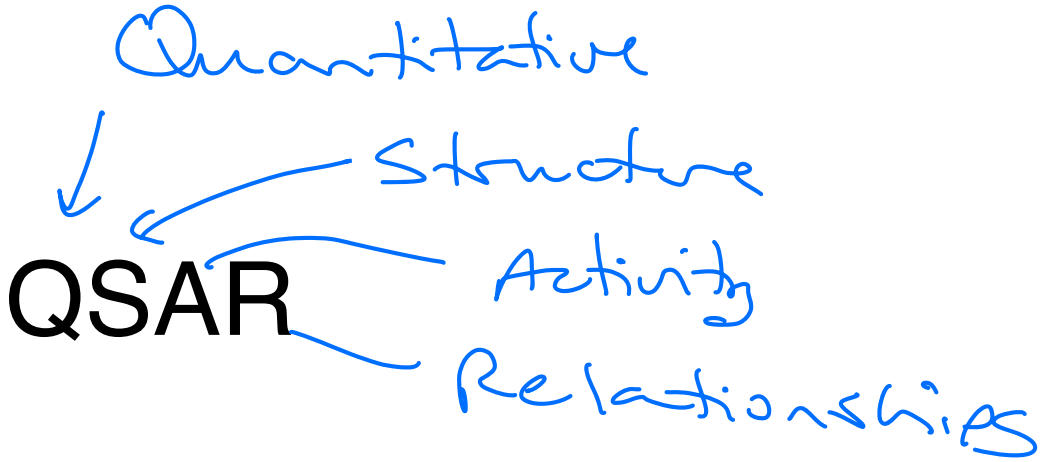
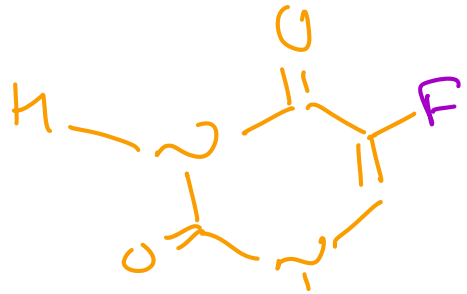

Quantitative
Structure
Activity
Relationships
QSAR

Drug Design : modifications to lead compounds

1. Disjunction – break into smaller pieces
2. Conjunction – adding – attaching molecules together
3. Ring Opening/Closing –
4. Change stereochemistry/orientation –
5. Isosteric substitutions ← often used with lead compounds that are naturally occurring

Antimetabolites



uracil

fluorouracil

antitumor

Isosteres : – atoms in which the outer layer of electrons is so similar we consider them the same

Hans Erlenmeyer definition

Examples :

-O- -NH- -CH $_2$-

6 5+1=6 4+2=6

-F -OH -NH $_2$ -CH $_3$

Grimm's Law of Hydride Displacement –

the addition of a hydride to an atom gives the resulting pseudoatom the properties of the atom with next highest #

Classification of Isosteres — by # valence electrons

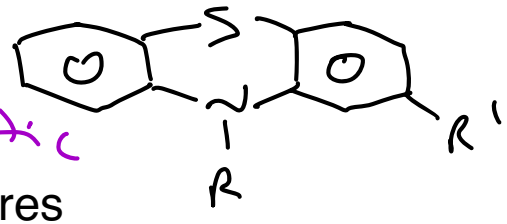
| | |
|---|---|
| Class I | halogens, -OH, -SH, $-NH_2$, $-CH_3$ |
| Class II | O, S, Se, Te, NH, $CH_2$ |
| Class III | N, P, As, CH |
| Class IV | C, Si, $N^+$, $P^+$, $S^+$, $As^+$ |
| Class V (annular isosteres) | CH=CH, S, O, NH |

} Classical isosteres

Annular equivalents : these are substitutions made to atoms in a ring.

