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Unit- 4

Molecular docking: Rigid docking, flexible docking, manual docking; Docking based screening. De novo drug design.

Quantitative analysis of Structure Activity Relationship
History and development of QSAR, SAR versus QSAR,
Physicochemical parameters, Hansch analysis, Fee Wilson
analysis and relationship between them.

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Molecular Docking

Molecular docking is a computational simulation technique in drug discovery and molecular biology.

It predicts the orientation and binding affinity of a ligand (drug, inhibitor, or small molecule) when it interacts with a biological macromolecule (protein, enzyme, DNA, RNA, receptor).

The ultimate goal is to identify the best fit between ligand and target, similar to a lock and key mechanism.

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Docking is based on molecular recognition, i.e., how molecules recognize and interact with each other.

Two fundamental models:

-Lock and Key Model: Binding site is rigid; ligand must perfectly fit.
-Induced Fit Model: Both ligand and binding site undergo conformational changes to achieve better fit.

A docking algorithm explores possible ligand conformations and orientations in the binding pocket, while a scoring function evaluates binding strength.

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Types of Molecular Docking-

Rigid Docking – Both ligand and protein are treated as rigid bodies (fast, less accurate).

Flexible Docking – Ligand and/or protein side chains are flexible (realistic, more accurate).

Blind Docking – Performed without knowing the active site; ligand is screened over the whole protein surface.

Site-Specific Docking – Binding site is predefined and docking is limited to that region.

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Steps in Molecular Docking

-Target Preparation

Obtain protein/macromolecule structure (from PDB, X-ray crystallography, NMR, or homology modeling).

Clean structure by removing water molecules/ions, add hydrogens, assign charges, and optimize geometry.

-Ligand Preparation

Draw or import ligand structure.

Optimize energy, generate 3D conformers, and assign proper charges.

-Docking Simulation

Place ligand into the target binding pocket.

Generate different orientations and conformations (poses).

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Scoring Function-

Calculate interaction energy between ligand and protein.
Parameters considered:
Hydrogen bonding
Hydrophobic interactions
Electrostatic forces
Van der Waals interactions
Steric complementarity

Ranking and Analysis-

Ligands are ranked according to binding scores.
Best poses are analyzed to study key interactions.

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Applications of Molecular Docking-

Drug Discovery and Development: Virtual screening of large compound libraries.
Lead Optimization: Designing analogs with improved binding.
Rational Drug Design: Structure-based design of new inhibitors or modulators.
Enzyme–Substrate Studies: Understanding enzyme catalysis mechanisms.
Protein–Protein / Protein–DNA / Protein–RNA Interactions: Studying molecular recognition.

Advantages

Cost-effective and less time-consuming than experimental methods.
Can screen millions of compounds rapidly.
Provides detailed information about binding orientation and interactions.
Useful in both early hit identification and advanced lead optimization.

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Rigid Docking

Molecular docking is a computer-based method used to predict how a small molecule (ligand) binds to a macromolecule (protein, enzyme, DNA, RNA). Rigid docking is one of the simplest docking approaches.

In this method, both the ligand and receptor are treated as rigid structures — no bond rotations or conformational changes are allowed.

In simple words: Rigid docking = fitting a solid key into a solid lock.

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Steps in Rigid Docking-

1. Protein Preparation

Obtain structure (from Protein Data Bank or modeling).

Remove water, add missing atoms, add hydrogens, assign charges.

2. Ligand Preparation

Build ligand structure in 3D.

Keep it rigid (one conformer, no bond rotation).

3. Pose Generation (Search)

The ligand is placed in many orientations and positions inside the binding pocket.

This involves rotation and translation of the ligand.

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Scoring-

Each pose is scored based on:

Shape complementarity (does it fit well in the pocket?)

Hydrogen bonds

Hydrophobic interactions

Electrostatic interactions

Ranking and Output-

Poses are ranked according to score.

Top-scoring poses are predicted binding modes.

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Scoring Functions in Rigid Docking-

Scoring functions are mathematical models that estimate binding energy. They usually include:

Steric fit / Shape complementarity → no clashes, good packing.

Van der Waals interactions → attraction/repulsion of atoms.

Electrostatics → interaction of charges.

Hydrogen bonding → stabilizing interactions.

Desolvation / Hydrophobic effect (simplified).

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Types of Rigid Docking-

Protein–Ligand Rigid Docking
Small rigid ligand docked into rigid protein.
Protein–Protein Rigid Docking
Used for large biomolecules like antibodies and enzymes.

Applications-

Initial virtual screening of large compound libraries (fast).
Protein–protein docking where conformational changes are minimal.
Preliminary binding analysis before flexible docking.
Drug discovery – early-stage filtering of candidates.

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Advantages

Simple and fast → suitable for millions of compounds.

Requires less computational power compared to flexible docking.

Useful for rigid systems (like protein–protein complexes).

Can give a quick first idea of binding modes.

Limitations

Ignores ligand flexibility (rotatable bonds).

Ignores protein flexibility (side chain movements, induced fit).

Binding energies may be inaccurate.

May produce false negatives (missing real binders that require flexibility).

Examples

HIV protease inhibitors → early docking studies sometimes used rigid docking.

Protein–Protein interactions (like antigen–antibody complexes) are often studied first with rigid docking.

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2. Flexible Docking -

Molecular docking can be rigid or flexible depending on how much structural flexibility is allowed.

Flexible docking is a more advanced form of docking where ligand (and sometimes the protein receptor) is allowed to change its conformation during the docking process.

This approach is based on the Induced Fit Model of molecular recognition, where both ligand and protein can adjust to achieve better binding.

In simple words: Flexible docking = fitting a bendable key into a slightly adjustable lock.

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-Flexible docking is a computational technique in which the ligand and/or protein are treated as flexible structures, allowing bond rotations, torsions, and conformational adjustments during docking, to predict the best binding mode and affinity.

