Over view on

MEDICINAL CHEMISTRY

COMBITORIAL CHEMISTRY

QSAR

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What is medicinal chemistry ?

In medicinal chemistry, the chemist attempts to design and synthesize a medicine or a pharmaceutical agent which will benefit humanity. Such a compound could also be called a 'drug‘. Latin ars medicina, meaning the art of healing

It involves:

• Synthesis

• Structure-Activity Relationships (SAR)

• Receptor interactions • Absorption, distribution, metabolism, and excretion (ADME)

According to IUPAC:

Medicinal chemistry it concerns the discovery, the development, identification and interpretation of mode of action of biological active compounds at the molecular level.

Medicinal chemistry covers the three stages

Discovery step: Involving choice of therapeutic target (receptor, enzyme & target group, cellularorinvivomodel) & identification or discovery and production of new active substances interactingwithselectedtargets. Such compounds called LEADCOMPOUND.

An optimization step: Which deals with improvement of lead compound.

•The optimization process takes primarily into account the increase in potency, selectivity and toxicity

Development stage: Whose purpose is continuation of improvement of pharmacokinetic properties.

History of Medicinal chemistry

2000 BC Materia Medica 250 vegetables drug And 120 mineral drugs

1500 BC Egyptian papyrus ebers 700 drugs originated from animal/plants/minerals

Emperor Frederick II issued the Magna Carta of pharmacy in 1240

Synthesis of Urea 1828 started Organic medicinal Chemistry

Ehrlich's "Side chain theory" and chemotherapy and Fischer's lock-and key theory Birth of Modern Med Chem 1800

Medicinal chemistry received formal recognition in academic pharmacy in 1932

Objective of medicinal chemistry !

Generally, we can identify the following stages in drug discovery, design and development.

Drug discovery-finding a lead

- Choose a disease.
- Choose a drug target.
- Identify a bioassay.
- Find a lead compound.
- Isolate and purify the lead compound if necessary.
- Determine the structure of the lead compound if necessary.

Drug design

- Identify structure-activity relationships (SARs)
- Identify the pharmacophore.
- Improve target interactions (pharmacodynamics).
- Improve pharmacokinetic properties,

Drug development

• Patent the drug.

• Carry out preclinical trials (drug metabolism, toxicology, formulation and stability test, pharmacology studies, etc).

• Design a manufacturing process (chemical and process development).

• Carry out clinical trials.

• Register and market the drug.

• Make money.

Finally Medicinal chemistry includes synthetic & computational aspects of the study of existing drugs and agents in development in relation to their bioactivities i.e., understandings a SARs (Structure Activity Relationships). OR • Itisatailoring ofdrug

What is combitorial chemistry?

Combinatorial chemistry is a technique by which large numbers of different but structurally similar molecules are produced rapidly and submitted for pharmacological assay.

This technique uses the same reaction conditions with the same reaction vessels to produce a large range of analogues.

Technique invented in the late 1980s and early 1990s to enable tasks to be applied to many molecules simultaneously

Combitorial library

Def: collection of finally synthesized compounds

Size: depends on the number of building blocks used per reaction and the number of reaction steps, in which a new building block is introduced

Typical: 10^2 up to 10^5 compounds

Random libraries	Focused or targeted libraries
Multiple libraries	Template –scaffold library
Multiple targets	One target
Highly diverse	Highly structural similarity
Mixtures	Single compounds
> 5000 compounds	< < 5000 compounds
Solid phase synthesis	Synthesis in solution, solid phase
Non purified compounds	Pure compounds
On bead screening, if possible	Screening in solution

Applications

- Applications of combinatorial chemistry are very wide Scientists use combinatorial chemistry to create large populations of molecules that can be screened efficiently.
- By producing larger, more diverse compound libraries, companies increase the probability that they will find novel compounds of significant therapeutic and commercial value.
- Provides a stimulus for robot-controlled and immobilization strategies that allow high-thrughput and multiple parallel approaches to drug discovery.

