relationship (QSAR)

- Lipophilic parameters

  Partition coefficient – often parabolic

$$\log (1/C) = -k_1 (\log P)^2 + k_2 \log P + k_3$$



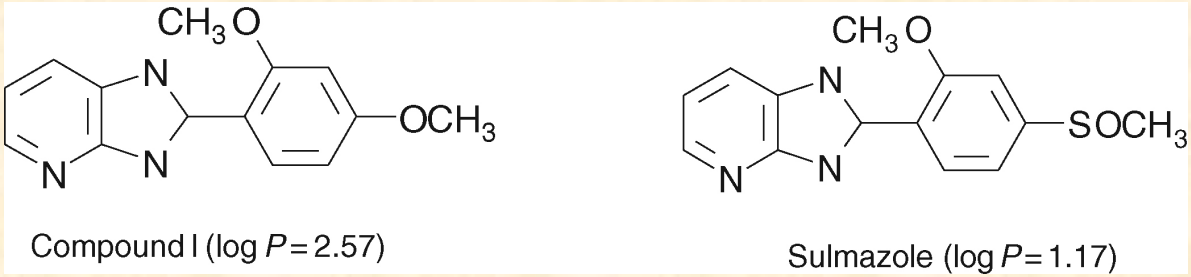
Quantitative Structure-Activity Relationship (QSAR)

- Lipophilic parameters

  hypnosis (mice) with barbiturates

  $\log (1/C) = - 0.44 (\log P)^2 + 1.58 \log P + 1.93$ (r=0.969)

  Hansch – log*P* ~ 2 hypnotic (CNS drug)



Compound I (log *P* = 2.57)

Sulmazole (log *P* = 1.17)

Quantitative Structure-Activity Relationship (QSAR)

- Lipophilic parameters

  lipophilic substituent constants (π) (or hydrophobic) contribution of substituents to P

  $\pi = \log P_X - \log P_H$

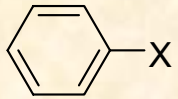
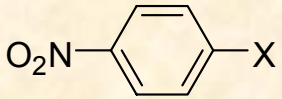
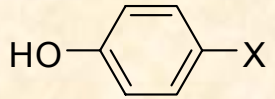
  $\pi = \log P_{(C6H5Cl)} - \log P_{(C6H6)} = 2.84 - 2.13 = 0.71$

  $\pi = \pi\,(\text{substituent 1}) + \pi\,(\text{substituent 2}) \ldots\ldots + \pi\,(\text{substituent n})$

Quantitative Structure-Activity Relationship (QSAR)

- Lipophilic parameters

lipophilic substituent constants (π)

Substituent X	Aliphatic systems R-X			
- H	0.00	0.00	0.00	0.00
- CH_3	0.50	0.56	0.52	0.49
- F	- 0.17	0.14		0.31
- Cl	0.39	0.71	0.54	0.93
- OH	- 1.16	- 0.67	0.11	- 0.87
- NH_2		- 1.23	- 0.46	- 1.63
- NO_2		- 0.28	- 0.39	0.50
- OCH_3	0.47	- 0.02	0.18	- 0.12

log (1/C) vs π high r and low s – important contributor

Quantitative Structure-Activity Relationship (QSAR)

- Lipophilic parameters

  distribution coefficients (*D*)