Example : -C=C- can be replaced by –S-

phenothiazines

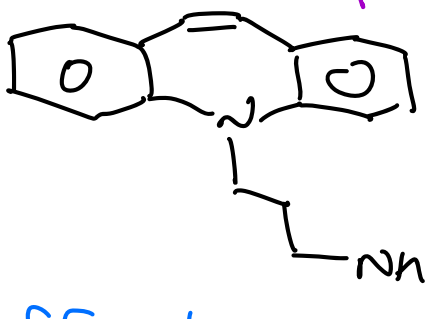


antipsychotic

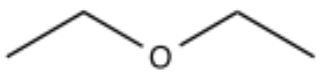
Bioisosteres

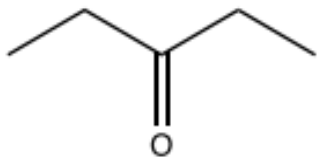
have similar biological effect

protriptyline



antidepressant





both anesthetic + narcotic

# Classical Isosteres

**TABLE 2.9** Classical Isosteres

1. Univalent atoms and groups

   a. $CH_3$ $NH_2$ OH F Cl
   b. Cl $PH_2$ SH
   c. Br *i*-Pr
   d. I *t*-Bu

2. Bivalent atoms and groups

   a. $-CH_2-$ $-NH-$ $-O-$ $-S-$ $-Se-$
   b. $-COCH_2R$ $-CONHR$ $-CO_2R$ $-COSR$

3. Trivalent atoms and groups

   a. $-CH=$ $-N=$
   b. $-P=$ $-As=$

4. Tetravalent atoms

   a. $-\overset{|}{\underset{|}{C}}-$ $-\overset{|}{\underset{|}{Si}}-$
   b. $=C=$ $=\overset{+}{N}=$ $=\overset{+}{P}=$

5. Ring equivalents

   a. $-CH=CH-$ $-S-$ (e.g., benzene, thiophene)
   b. $-CH=$ $-N=$ (e.g., benzene, pyridine)
   c. $-O-$ $-S-$ $-CH_2-$ $-NH-$ (e.g., tetrahydrofuran, tetrahydrothiophene, cyclopentane, pyrrolidine)

SAR – Structure activity relationship

QSAR – Quantitative
↑ look for measurable numerical relationships between structure + activity

Hansch Analysis

1964

Proposed the biological activity of a group of related compounds could be mathematically related to structure

$$\log \frac{1}{C} = a\pi + b\sigma + cE_s + d$$

$\log \frac{1}{C}$ – Activity of drug

$\pi$ – hydrophobicity

$\sigma$ – electronic character

$E_s$ – size + steric interactions

C = conc. of drug to get response

## Hansch Recommendations for SAR

- test several physicochemical parameters
- accept simplest model
- be be able to explain the relationship

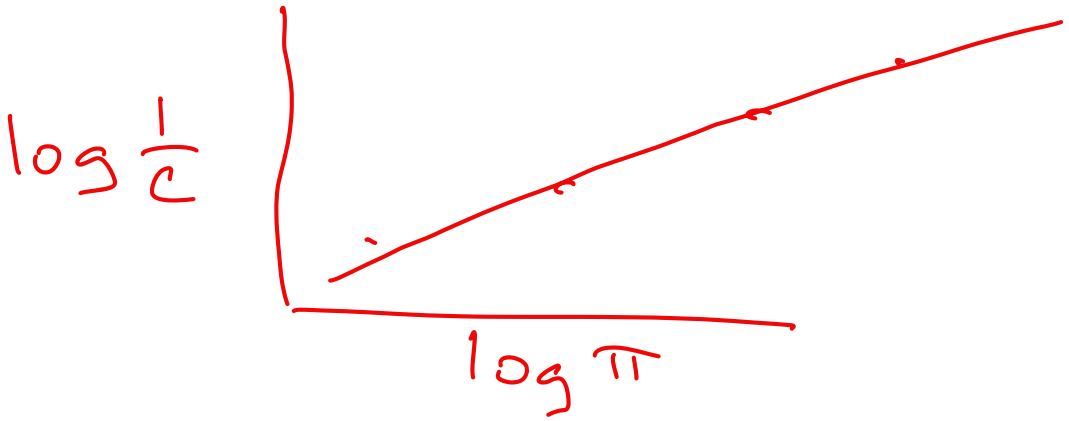
Physicochemical Properties for QSAR

Hydrophobicity — P partition coefficient (whole molecule); π hydrophobicity of a side chain