Techniques in combitorial chemistry

- ✓ Solid support synthesis: (on solid phase such as resin bead, pins, or chips)
- ✓ Split and mix method
- ✓ Parallel synthesis
- ✓ Solution phase synthesis (in solvent in the reaction flask

Solid phase synthesis

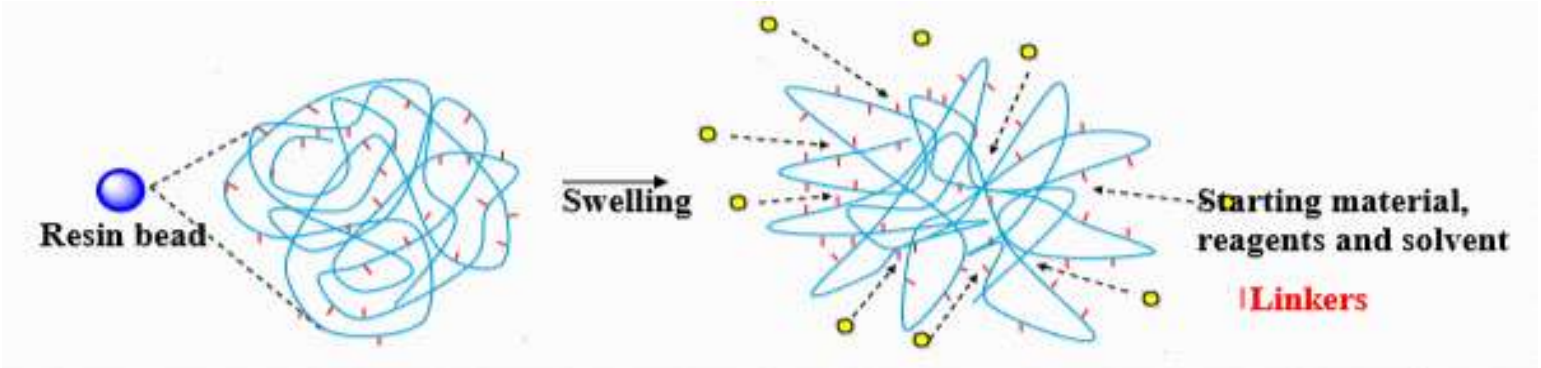
Reactants are bound to a polymeric surface and modified whilst still attached. Final product is released at the end of the synthesis.

Examples of solid phase supports:

- Partially cross-linked polystyrene beads hydrophobic in nature causes problems in peptide synthesis due to peptide folding
- Sheppard's polyamide resin - more polar
- Tentagel resin - similar environment to ether or THF
- Beads, pins and functionalized glass surfaces

Method

- Beads must be able to swell in the solvent used, and remain stable
- Most reactions occur in the bead interior



Anchor or linker

A molecular moiety which is covalently attached to the solid support, and which contains a reactive functional group

- Allows attachment of the first reactant
- The link must be stable to the reaction conditions in the synthesis but easily cleaved to release the final compound
- Different linkers are available depending on the functional group to be attached and the desired functional group on the product
- Resins are named to define the linker e.g. Merrifield, Wang, Rink

Solid phase synthesis: protecting groups

A few protecting groups used in solid phase synthesis.

For amines:

Boc (t-butoxycarbonyl)

Fmoc (9-fluorenylmetoxy carbonyl)

Tmsec (2 [trimethylsilyl] ethoxycarbonyl)

For carboxylic acids:

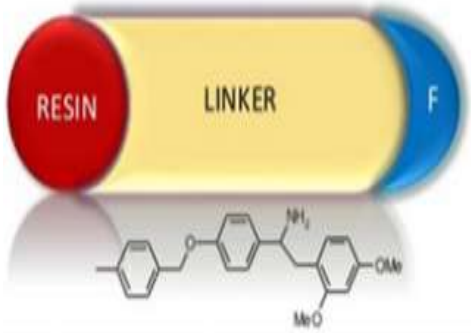
Tert Bu ester(t-butyl ester)

Fm ester(9-fluronyl methyl ester)

Tmse ester(2 [trimethylsilyl] ethyl)

WANG RESIN: linker suitable for attachment & release of carboxylic acids.

MERRIFIELD RESIN : linker suitable for peptide products.

