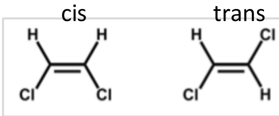
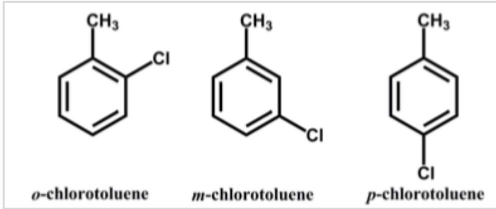
Lecture 2: Binding to a target – shape and intermolecular forces (08/03/18)

Shape: determined by isomers and the number of electron groups around a central atom



- ○ Isomers: geometric (cis – same side/trans – opposite side isomers) and occurs in molecules with restricted rotation about a C=C
  - structural isomers: different connectivity of groups – ortho (position 2), meta (position 3) and para (position 4 – directly opposite)
  - configurational isomer: different spatial sequence of atoms or groups connected to a central atom - interconversion requires breaking and reforming covalent bonds (optical isomers R- and S-)
  - conformational isomer: same connectivity and interconversion involves rotation(s) about a single bond(s)



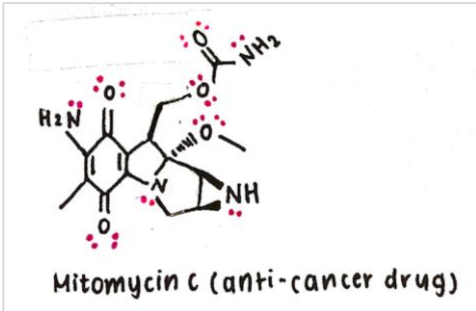
ortho meta. para

Lewis structures: only the valence shell electrons are considered – trying to achieve the octet rule (8 valence electrons) for stability

- ○ Single bond = 2 shared electrons, double bond = 4 shared electrons and triple bond = 6 shared electrons
- ○ Valence Shell Electron Pair Repulsion (VSEPR) theory is used where each group of valence electrons around a central atom is located as far away as possible from others to minimise repulsions
- ○ Shows the type of bonding and the distribution of non-bonding electrons

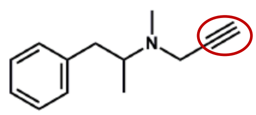
→ *Draw non-bonding electrons onto 2-dimensional representations of a drug.*

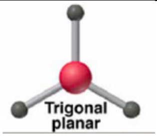
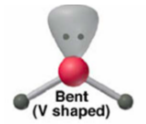
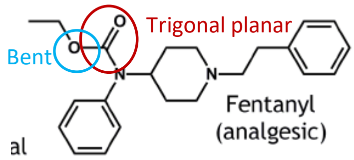
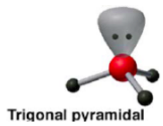
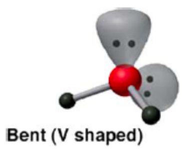
- ○ Dots placed next to an atom are used to represent non-bonding electrons



→ *Assign local structures to regions of the drug.*

- ○ Electron group can be an atom or non-bonding electron pair
- ○ Molecular arrangement: geometry that we can construct that gives the maximal distance between the electron groups
- ○ Molecular shape: defined only by the atoms

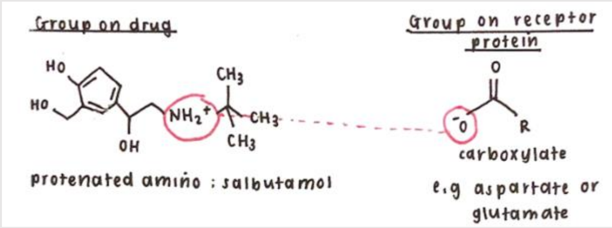
Number of electron groups	Number of atoms	Number of non-bonded electron pairs	Molecular arrangement	Molecular shape	Examples
2	2	0	Linear  Bond angle: 180°	Linear	 Selegiline (antiParkinsonian) – Central atom is carbon – satisfies the octet rule
3	3	0	Trigonal planar	Trigonal planar	

			 Bond angle: 120°		
	2	1	Trigonal planar	Bent 	
4	4	0	Tetrahedral  Bond angle: 109.5°	Tetrahedral	
	3	1	Tetrahedral	Trigonal pyramidal 	
	2	2	Tetrahedral	Bent 	