Electronic Properties — σ Hammet substitution constant

Steric Properties — $E_s$ or ~~MR~~ (Taft's steric factor)

Others: polar surface area, dipole moment, rotatable bonds, MW……



Hydrophobicity

- determines how easily a drug passes a membrane
- interactions between drug + target

Properties of Lipophilic Drugs:

- ☺ easy to absorb
- ☺ readily distributed
- ☹ low bioavailability
- ☹ CNS side effects

Partition Coefficient

## Hydrophobicity

$[drug]_{H_2O} \rightleftharpoons [drug]_{organic}$

Described by log P, $P_c$

$$P = \frac{[drug]_{organic}}{[drug]_{water}}$$

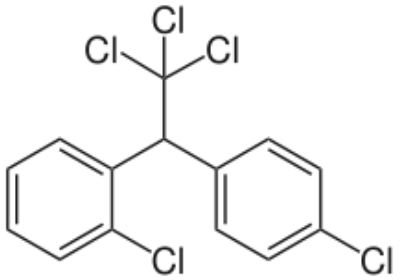
$K_{eq}$

Can use octanol here

$-\log P$ drug has higher affinity for water

$+\log P$ organic phase

DDT (dichlorodiphenyltrichloroethane)




$K_{ow} = 9.55 \times 10^5$ very lipophilic

↑ Pc

If I put 0.0100 moles in 100 ml of water then equilibrate with 100 ml of octanol, how many moles will be in the octanol?

$$K_{eq} = K_{oc} = \frac{[DDT]_o}{[DDT]_{H_2O}} \rightarrow \frac{\left[\frac{x}{.1L}\right]}{\left[\frac{.01-x}{.1L}\right]}$$

$$9.55 \times 10^5 = \frac{x}{0.01-x}$$

$$9.55 \times 10^5 (0.01-x) = x$$

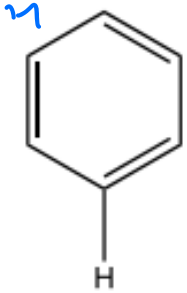
$$x = 9.999895 \times 10^{-3} \text{ moles}$$

## Hydrophobicity of substituents

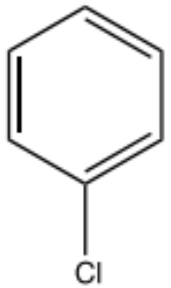
$$\pi_x = \log P_x - \log P_H$$

Compare log P for benzene to log P for substituted benzene

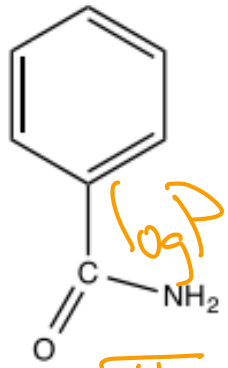
$\log P_H = 2.13$




$\log P_{Cl} = 2.84$




$\log P = 0.64$




$\pi_{Cl} = 0.71$

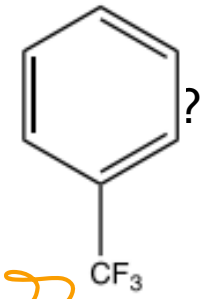
+π is more hydrophobic

$\pi_{amide} = -1.49$

−π more hydrophilic

| -$CH_3$ | -tBu | -OH | -$CF_3$ | -Cl | -Br | -F |
|---|---|---|---|---|---|---|
| 0.52 | 1.68 | -0.67 | 1.16 | 0.71 | 0.86 | 0.14 |

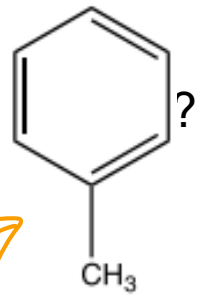
| $-CH_3$ | -tBu | -OH | $-CF_3$ | -Cl | -Br | -F |
|---|---|---|---|---|---|---|
| 0.52 | 1.68 | -0.67 | 1.16 | 0.71 | 0.86 | 0.14 |

What is log P for 

?