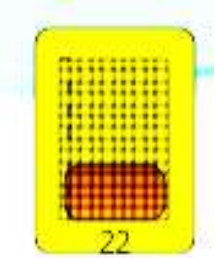


RINK RESIN : Linker suitable for attachment & release of carboxamide.

Parallel Synthesis

- To use a standard synthetic route to produce a range of analogues, with a different analogue in each reaction vessel, tube or well.
- The identity of each structure is known
- Useful for producing a range of analogues for SAR or drug optimisation.

Procedure for parallel synthesis!



Houghton's Tea Bag Procedure:

- ✓ Each tea bag contains beads and is labelled
- ✓ Separate reactions are carried out on each tea bag
- ✓ Combine tea bags for common reactions or work up procedures
- ✓ A single product is synthesised within each teabag
- ✓ Different products are formed in different teabags
- ✓ Economy of effort - e.g. combining tea bags for workups
- ✓ Cheap and possible for any lab
- ✓ Manual procedure and is not suitable for producing large quantities of different products

Automated parallel synthesis:

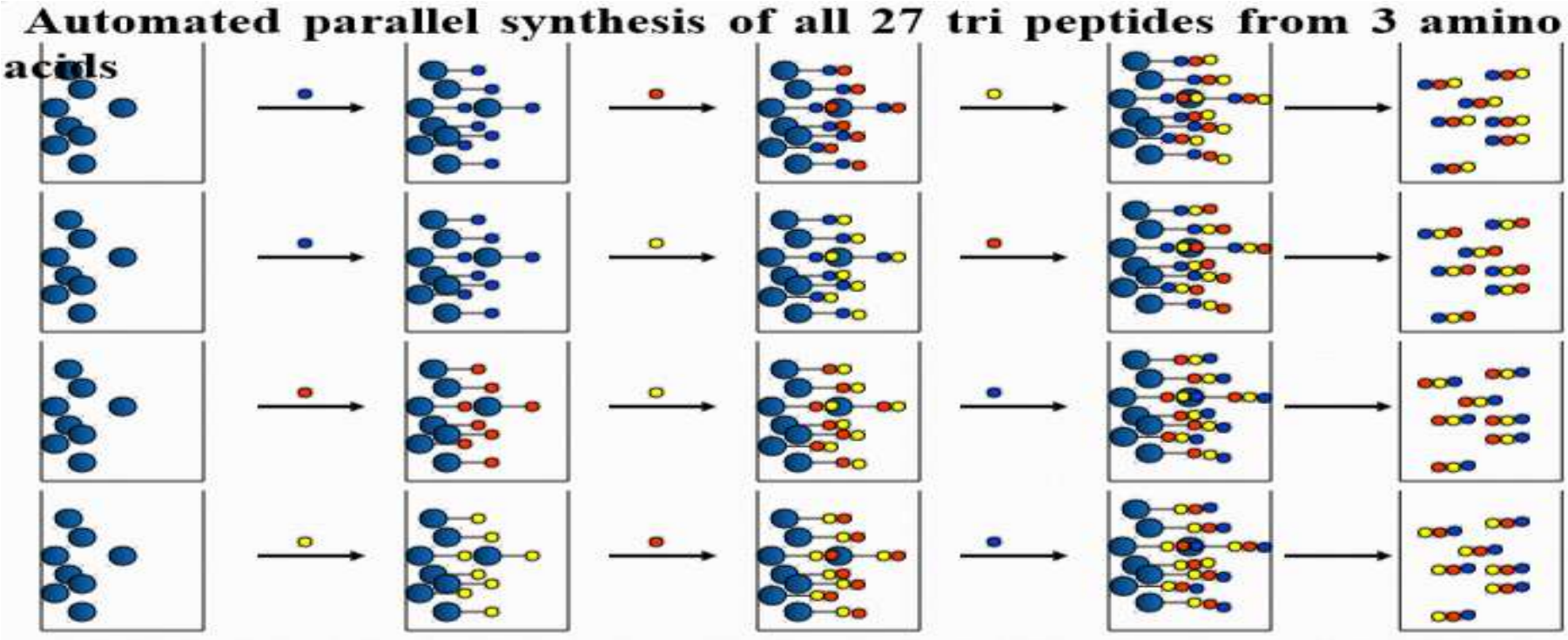
Automated synthesizers are available with 42, 96 or 144 reaction vessels or wells