  ionization

$$D = \frac{[\,HA_{organic}\,]}{[\,H^{+}_{aqueous}\,] + [\,A^{-}_{aqueous}\,]}$$

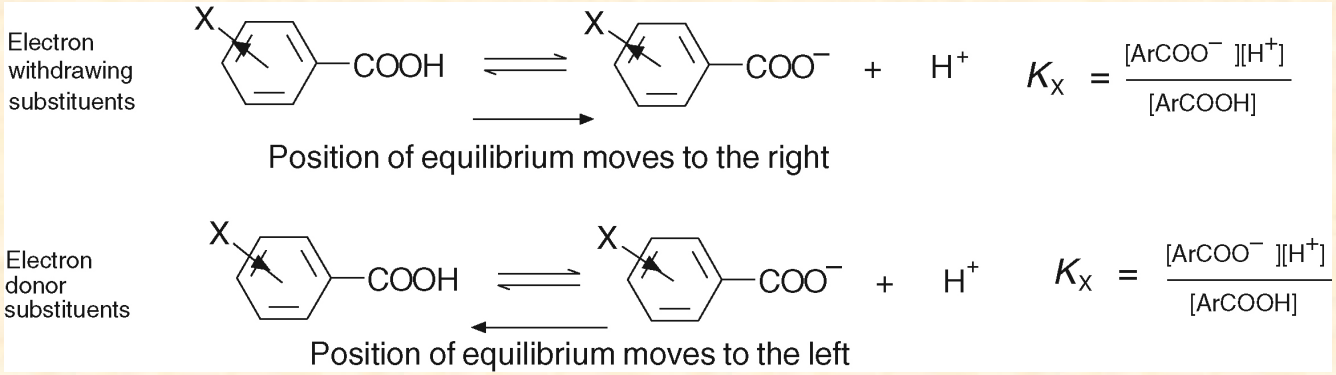
for acids $\log (P/D-1) = pH - pK_a$

for bases $\log (P/D-1) = pK_a - pH$

Quantitative Structure-Activity Relationship (QSAR)

- Electronic parameters

The Hammett constant (σ)



$$\sigma_x = \log \frac{K_x}{K}$$

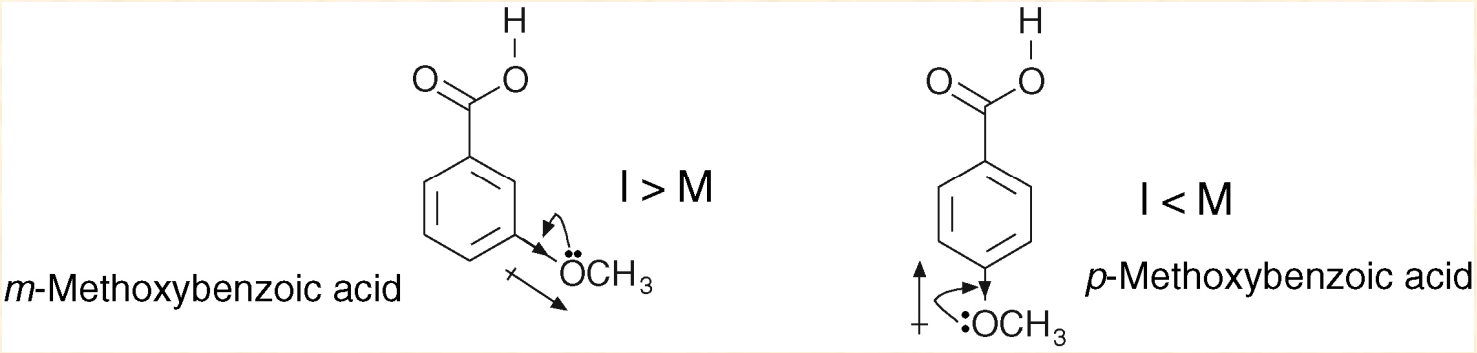
$$\sigma_x = \log K_x - \log K$$

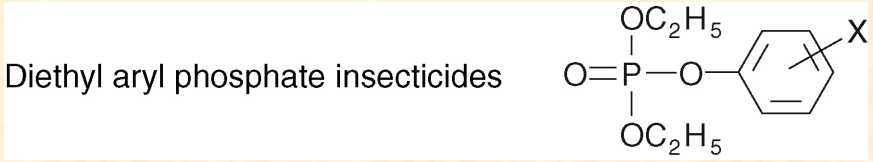
$$\sigma_x = pK - pK_x$$

Quantitative Structure-Activity Relationship (QSAR)

- Electronic parameters

The Hammett constant (σ)



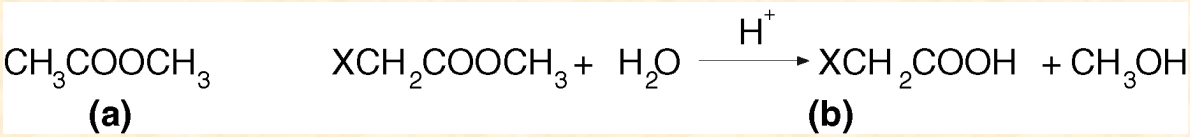


$\log (1/C) = 2.282\ \sigma - 0.348$

Quantitative Structure-Activity Relationship (QSAR)

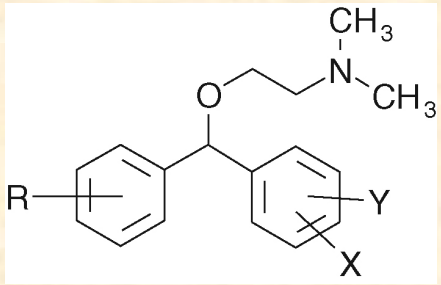
- Steric parameters

The Taft steric parameter (E_s)



$$E_s = \log \frac{k_{(XCH2COOCH3)}}{k_{(CH3COOCH3)}} = k_{(XCH2COOCH3)} - k_{(CH3COOCH3)}$$

log BR = 0.440E_s - 2.204 (n=30; s=0.37; r= 0.886)