Types of Flexibility in Docking-

1. Ligand Flexibility Only

Protein is rigid.

Ligand can rotate around its bonds and adopt multiple conformations.

Most common type (used in many virtual screening tools).

2. Protein Flexibility Only

Ligand is rigid.

Side chains or loops of the protein can adjust.

Used when the protein's binding pocket is known to move.

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3. Full Flexibility (Both Ligand and Protein)-

Both ligand and protein are flexible.
Most realistic, but also most computationally expensive.

Steps in Flexible Docking-

1. Protein Preparation
Obtain 3D structure, clean it (remove water, add hydrogens, assign charges).
Select flexible regions if protein flexibility is considered.

2. Ligand Preparation
Build ligand structure.
Define rotatable bonds to allow conformational changes.

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3. Pose Generation-
Docking program generates many conformations of ligand (and protein if flexible).
Ligand is rotated, translated, and twisted to fit binding site.

4. Scoring Function
Each pose is scored based on binding energy:
Hydrogen bonding
Hydrophobic interactions
Electrostatic forces
Steric complementarity
Conformational energy penalty (for adopting certain shapes)

5. Ranking and Analysis
Best scoring poses are selected.
Detailed analysis of ligand–protein interactions is performed.

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Applications-

Drug discovery - accurate prediction of binding modes.
Lead optimization - testing analogs with different flexible side groups.
Protein-ligand interactions where conformational changes are expected.
Enzyme-substrate studies where the active site adjusts during catalysis.
Virtual screening for selecting hits from compound libraries.

Advantages-

More realistic compared to rigid docking.
Can model induced fit and flexibility of molecules.
Gives better accuracy in predicting binding modes and affinities.
Useful for proteins with dynamic binding pockets.

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Limitations

Computationally expensive (takes more time and power).

Requires complex algorithms and more input data.

May generate too many conformations → difficult to analyze.

Accuracy still depends on scoring functions (which are not perfect).

Examples

Kinase inhibitors: Kinase binding pockets are flexible, so flexible docking is necessary.

HIV reverse transcriptase inhibitors: Ligands often induce conformational changes in the enzyme.

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Manual Docking

Before the development of advanced computational docking algorithms, researchers used manual docking to predict how a ligand binds to its target protein.

It is the oldest and simplest docking approach, carried out by manually fitting the ligand into the binding pocket of a protein structure.

It is often guided by visual inspection, chemical knowledge, and stereochemical rules rather than automated calculations.

In simple words: Manual docking = scientist using trial and error to fit a molecule into a protein like placing a puzzle piece.

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Manual docking is a non-computational or semi-computational method of docking in which a researcher manually places a ligand into the binding site of a protein based on structural knowledge, and then evaluates interactions visually or through simple energy calculations.

3. Theoretical Basis

Based on Lock and Key Concept (Emil Fischer, 1894).

Relies on visual observation of complementarity between ligand and binding site.

Simple rules are used to judge whether binding is possible:

No steric clashes.

Proper hydrogen bonding.

Hydrophobic regions overlap with non-polar ligand parts.

Charged groups align with opposite charges.

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Procedure in Manual Docking-

1. Protein Structure Selection

Protein's 3D structure obtained (X-ray crystallography, NMR, or models).

2. Ligand Selection

Ligand structure is drawn or modeled.

3. Manual Placement

Using physical molecular models (earlier) or visualization software (nowadays).

Researcher rotates, translates, and positions ligand inside the binding pocket.

4. Evaluation of Fit

Visual check for complementarity.

Simple scoring may be done (e.g., hydrogen bonds, steric fit).

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Applications-
Early drug design era (before computational methods) – used in the 1970s–1980s.
Educational purposes – teaching basics of docking.
Initial hypothesis generation when computational tools are not available.
Can be used as a starting step before computational docking.

Advantages-
Very simple and easy to perform.
Requires no advanced software.
Helps researchers develop intuition about binding interactions.
Useful for small systems and simple structures.

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Limitations-

Highly subjective → depends on researcher's judgment.

Not accurate for real biological systems.

Cannot handle flexibility of protein or ligand.

Not suitable for screening large compound libraries.

Replaced by automated docking in modern research.

Example-

Early studies on enzyme–substrate interactions were done by fitting substrate molecules into enzyme active sites using plastic or wooden molecular models.

Example: Early attempts to design protease inhibitors used manual docking before computational tools were available.

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Docking based screening

In drug discovery, researchers need to test millions of compounds to find potential drugs.

Experimentally screening such huge libraries is time-consuming and expensive.

Docking-based screening (also called structure-based virtual screening) uses molecular docking to computationally test compounds against a target protein and identify promising hits.

-In simple words: Docking-based screening = using computer docking to filter millions of compounds and pick out likely drug candidates.

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Steps in Docking-Based Screening

1. Target Preparation

Select and prepare protein structure.

Define binding site or grid box.

2. Compound Library Preparation

Use databases (e.g., ZINC, PubChem) or designed molecules.

Convert into 3D structures, optimize, and assign charges.

3. Docking Simulation

Each compound is docked into the target binding pocket.

Multiple poses are generated.

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4. Scoring & Ranking

Scoring functions estimate binding affinity.

Compounds are ranked based on scores.

5. Hit Selection

Top-ranked compounds are chosen as hits.

These can be tested in in vitro and in vivo experiments.

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5. Applications

Hit identification in early-stage drug discovery.

Screening for enzyme inhibitors (e.g., protease, kinase inhibitors).

Studying protein–ligand interactions.

Identifying potential repurposed drugs.

Reducing cost and time compared to experimental screening.

6. Advantages

Fast and cost-effective compared to lab experiments.

Can screen millions of compounds virtually.

Reduces the number of compounds for experimental testing.