Use beads or pins for solid phase support

Reactions and work ups are carried out automatically

Same synthetic route used for each vessel, but different reagents

Different product obtained per vessel



Mixed Combinatorial Synthesis:

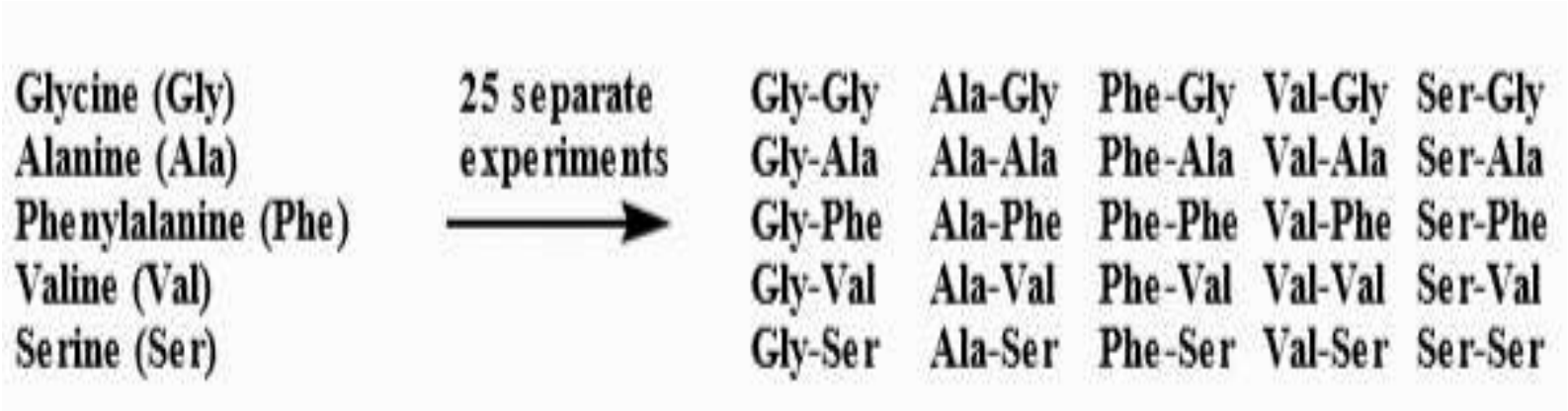
- To use a standard synthetic route to produce a large variety of different analogues where each reaction vessel or tube contains a mixture of products
- The identities of the structures in each vessel are not known with certainty
- Useful for finding a lead compound
- Capable of synthesizing large numbers of compounds quickly
- Each mixture is tested for activity as the mixture Inactive mixtures are stored in combinatorial libraries
- Active mixtures are studied further to identify active component

The Mix and Split Method:

Example - Synthesis of all possible dipeptides using 5 amino acids

Standard methods would involve 25 separate syntheses.

Combinatorial procedure involves five separate syntheses using a mix and split strategy



Quantitative structure activity relationship (QSAR)

- QSAR is a mathematical relationship in the form of an equation between the biological activity and measurable physiochemical parameters.
- QSAR attempts to identify and quantify the physicochemical properties of a drug and to see whether any of these property has an effect on the drugs biological activity
- The parameters used in QSAR is a measure of the potential contribution of its group to a particular property of the parent drug.
- Activity is expressed as log(1/C). C is the minimum concentration required to cause a defined biological response.
- Physicochemical property as log p

Various parameters used in QSAR studies are

Lipophilic parameters: partition coefficient, π- substitution constant.

Electronic parameters: Hammet constant.

Steric parameters: Taft's constant, molar refractivity, Verloop steric parameter.

LIPOPHILIC PARAMETERS

Lipophilicity is partitioning of the compound between an aqueous and non-aqueous phase.