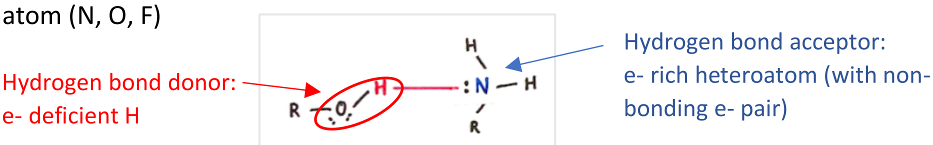
→ *Indicate regions of a molecule that could participate in intermolecular interactions and nominate the type of interaction.*

Intermolecular forces:

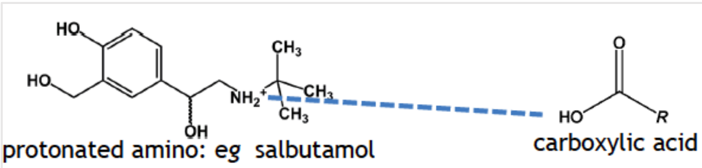
- Electrostatic or ionic – positive charged entity (from drug or target) interact with negatively charged entity (from drug or target)



- Hydrogen bonding – weak to moderate attractive force that exists between a hydrogen atom covalently bonded to a very electronegative atom and a pair of electrons on another small, electronegative atom (N, O, F)



- Ion-dipole – when an ion and a polar molecule interact - one entity is charged, and the binding entity is uncharged leading to unequal distribution of charge

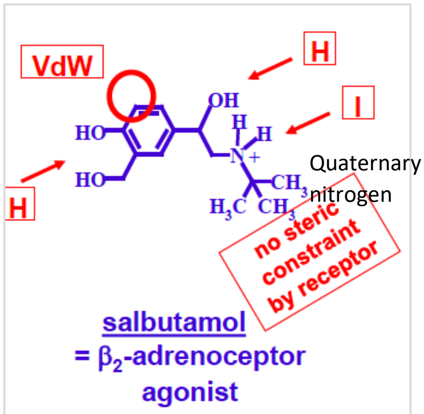


- Dipole-dipole – arise from a degree of charge separation in polar molecules
- Cation-π interactions – interaction between an electron rich π systems e.g. benzene, ethylene, acetylene) and a cation (positively charged ion)

Lecture 3 and 4: Quantitative structure activity relationships (QSAR) 1 and 2 (14/03/18, 15/03/18)

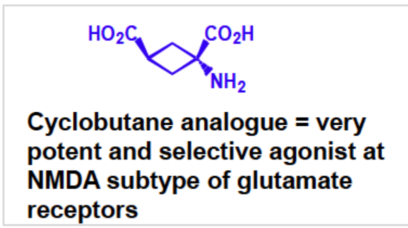
→ *Understand the types of chemical properties that may affect the effectiveness of a drug*

- Multiple binding groups (3-4) in drugs to interact with various regions of the biological target
- Pharmacophore: binding groups that are relevant for the molecule to interact with its biological target and their relative positions in space



Designing agonists:

- Drugs are active if: appropriate binding groups are in correct position, molecule is the right size, extra groups fit into pockets at the receptor
- Conformational restriction can give better selectivity/potency – orientating the binding groups in a static conformation



Optimising activity and design:

- Can use: experience from other series, change distance between binding groups, bioisoteric groups (including ring substitution), conformational restriction, molecular modelling

Bioisostere: compound resulting from the exchange of an atom or group of atoms with another to a similar type of motif with the aim of improving the pharmacokinetics of a given compound

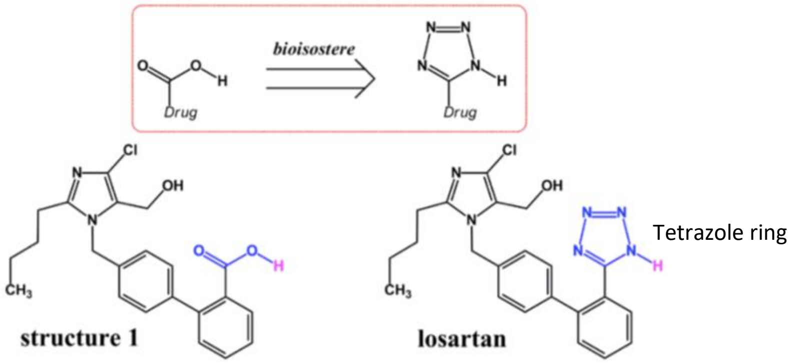
- Subtle change occurs – hope to get improved affinity and/or selectivity

E.g. 1) Bioisosteric replacement of the carboxylic acid group of glutamic acid gives AMPA

glutamic acid α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)

- The bioisosteric replacement makes AMPA more potent and selective agonist at the AMPA subtype of glutamate receptors