Provides binding mode information in addition to hit identification.

Can explore large chemical space.

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Limitations-

Accuracy depends on:

Quality of protein structure.

Accuracy of docking algorithm.

Limitations of scoring functions.

May give false positives (inactive compounds predicted as active).

May miss true binders if flexibility or solvent effects are important.

Examples-

HIV protease inhibitors → Docking-based screening helped identify leads.

Kinase inhibitors → Many anti-cancer drugs were first found using docking-based screening.

COVID-19 drug discovery → Repurposing FDA-approved drugs against SARS-CoV-2 main protease.

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De novo drug design

Introduction

In drug discovery, sometimes there are no known drug molecules for a new disease target.

In such cases, scientists design new molecules from the beginning using computer programs.

This is called De Novo Drug Design.

Create a New Brand Molecule.

-Meaning: "Designing a drug from scratch" based on the structure of the target protein.

De Novo Drug Design- is a computer-aided drug design method in which new chemical structures are created from scratch to fit exactly into the binding site of a biological target (like an enzyme, protein, or receptor).

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Concept / Theoretical Basis-

Works on the idea of molecular recognition (drug must fit into the target's binding site).
Requires 3D structure of target protein (from X-ray, NMR, or modeling).
New molecules are designed to match:

Hydrogen bonding areas
Hydrophobic regions
Charged or polar sites
Shape of the binding pocket

The computer builds molecules atom by atom or fragment by fragment to perfectly complement the target.

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Approaches in De Novo Drug Design-

Fragment-Based Approach
Small fragments are placed inside binding pocket.
They are joined or grown into a complete molecule.

Atom-Based Approach
Molecules are built atom by atom inside the pocket.
Ensures very close fit, but is complex.

Ligand-Based Approach
Uses knowledge of existing active molecules.
Designs new molecules with improved properties.

Structure-Based Approach
Uses the protein's 3D structure directly to guide molecule design.

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Steps in De Novo Drug Design-

Target Selection → Identify protein/enzyme involved in disease.
Structure Determination → Obtain 3D structure (X-ray/NMR).
Binding Site Analysis → Find active site shape, size, and key residues.
Molecule Generation → Design new molecules (atom by atom or fragment by fragment).
Scoring and Ranking → Calculate binding affinity using scoring functions.
Drug-Likeness Filtering → Apply rules like Lipinski's Rule of 5.
Optimization → Modify molecules for better activity, stability, and ADME.
Synthesis and Testing → Chemically make the best molecules and test experimentally.

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Advantages

Can create brand-new chemical entities (NCEs).
High specificity for the target site.
Saves time compared to random screening.
Useful when no template molecules are available.

Limitations

Computationally expensive (needs advanced software and power).
Designed molecules may be difficult to synthesize.
Scoring functions are not always accurate.
Needs high-quality protein structures to be effective.

Examples-
Programs like LUDI, SPROUT, LigBuilder are used for de novo design.

HIV protease inhibitors – early examples designed partly with de novo methods.

COVID-19 research – new inhibitors for SARS-CoV-2 designed using this method.

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QSAR

We are trying to relate Structure & Chemical activity with Biological activity. Using a Mathematical relationship.

I.

(Quantitative Structure Activity Relationship).

Physicochemical Parameters. ⇒ Partition Coefficient, HAMMETT'S Electronic & TAFT'S Steric Parameter

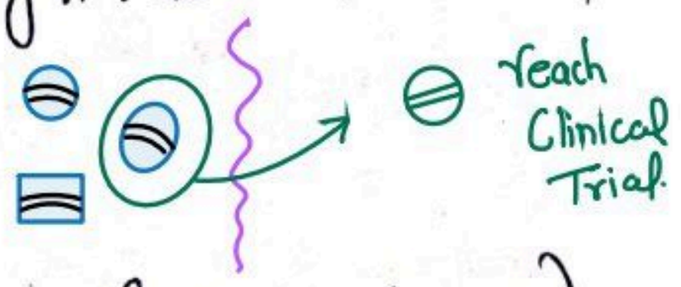


→ As We Know ⇒ Identification of New drug Molecule

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Required a lot of → Synthesis.
→ Time.
→ Money.

It was identified that out of billion molecule synthesized around One or two molecule reach the Clinical trials.



⇓

This produce hurdle (बाधा) in the discovery of New Chemical Entity (NCE's) for the treatment of Various disease.

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⇓

The QSAR (Quantitative Structure Activity Relationship) approach has proved extremely Useful in tackling this problem.

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2.

• QSAR is a Mathematical relationship b/w Biological Activity of a Molecular System & it's Geometric & Chemical Characteristics.

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☆ QSAR approach attempts to identify & Quantify the physicochemical Properties of a drug & to see wether any of these properties has an effect on the drug's biological activity.

⊖ → To identify Physicochemical Parameter of drug. → To see either they Have effect on Biological activity or Not.

QSAR derived equation take the general form ⇒

Biological Activity of drug = function (Physicochemical Parameter).

Biological activity is a function of Physicochemical Property.

Partition coff. → Hydroph.
Lipophilicity
pH

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↳ This Biological activity is expressed as:

↓

log (1/C) → C = Minimum effective dose.

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If we want to design a drug then with the help of QSAR equation we can easily Identify the Biological activity of drug (ADME). & We can easily Make Changes (on electronic, steric, Parameter) according to Our Need. or The QSAR equation will predict the Biological activity for the new drug molecule to be designed.

QSAR is essential tool for development of Lead Molecule = Good Binding property, Good Physicochemical Property, Good Pharmacokinetic property, Good Biological Activity.