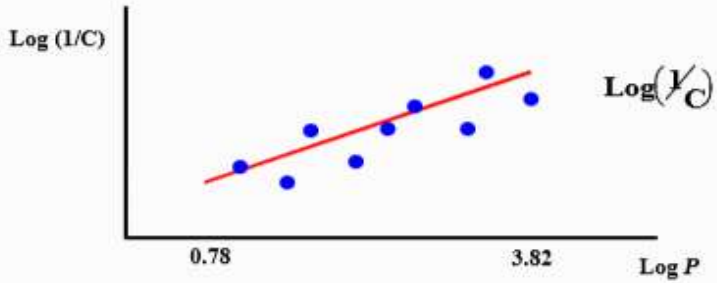
Partition coefficient: P=[drug] in octanol/[drug] in water

High *P* → **High hydrophobicity**

Linear relationship between Log p and Log 1/C

- Activity of drugs is often related to *P*

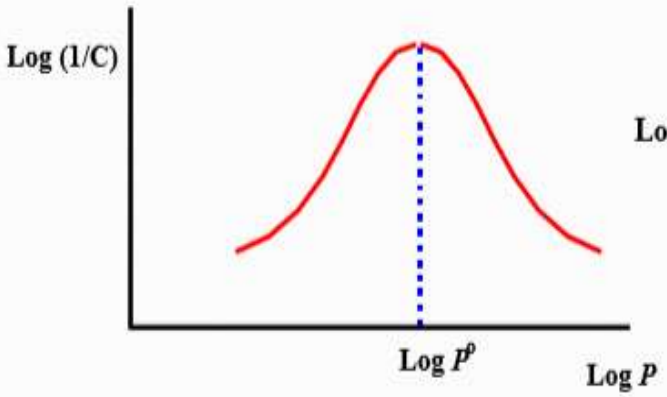
e.g. binding of drugs to serum albumin
(straight line - limited range of log *P*)



$$\text{Log}\left(\frac{1}{C}\right) = k1 \log P + k2$$

- Binding increases as log *P* increases
- Binding is greater for hydrophobic drugs

Example 2 General anaesthetic activity of ethers
(parabolic curve - larger range of log *P* values)



$$\text{Log}\left(\frac{1}{C}\right) = -k1\,(\log P)^2 + k2 \log P + k3$$

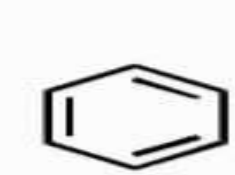
Optimum value of log *P* for anaesthetic activity = log P^0

Non –linear relationship between Log P and Log 1/C

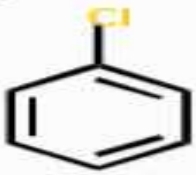
π-substituent constant or hydrophobic substituent constants:

- ✓ The π-substituent constant defined by Hansch and co-workers.
- ✓ Measure of how hydrophobic a substituent is, relative to H.

$$\pi x = \log Px - \log PH$$

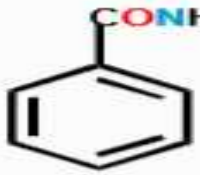


Benzene
(Log P = 2.13)



Chlorobenzene
(Log P = 2.84)

$\pi_{Cl} = 0.71$



Benzamide
(Log P = 0.64)