$\log P_{CF_3} = 2.13 + 1.16$

$\log P = 3.29$

Is it more or less hydrophobic than 

?

$\log P_{tol} = 2.13 + 0.52$

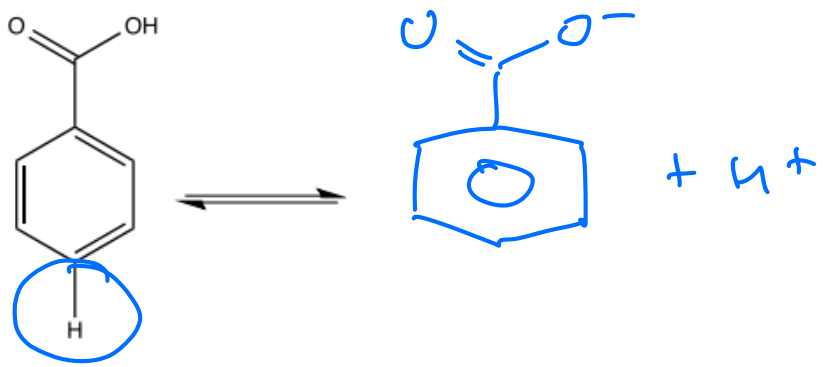
$= 2.65$

more polar than

## Electronic Properties

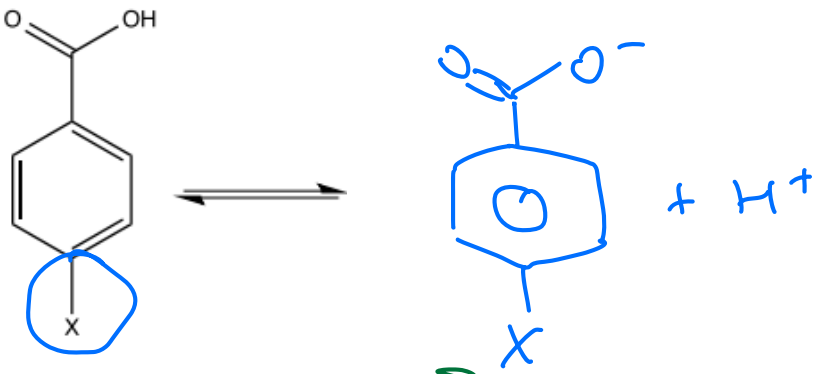
e- donating or withdrawing ability

### Hammet constant (σ)




$+ H^+$

$$K_H = \frac{[ArCO_2^-][H^+]}{[ArCO_2H]}$$




$+ H^+$

$$K_X = \frac{[ArXCO_2^-][H^+]}{[ArXCO_2H]}$$

if X is e- withdrawing stabilizes this product

$K_X \uparrow$

$$\sigma_X = \log\left(\frac{K_X}{K_H}\right)$$

σ positive

σ values

Para position

| Electron Withdrawing Groups | |
|---|---|
| -Cl | 0.23 |
| -CN | 0.66 |
| $-NO_2$ | 0.78 |

| Electron Donating Groups | |
|---|---|
| $-CH_3$ | -0.17 |
| -OH | -0.27 |
| $-NH_2$ | -0.66 |