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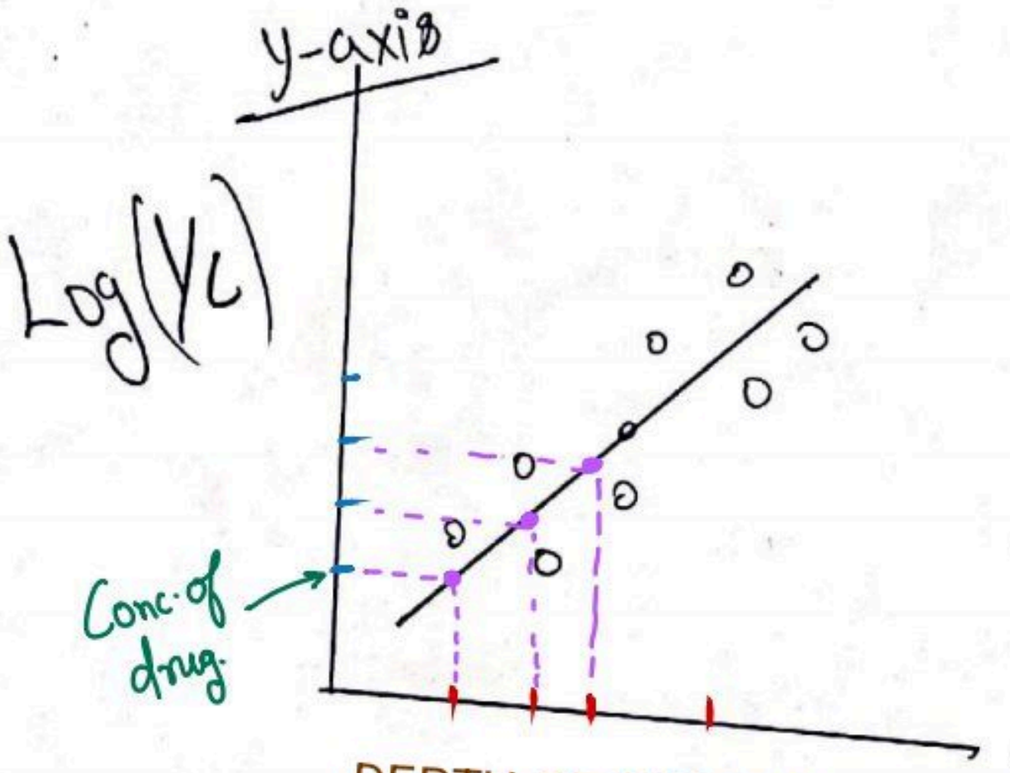
(#) Graphs & Equation

A range of Compound is synthesized in Order to Vary one Physicochemical property & to test how this affect the Biological activity.

A graph is plot b/w Biological activity & Physicochemical feature

y-axis → Biological Activity.

X-axis → Physicochemical feature.



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QSAR equation derived is ⇒

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$$\log(\text{activity}) = y_{calc.} = K_1X + K_2 .$$

$y_{calc.}$ = log (observed Capacity).

X = Physicochemical Property.

K_1 & K_2 = Rate Constant.

Anti-Inflammatory. → 3. Need Particular action Then

Then we obtain some data points, when we link those data point Then a line is obtained This line is Called QSAR equation.

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(#) Steps involved in QSAR

1. Selection of Biologically Active Series. (To check the Biological Activity).
   ↳ eg → Anticancer, Antiinflam.
2. Calculation of Various Physico Chemical Parameter
3. Found Correlation b/w Physicochemical property & Biological activity by QSAR Method.

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4. Getting Equation.
5. Designing of the Compound based upon QSAR equation.
6. Predicting the Biological activity of the Designed Compound.
7. Synthesis of the Compound.

(#) Physicochemical Parameters.

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1. Hydrophobicity. → Partition Coeff. (logP), Hanschis Substitution Constant.
   ↳ Distribution Coeff., LogD.
2. Steric Parameter. → Taft's Constant, Vander Wall radius & Volume.
3. Electronic parameter. → Hammet Constant, Dipole Moment, Ionization Constant, Pka, ΔPka.

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1. Hydrophobicity.

(a) Log P (Partition Coefficient). →

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Lipid is the Vital Constituent of Cell membrane

The Hydrophobicity / Lipophilicity of a drug is an important Parameter Play a Vital role from drug administration, distribution & Interaction with receptor or protein or target site to produce the Biological response.

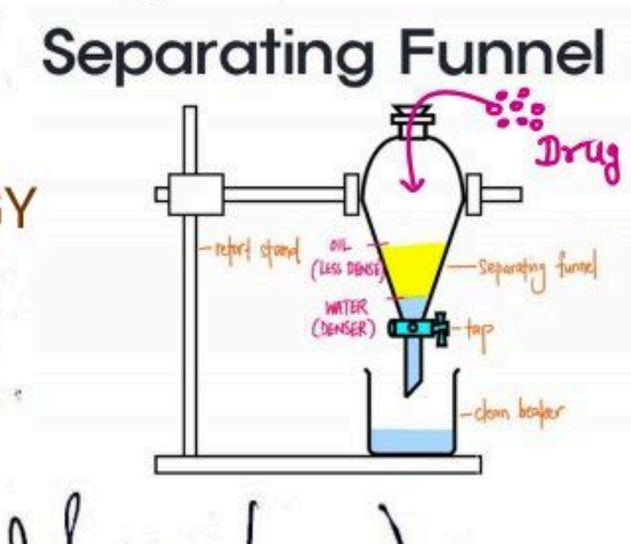
☆ The optimum Hydrophobicity / Lipophilicity is required to transport the drug to the site of action.

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⇒ Hydrophobicity of a drug is Measured experimentally. by testing the drug relative distribution known as Partition Coefficient.

Partition Coefficient →

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Partition Coefficient (P) Usually expressed as log P

☆ This is generally found by Ideal Solvent n-Octanol & H2O (aq.).