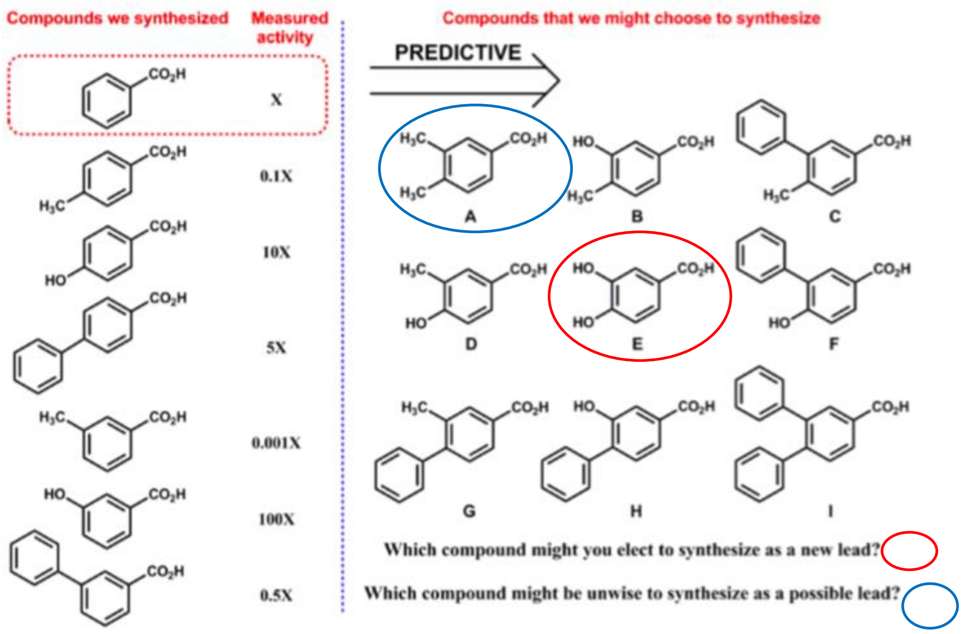
E.g. 2)



- Structure 1 inhibits the angiotensin II receptor but was poorly absorbed
- Bioisosteric replacement of the acid with a tetrazole ring resulted in losartan
- Tetrazole ring: Hydrogen is lost at physiological pH (pKa lower than 7.4) and ring is quite lipophilic – helps it partition across the membrane
- The ability to cross the membrane is described as a degree

Quantitative Structure-Activity Relationships: (QSAR)

- QSAR techniques can inform what is a sensible drug to make and what particular substitutions are useful or not useful
- Broad screening of compounds using QSAR technique will reduce the cost of initial discovery



Addition of CH_3 decreased the activity

Addition of OH increased the activity

Which compound might you elect to synthesize as a new lead? E

Which compound might be unwise to synthesize as a possible lead? A

Early QSAR studies:

- Looked at logP through regression analysis – how a particular compound partitioned into a fatty phase

→ *Understand the relevance of logP values and the relationship with drug availability*

Partition coefficients: (logP) – fatty vs water

- Describes how a drug will distribute through an organic phase (octanol) or an aqueous phase (water)
- LogP is used instead due to the large numbers involved

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

→ *Use the relevant Hammett equations to predict K_a, π and σ values*

Hydrophobic Substituent Constant: determines if a substituent increases or decreases hydrophobicity

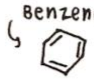
- Equation for hydrophobic substituent constant (π_X) from first principles

$$\pi_X = \log P_X - \log P_H$$

H = parent unsubstituted compound

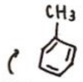
X = substituent attached to parent compound

Benzene



$\log P_{(H)} = 2.13$
↳ parent unsubstituted compound

CH_3

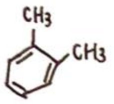


Toluene

CH_3 = lipophilic
$\log P_{(X)} = 2.69$
↳ type of substituent added to the parent compound.

$\pi_X = \log P_X - \log P_H$
$= 2.69 - 2.13 = 0.56$

↳ adding CH_3 group makes the parent compound more lipophilic



$\log P_? = \log P_H + 2(\pi CH_3)$ (additive)
$= 2.13 + 2(0.56)$
$= 3.25$

predicting log P

dimethyl-benzene

A logP of ~2 means that if 101 molecules of benzene are partitioned in a beaker with 50 mL octanol (fatty) and 50 mL of water and it is shaken and allowed to equilibrate

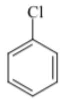
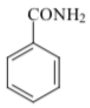
100 molecules will be partitioned into octanol and 1 molecule will partition into water