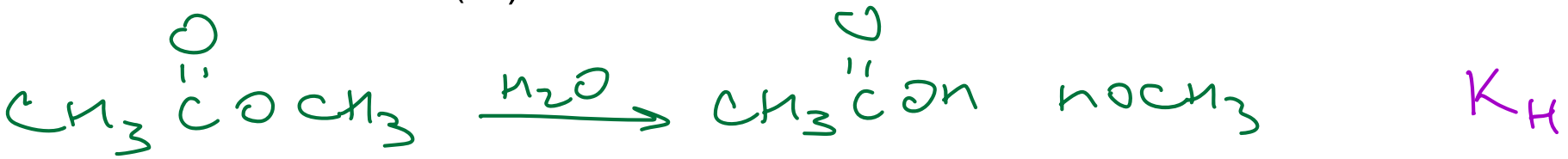
↑↑ positive EWG

↑↑ EDG

## Steric Properties

Determined by comparing reaction rates for ester hydrolysis

### Taft Parameter ($E_s$)

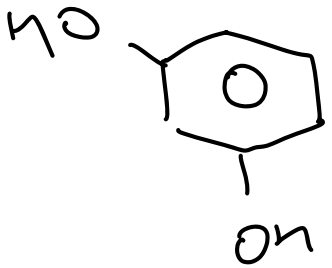


$$E_s = \log K_X - \log K_H$$

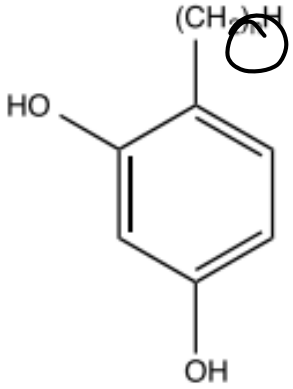
always 0 or negative

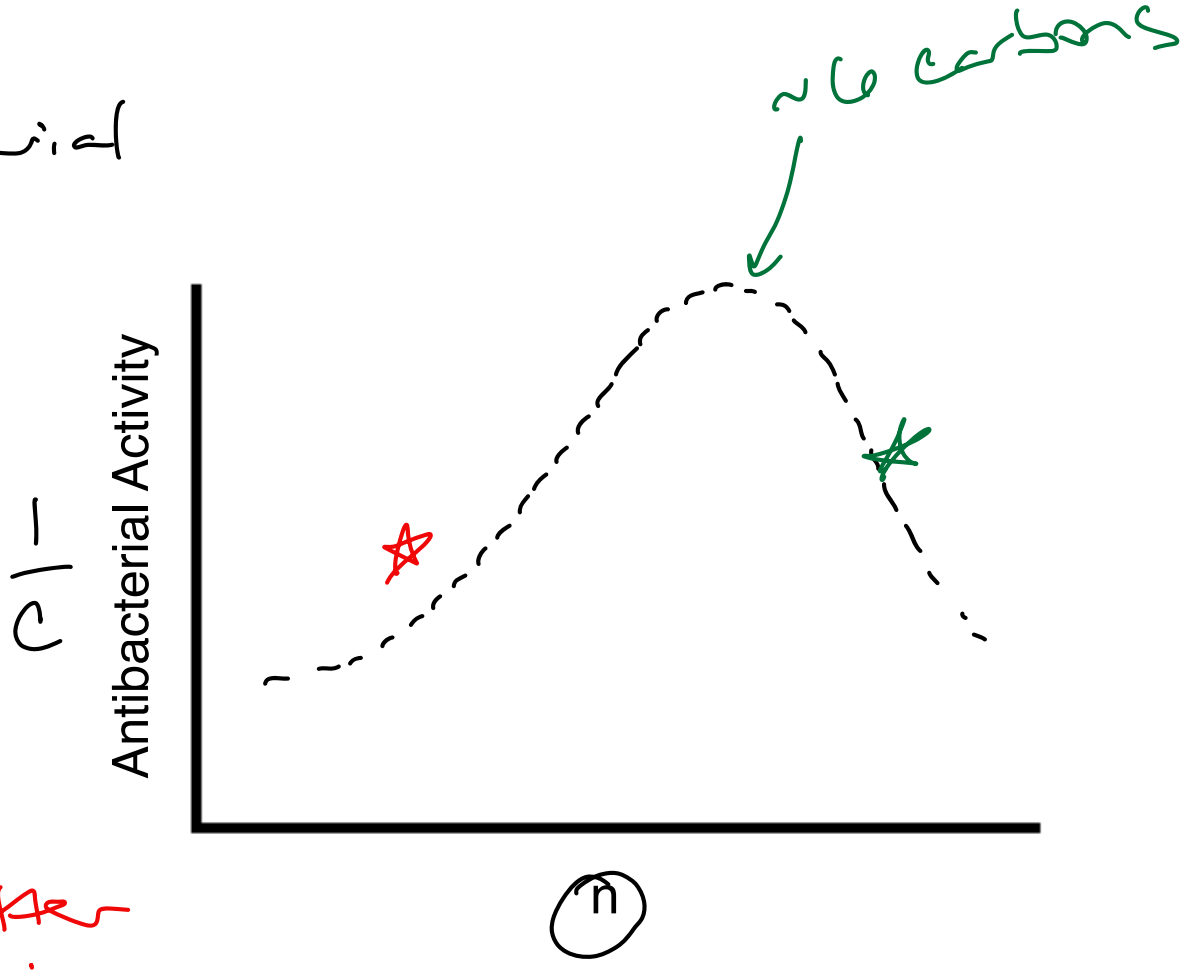
### Molar Refractivity (MR)