It is defined as ⇒ $$P = \frac{\text{Conc. of Octanol drug.}}{\text{Conc. of Aqueous drug.}}$$

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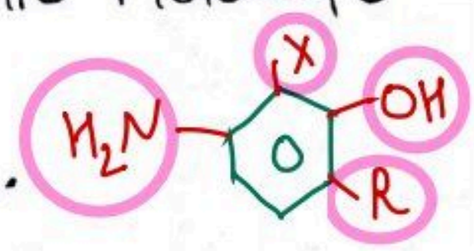
→ In Simple term partition Coefficient is the ratio of drug in n-Octanol & H_2O.

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n-Octanol → Mimic the Lipid (Oil) Compartment in the body.

Water → Mimic the aqueous Compartment of the body.

☆ The whole Organic Molecule Comprised of Basic Skeleton plus Various Substituents.



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The Contribution of Hydrophobicity by Substituent is expressed as π

& Sum of π is equal to Log P

$$\log P = \Sigma \pi$$

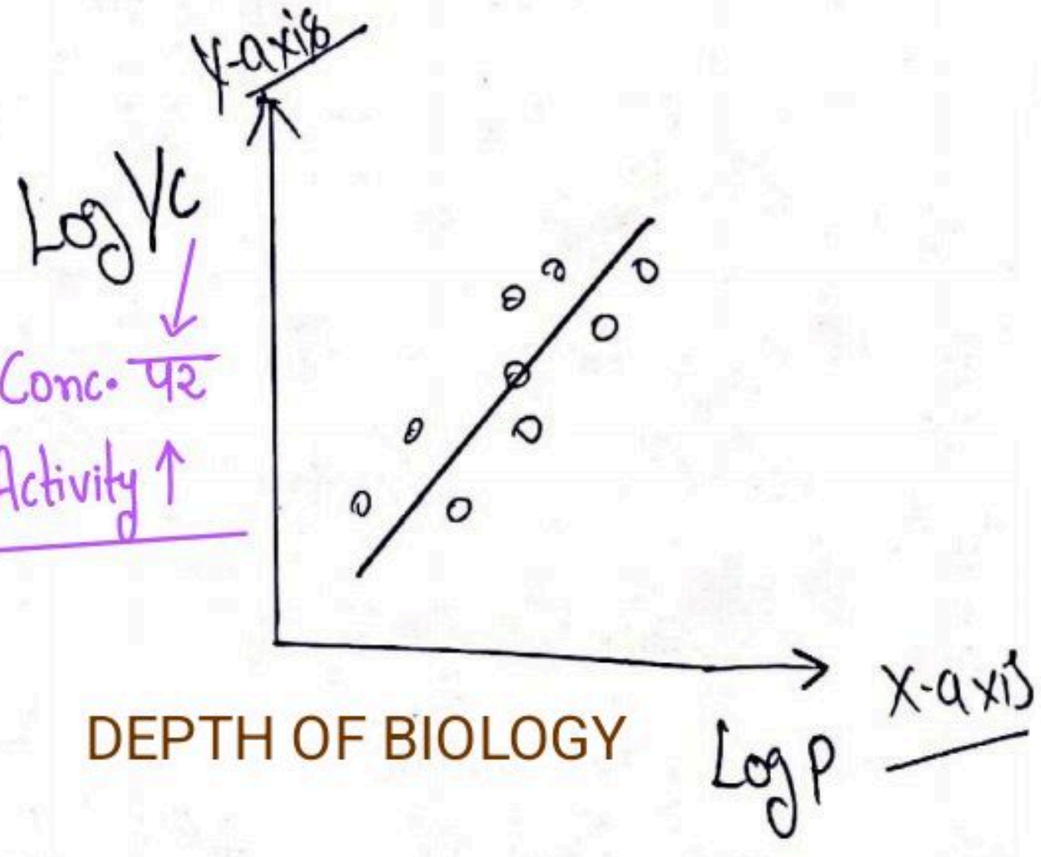
→ Hydrophobic Substituent Constant.

$$\text{Log}P = \frac{[\text{drug}] \text{ in Octanol}}{[\text{drug}] \text{ in } H_2O}$$

Plot (log 1/c) Vs. (Log P.)

↑ Biological Activity. ↓ y-axis

↑ Partition Coefficient. ↓ X-axis.