Quantitative Structure-Activity Relationship (QSAR)

- Steric parameters

Molar refractivity (*MR*)

$$MR = \frac{(n^2 - 1)\, M}{(n^2+2)\, \rho}$$

additive – functional groups

Quantitative Structure-Activity Relationship (QSAR)

- Hansch analysis

drug activity vs. measurable chemical properties
multiparameter approach

two stages: - transport to the site of action
- binding to the target site

$$\log 1/C = k_1(\text{partition parameter}) + k_2(\text{electronic parameter}) + k_3(\text{steric parameter}) + k_4$$

$$\log 1/C = k_1 P - k_2 P^2 + k_3 \sigma + k_4 E_s + k_5$$

Quantitative Structure-Activity Relationship (QSAR)

- Hansch analysis

Accuracy :

- Greater number of analogs – n=5x (x= number of parameters)
- biological data
- the choice of parameters

Use:

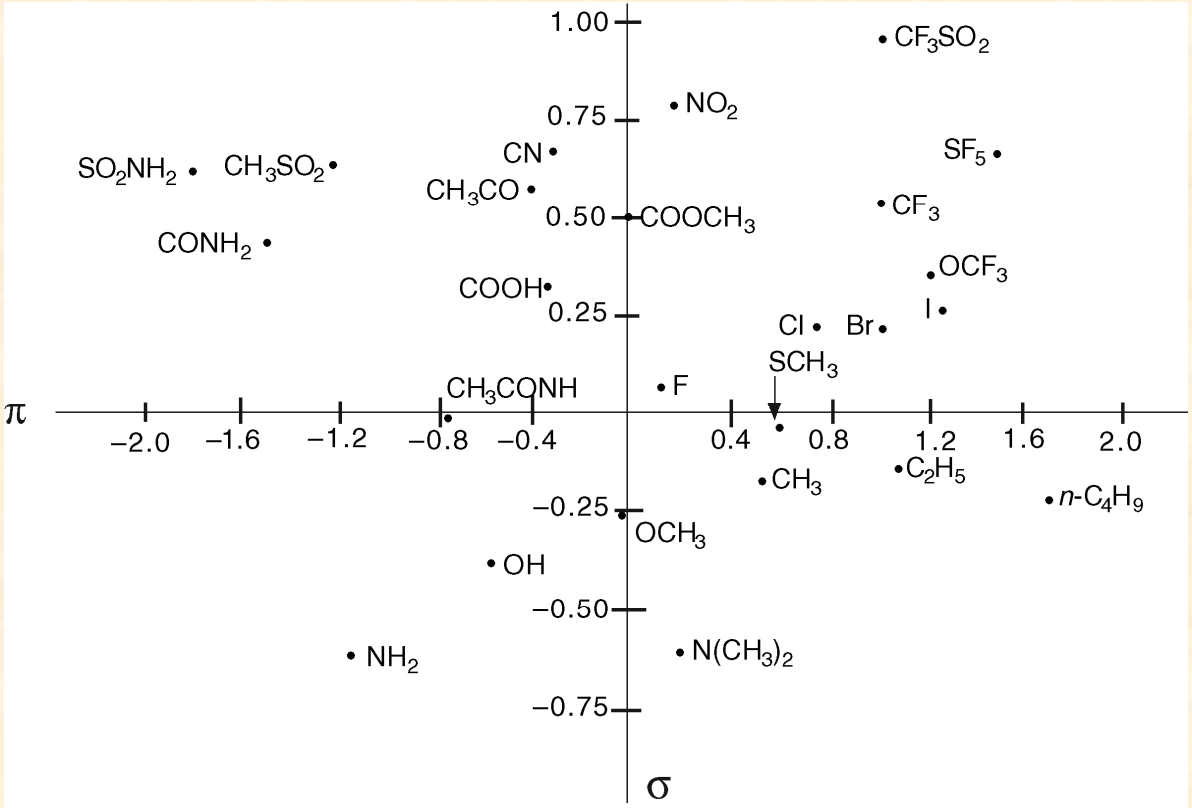
- Asses the factors controlling the activity
- predict optimum activity (ideal parameter values)

Sources of parameters

- CRC, CAS, Merck Index, etc.

Quantitative Structure-Activity Relationship (QSAR)

- Craig plots



Use with Hansch analysis:

$$\log 1/C = 2.67\pi - 2.56\sigma + 3.92$$