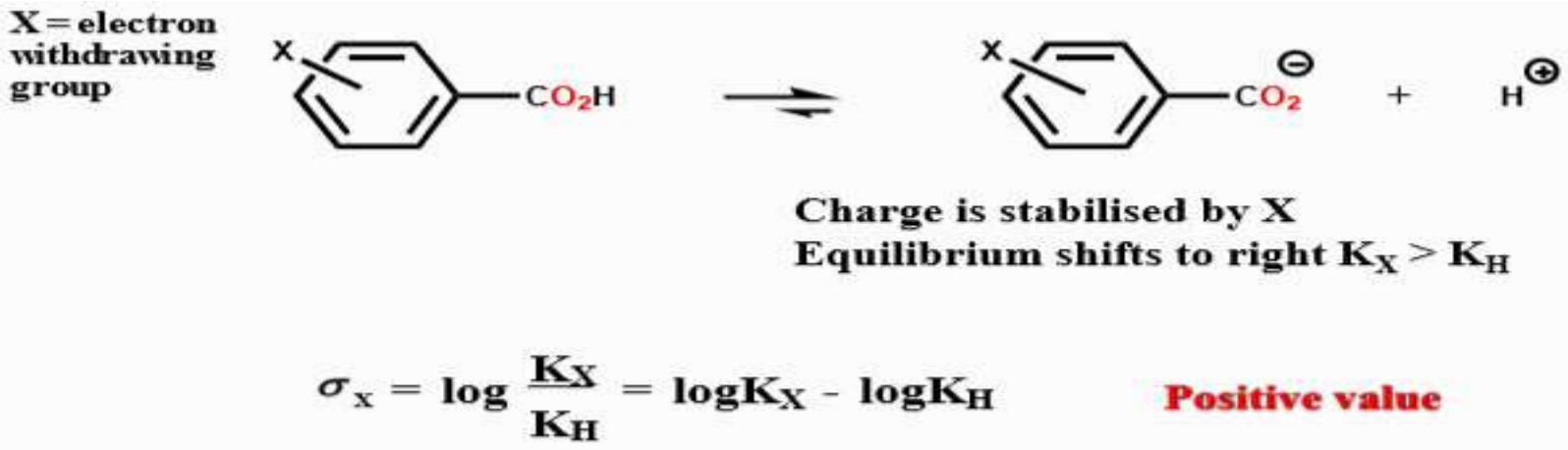
$\pi_{CONH_2} = -1.49$

- Positive values imply substituents are more hydrophobic than H
- Negative values imply substituents are less hydrophobic than H
- A QSAR equation may include both P and p.
- P measures the importance of a molecule's overall hydrophobicity (relevant to absorption, binding etc.)
- p identifies specific regions of the molecule which might interact with hydrophobic regions in the binding site

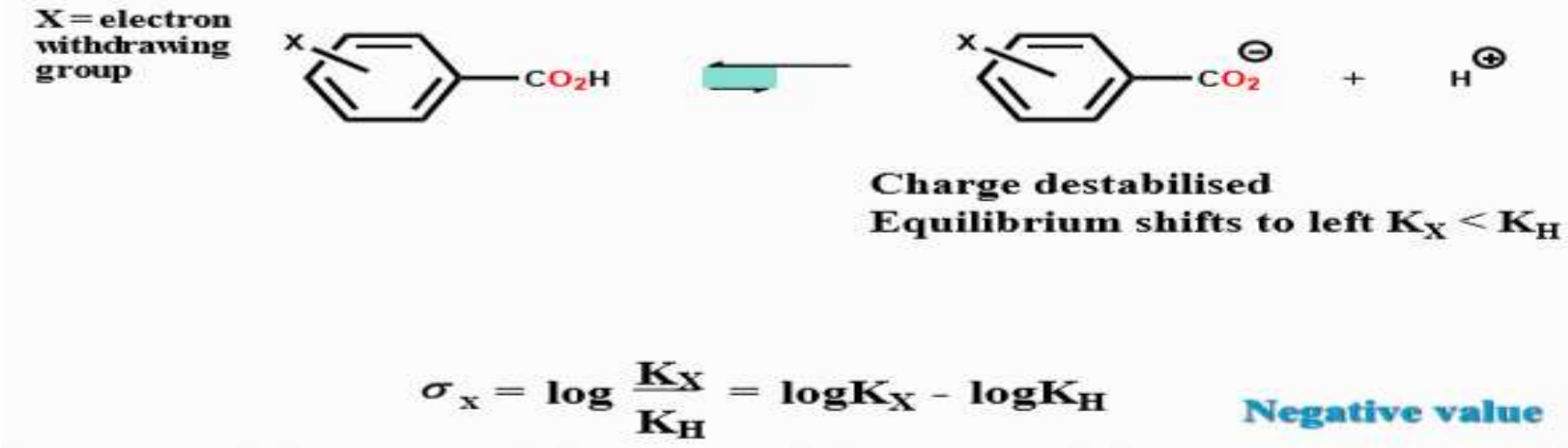
ELECTRONIC PARAMETERS

Hammett Substituent Constant (σ):