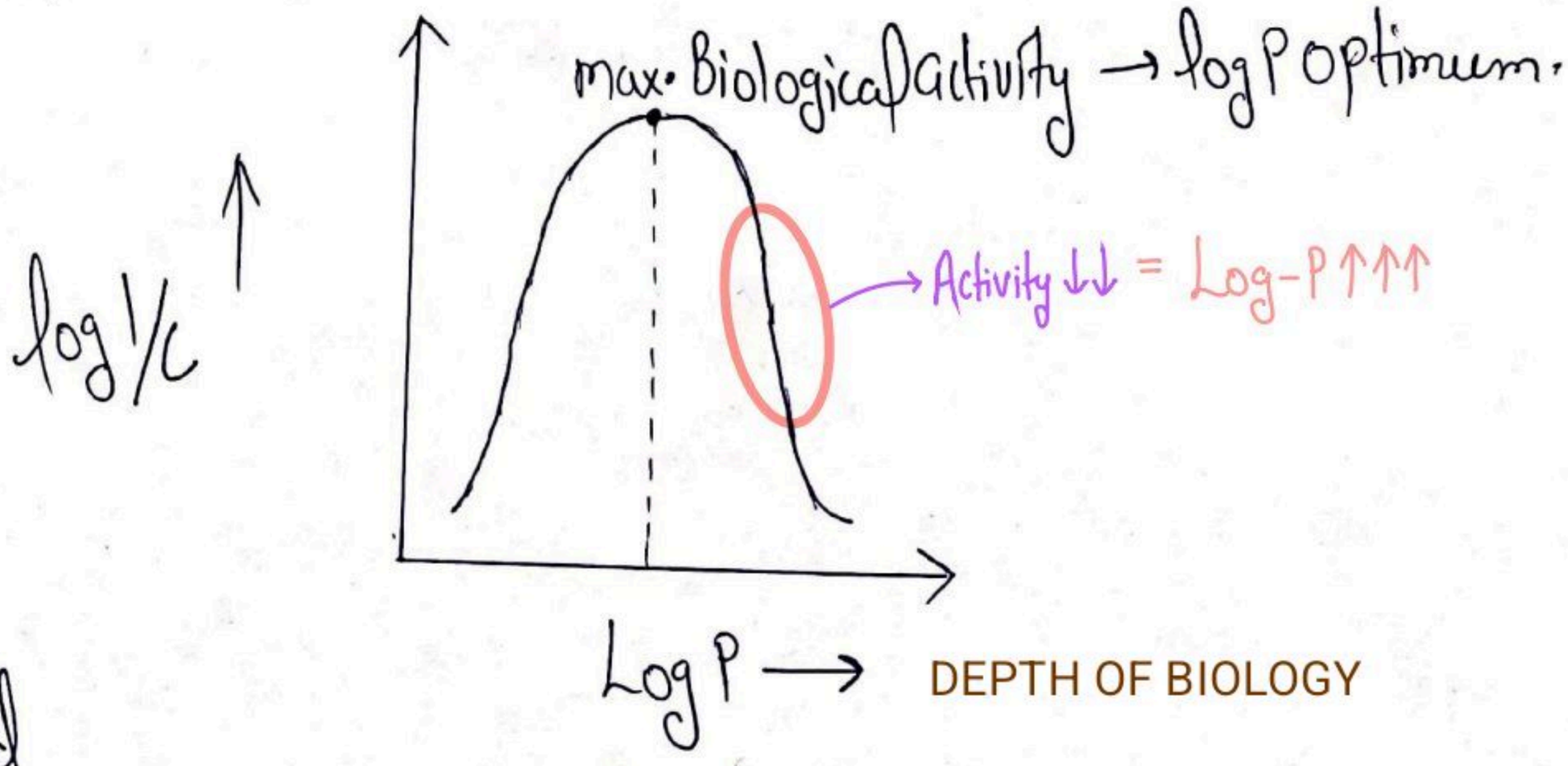
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⇒ If graph is extended to Very High log-P Values then get Parabolic Curves.

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Equation Obtained →

$$\text{Log } 1/C = -k(\log P)^2 + k_2 \log P + k_3 .$$

☆ Generally the Biological response obey the parabolic Curve ie

[The drug show low Biological response when log P is low].

→ The drug show Maximum Biological response when log P is Optimum.

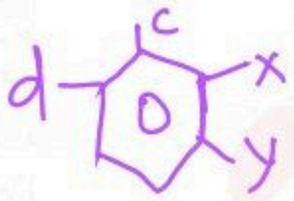
→ The Biological activity of drug is declined when log P is very High.

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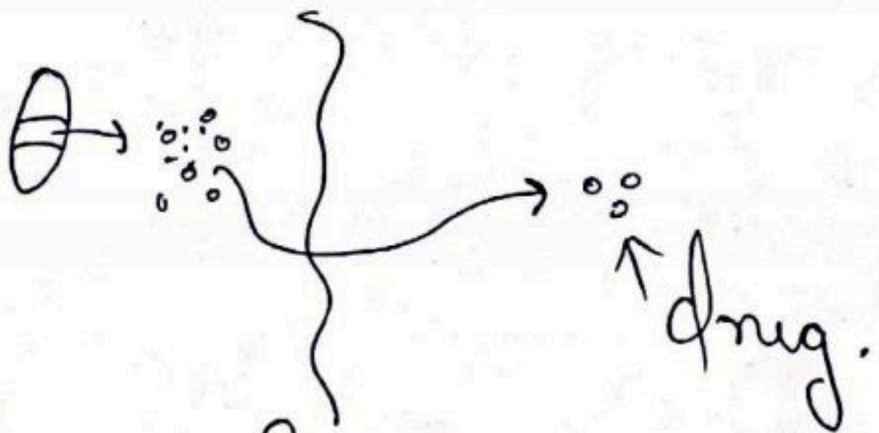
2. Electronic Parameter

The electronic effect of various substituent will clearly have an effect on drug Ionization & Polarity. (charge).

⇒ Also, have an effect on how easily drug can pass through the Cell Membrane - or how strongly it can interact with a binding site.

⇒ The distribution of electron in the molecule influence the activity of drug molecule.

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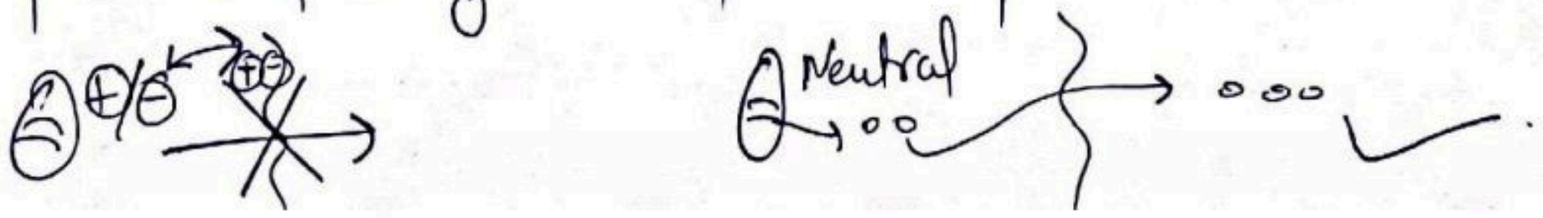


1. ☆ The drug should Cross the various Barrier to reach the site of action & to produce the biological action.