- If a substituent has <u>no effect</u> on the partitioning of benzene into organic phase, <u>$\pi_X = 0$</u>
- If a substituent <u>increases the partitioning</u> of the compound <u>into the organic phase</u>, <u>π_X is positive</u>, and the substituent is <u>hydrophobic</u>
- If a substituent <u>decreases the partitioning</u> of the compound <u>into the organic phase</u>, <u>π_X is negative</u>, and the substituent it <u>hydrophilic</u>

Common hydrophobic (increase partitioning into organic phase) and hydrophilic (increase partitioning into water phase) substituents:

Hydrophobic		Hydrophilic	
Substituent	π	Substituent	π
$-CH_3$	0.56	$-NO_2$	−0.28
$-C(CH_3)_2$	1.98	$-OH$	−0.67
$-C_6H_5$	1.96	$-CO_2H$	−0.34
$-C_6H_{11}$	2.51	$-NH_2$	−1.23

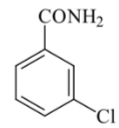
E.g. 2) Hydrophobic Substituent constant

logP (benzene) 	= 2.13
 logP (chlorobenzene)	= 2.84
 logP (benzamide)	= 0.64

π_{Cl} = logP (chlorobenzene) (substituted) – logP (benzene) (parent)

= 2.84 – 2.13 = 0.71

π_{CONH2} = 0.64 – 2.13 = - 1.49



meta-chlorobenzamide

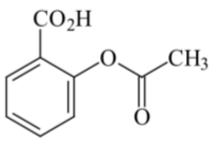
Rearrange equation:

logP (meta-chlorobenzamide) = logP (benzene) (parent) + πCl + πCONH2

= 2.13 + 0.71 + (- 1.49) = 1.35

Similar to the experimental value: logP (meta-chlorobenzamide) = 1.51

<u>*Question*</u>: Given that logP for benzene = 2.13 and π_{CO2H} = - 0.34 and πOC(O)CH3 = - 0.6, calculate the logP value for aspirin



aspirin

logP (aspirin) = logP (benzene) + π_{CO2H} + $\pi_{OC(O)CH3}$

= 2.13 + (- 0.34) + (- 0.6)

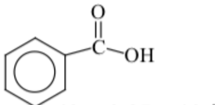
= 1.19

Electronic Substituent Constant (K_a): extent of dissociation of an acid

$$\rho\sigma_X = \log K_X - \log K_H$$

- Substituents with <u>$\sigma < 0$</u> are <u>electron donating</u> – disfavour dissociation of an acid
- Substituents with <u>$\sigma > 0$</u> ae <u>electron withdrawing</u>
- The position (ortho, meta or para) of the substituent is very important due to inductive and resonance effects
- In instances not told otherwise, assume ρ = 1

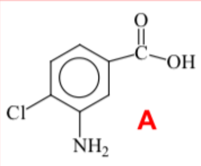
Question: Does drug A or B dissociate to a lesser extent than benzoic acid?

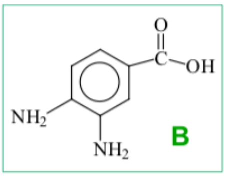


$K_a = 6.25 \times 10^{-5}$ M
$pK_{a\,(H)} = 4.20$

Benzoic acid

Given:
σ_{meta} (NH_2) = –0.16
σ_{para} (NH_2) = –0.66
σ_{para} (Cl) = 0.45





Note: a greater pKa = dissociation to a lesser extent

$[\rho\sigma_x = \log k_x - \log k_H]$ ($\log k_x$ unknown)

$[pH = -\log H^+$; $pK_a = -\log K_a]$

$-\log k_x = -\log k_H - \rho\sigma_x$

$pK_{a(x)} = pK_{a(H)} - \rho\sigma_x$

$= 4.20 - \rho\sigma_x$

Drug A:

$= 4.20 - 1(0.29)$

σ_x para (Cl) = 0.45 $= 3.91$

σ_x meta (NH_2) = -0.16

$\Sigma\sigma_x = 0.29$

Drug B:

$pK_a(x) = 4.20 - \rho\sigma_x$

$= 4.20 - 1(-0.82)$

σ_x meta (NH_2) = -0.16 $= 5.02$

σ_x para (NH_2) = -0.66

$\Sigma\sigma_x = -0.82$

Drug B dissociates to a lesser extent than Drug A as pK_a (B) > pK_a (A)

↳ conjugate base is less stable than benzoic acid.

The Hansch Equation:

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

- The values for the coefficients, a-c tell us how important the parameters are in terms of activity
- The $(\log P)^2$ term highlights that there is an optimum value for P

C = dose required to produce a standard effect

Biological activity is expressed as 1/C because for a high performing drug, the C will be small (small amount is needed to achieve the defined biological activity)

π = hydrophobic

σ = electronic

E_s = steric