$$MR = \left(\frac{n^2 - 1}{n^2 + 2}\right)\left(\frac{MW}{d}\right)$$



resorcinol
antibacterial




* as C ↑ it is better at killing bacteria
more C's
more lipophilic
better at inserting in membranes
to disrupt membrane

* effectiveness decreases
limited by solubility

Inhaled

## Drug Activity and Hydrophobicity : Anesthetics

| | Log P | %required for effect |
|---|---|---|
| Ether | 0.98 | 5% ← |
| $CHCl_3$ | 1.97 | 1-2% ← |
| Halothane | 2.3 | 0.7% ← |

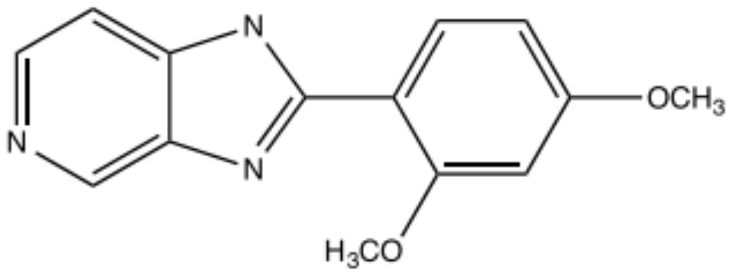
as P ↑
we need less drug

more hydrophobic
better able to
dissolve in membranes

Drug Activity and Hydrophobicity : CNS side effects

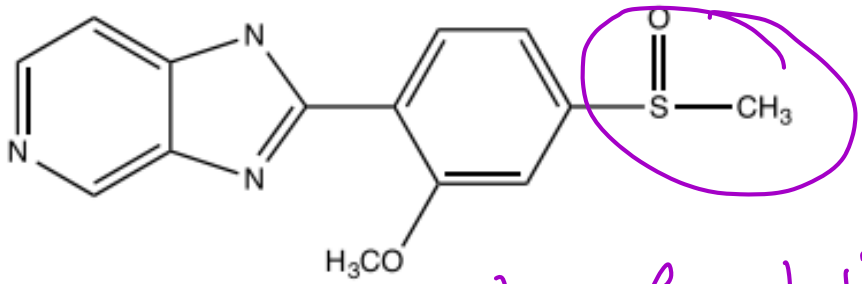
Drugs with log P close to 2
are often able to enter CNS
⇒ side effect

lead compound
↓ log P = 2.49




Cardiotonic drug
CNS - bright
vision

Sulmazole




log P = 1.17

Cardiotonic

positive inotropic

agent

Lipinski's Rule of 5 for whole drug

less than 5 H bond donors

mw < 500

log P < 5

Rule of 3 for drug fragments

< 3 H bonds

mw < 300