2. ☆ Generally the Unionized drug are easily transported across the Membrane than the Ionized molecule.

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3. ☆ → The reason behind is the Ionized & Charged molecule are opposed by the electrical Charge ⊕ ⊖ ⊕ ⊖ in Membrane. Neutral molecule have no Charged so that their transport across the membrane is facilitated without any electrical Interruption.



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Hammett Constant (σ). ⇒

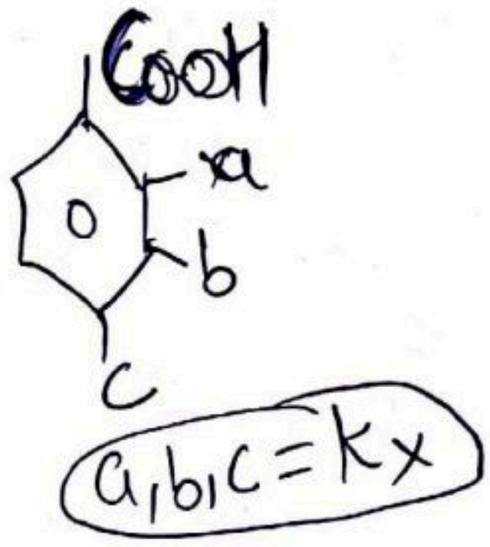
In 1952 Robert W. Taft Modified the Hammett equation.

σ Values are the logarithm of the effect of the substituent on the acid dissociation Constant of Benzoic Acid.

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$$\sigma_x = \log (K_x/K).$$

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



K = Equilibrium Constant for Parent Compound. (Benzoic Acid).

K_x = Equilibrium Constant for Substituted Benzoic acid.

→ a,b,c → Substituent May be electron donor group or electron acceptor group.

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Here we Measure the electron Withdrawing or electron donating ability of a Substituent.

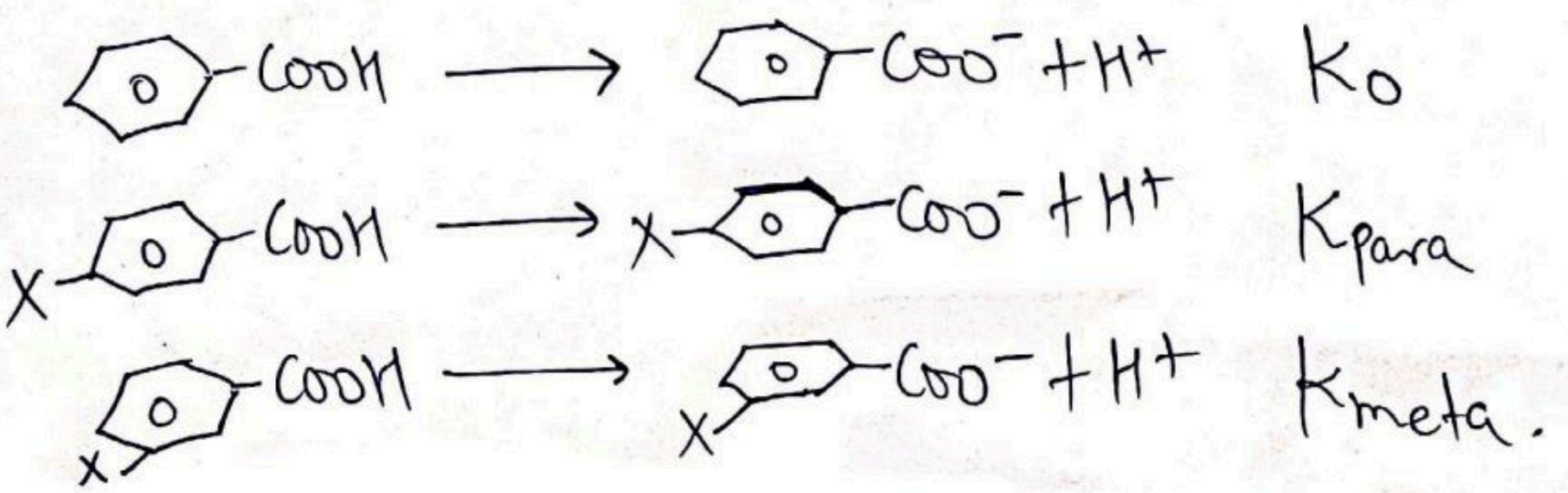
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E.W.G → Kx value ↑ → Equilibrium shift more to Ionized form. (⊕ve σ-Value)

E.D.G → Kx value ↓ → eg → Alkyl (Carboxylate ion less stabalize).

(⊖ve σ-Value)

Unionised form.

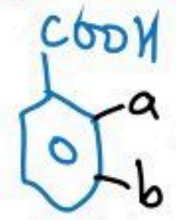


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Hammett Used equilibrium Constant to study the relationship blw the Structure of Aromatic acid & Acid Strength



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He Calculate Constant know as Hammett Substitution Constant 6x for a Variety of ring Substituted/Substituents of benzoic acid.

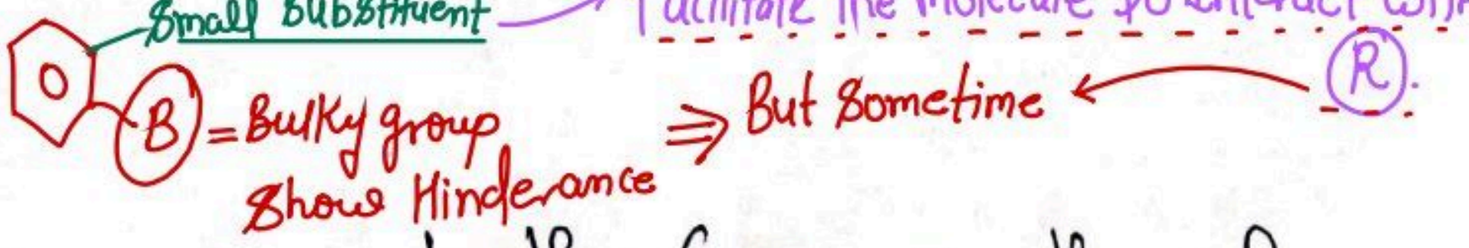
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Major difference b/w Hammett & Taft equation is (PTO) → Taft's Steric Factor (Es).