Eg. X= electron withdrawing group (e.g. NO_2)



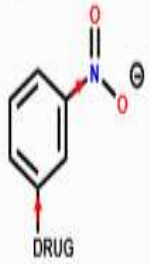
X= electron donating group (e.g. CH_3)



- ✓ σ value depends on inductive and resonance effects
- ✓ σ value depends on whether the substituent is meta or para
- ✓ ortho values are invalid due to steric factors

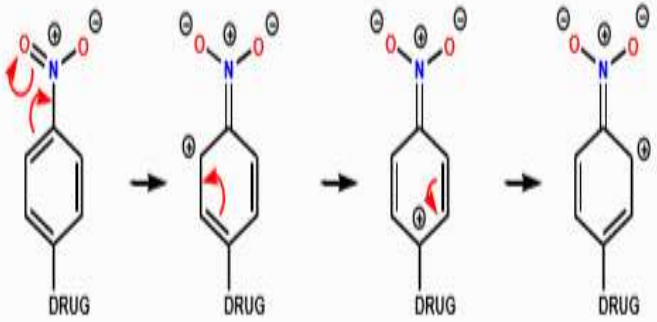
EXAMPLES: $\sigma_p(NO_2) = 0.78$ $\sigma_m(NO_2) = 0.71$

meta-Substitution



e-withdrawing (inductive effect only)

para-Substitution



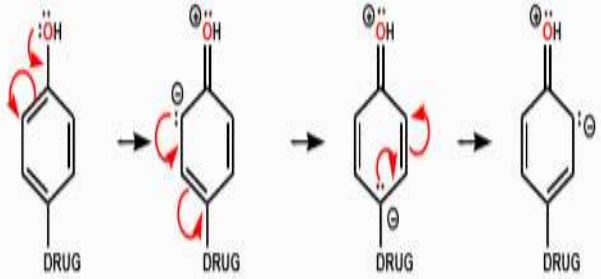
e-withdrawing (inductive + resonance effects)

EXAMPLES: $\sigma_m(OH) = 0.12$ $\sigma_p(OH) = -0.37$

meta-Substitution

e-withdrawing (inductive effect only)

para-Substitution



e-donating by resonance more important than inductive effect

STERIC SUBSTITUTION CONSTANT

It is a measure of the bulkiness of the group it represents and it effects on the closeness of contact between the drug and receptor site. It is much harder to quantitate.

Taft’s steric factor (Es') : Measured by comparing the rates of hydrolysis of substituted aliphatic esters against a standard ester under acidic conditions

$$\mathbf{Es = \log kx - \log ko}$$

kx represents the rate of hydrolysis of a substituted ester

ko represents the rate of hydrolysis of the parent ester

Molar refractivity (MR): Measure of the volume occupied by an atom or group--equation includes the MW, density(d), and the index of refraction

(n)– $MR=(n^2-1)MW/(n^2+2)d$

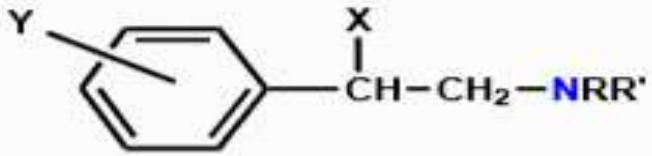
Verloop steric parameter: computer program uses bond angles, van der Waals radii, bond lengths.

Hansch Equation

- A QSAR equation relating various physicochemical properties to the biological activity of a series of compounds
- Usually includes log P, electronic and steric factors
- Start with simple equations and elaborate as more structures are synthesised
- Typical equation for a wide range of log P is parabolic

$$\mathrm{Log}\left(1/C\right) = -k_1(\log P)^2 + k_2 \log P + k_3 \sigma + k_4 E_s + k_5$$

Example: **Adrenergic blocking activity of β-halo-β-arylamines**



$$\text{Log}\left(1/C\right) = 1.22\,\pi - 1.59\,\sigma + 7.89$$

Conclusions:

- Activity increases if p is +ve (i.e. hydrophobic substituents)
- Activity increases if s is negative (i.e. e-donating substituents)

Thank You and Questions