The Shape & Size of the Molecule are Very Important for a drug to bind on it's active Site (Hammett doesn't account for steric effect. The Taft equation account for this problem.

A Small Substituent may facilitate the Molecule to interact with the Receptor freely whereas bulky group may offer the Hindrance.

However Sometime bulky Substituent may orient the molecule to receptor effectively.



According to Taft → It is measure by the Comparing the rate of Hydrolysis of Aliphatic ester against a standard ester Under acidic Condition

$$Es = \log k_x - \log k_o$$

k_x = represents the rate of Hydrolysis of a substituted ester.

k_o = represent the rate of Hydrolysis of the Parent ester.

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Hansch Analysis.

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Hansch Analysis is a statistical method Used to Corelate Physicochemical parameter of legand with it's Biological Activity (also called descriptor).

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⇒ In Hansch Analysis, at least two descriptor required like Lipophilicity (required for drug Journey) & electronic factor (for drug Interaction at Site of action) - are Consider for Biological response.

↓

Receptor.

Hansch Equation ⇒

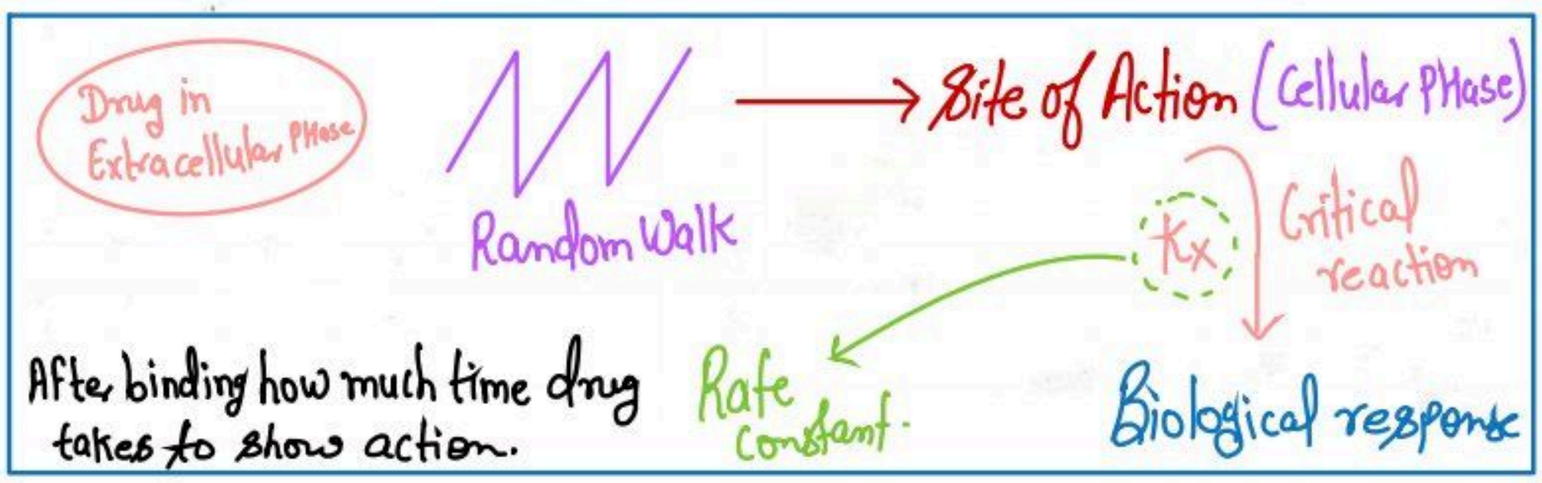
$$\left[\text{Log } 1/C = -k\pi^2 + k'\pi + s\sigma + k''\right]$$

- $-k\pi^2$ → relates expectation of optimum Lipophilicity.
- $k'\pi$ → Hydrophobic Constant.
- $s\sigma$ → Hammett Constant.
- k'' → regression Coefficient.
- Log 1/C → Biological Activity

Lower the Conc. of drug & drug activity is good then it is prefered.

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Coefficient.



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Importance of *Steric effect & *Molecular Shape for receptor interaction an Es term & other Topography terms (s) are included In Hansch Equation.

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$$\left[\text{Log } 1/C = -\underset{\sim}{a}\pi^2 + \underset{\sim}{b}\pi + \underset{\sim}{g}\sigma + \underset{\sim}{c}Es + \underset{\sim}{d}(S) + \underset{\sim}{e}\right]$$

- π^2 → Hydrophobic Constant
- σ → Hammett Constant.
- Es → Taft's Steric Constant.
- (S) → Topography.

~ = Regression Coefficient.

Hansach analysis also called as Extrathermodynamic method, It is a Linear free energy approach to drug design in Congeneric (Similar type) series in which equation is set up involving different Combination of Physicochemical parameter.

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⇓

Once this equation is established, it can be Used to test activity of Untested Compound.

Limitation → ① Conformational Changes in receptor are Ignored.

② Metabolism of drug is Not Considered.

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③ The potency - Lipophilicity relationship may be Parabolic.

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Advantages- ⇒ Explained by Martin & Tute.

(1) The Method is easy to Use & Inexpensive

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(2) The Use of descriptors (Physicochemical parameter) (π, σ, E_s).

Can be Utelized for Prediction of Biological activity in Complex System.

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