A Value Addition Project Report

Submitted On

“Synthesis, Characterization and Pharmacological Evaluation of Novel Drugs”

Submitted

By

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(2020-21)

CERTIFICATE

This is to certify that **Mr. Mohd Islam**(Roll No. 1900140500039), S/o **Mr. Liyakat Hussain** has successfully completed value addition program on the topic "Synthesis, Characterization and Pharmacological Evaluation of Novel Drugs" as mentored by **Dr. Mohit** during the academic session 2020-21 as per guidance.

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Associate Professor,
SRMS CET Pharmacy, Bareilly

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- History of pro drug design
- Properties of pro drug
- Classification of pro drug

VALUE ADDED COURSES

Value added courses are the types of **courses** which help a particular individual to develop their **own skills in their chosen field of the study**.

Aim –

To provide additional learner centric graded skill oriented technical training, with the primary objective of improving the **employability skills of students.**

Objectives -

- To provide students an understanding of the expectations of industry.
- To bridge the skill gaps and make students industry ready.
- To provide an opportunity to students to develop **inter-disciplinary skills.**

Interdisciplinary studies, **is** a planned approach to **learning** which uses links across different subjects or disciplines to enhance **learning**. It promotes the development and application of what has been taught and learned in new and different ways.

Skills-

Skills are the expertise or talent needed in order to do a job or task. Job skills allow you to do a particular job and life skills help you through everyday tasks. There are many different types of skills that can help you succeed at all aspects of your life whether it's college, work, or even a sport or hobby.

- Teamwork

- Problem solving
- Leadership
- Organization
- Motivation
- Ability to work under pressure
- Confidence
- Critical thinking and problem-solving.
- Agility **(ability to move quickly and easily)** and adaptability.
- Initiative
- Effective oral and written communication.
- Accessing and analyzing information.
- Curiosity and imagination.

SYNTHESIS, CHARACTERIZATION AND PHARMACOLOGICAL EVALUATION OF NOVEL DRUGS

Synthesis-

- To make (something) by combining different things.
- The production of chemical compounds by reaction from simpler materials.

Characterization-

Chemical characterization is the process of defining the chemical properties of one or more components of a substance.

Pharmacological-

Relating to the branch of medicine concerned with the uses, effects, and modes of action of drugs.

Evaluation-

To judge the value.

Novel Drugs-

A **Novel Drug** or a New Molecular Entity (NME) is an active compound, complex, molecule that previously has not been approved by the Food and Drug Administration (**FDA**).

Pharmacy- The word 'Pharmacy' is derived from the Greek work 'Pharmakon', meaning **drug.**

"Pharmacy is the art and science of preparing, compounding and dispensing medications".

Pharmacist

A pharmacist is one who is educated and licensed to prepare and dispense drugs and to provide drug and related information to the public.

.An expert on drugs………..Pharmacist.

Drug & Medicine

- A **drug** is any substance that acts on the living body to alter the physiological process and are used for the prevention, diagnosis and treatment of diseases.
- **A medicine** is any drug which has a definite form & dose and are *therapeutically used for the treatment of diseases of living subjects.

***Therapeutics-** attempt to cure, improve, mitigate (serious or painful), treat or prevent disease and other conditions in humans.

Bascis Fundamentals of Organic Chemistry-

1. ALIPHATIC HYDROCARBONS

a) Alkane-

An alkane, or paraffin, is an acyclic saturated hydrocarbon.

In other words, an alkane consists of hydrogen and carbon atoms arranged in a tree structure in which all the carbon–carbon bonds are single.

General Chemical Formula - CnH_2n_{+2}

Ex.- Methane (CH_4)

b) Alkene-

An alkene is a hydrocarbon that contains a carbon–carbon double bond.

The term is often used as synonym of olefin, that is, any hydrocarbon containing one or more double bonds.

General Chemical Formula - CnH2n

Ex.- Ethylene (C_2H_4)

c) **Akyne-**

An alkyne is an unsaturated hydrocarbon containing at least one carbon—carbon triple bond.

The simplest acyclic alkynes with only one triple bond.

General Chemical Formula - CnH2n-2

Ex.- Ethyne or Acetylene (C_2H_2)

d) **Dienes-**

A diene is a covalent compound that contains two double bonds, usually among carbon atoms.

They thus contain two alkene units, with the standard prefix di of systematic nomenclature.

Ex.- Butadiene

e) **Alkyl halide-**

The haloalkanes are a group of chemical compounds derived from alkanes containing one or more halogens.

General formula – R-X

Where R is an alkyl or substituted alkyl group and

X is a halogen (F, Cl, Br, I).

Ex.- Ethyl Chloride (C_2H_5Cl)

f) **Alcohals-**

Alcohol is an organic compound that carries at least one hydroxyl functional group bound to a saturated carbon atom.

The term alcohol originally referred to the primary alcohol ethanol, which is used as a drug and is the main alcohol present in alcoholic beverages.

Genral Formula- $C_nH_{2n+1}OH$

Ex.- Ethyl Alcohal (C_2H_5OH)

g) **Aldehyde-**

An aldehyde is a compound containing a functional group with the structure −CHO, consisting of a carbonyl center with the carbon atom also bonded to hydrogen and to an R group, which is any generic alkyl or side chain.

The group—without R—is the aldehyde group, also known as the formyl group.

General Formula – RCHO

Ex.- CH_3CHO

h) **Ketone-**

Ketones contain a carbonyl group.

General Formula - Ketone is a functional group with the structure $R_2C=O$, where R can be a variety of carbon-containing substituent.

Ex.- The simplest ketone is acetone, with the formula CH_3COCH_3.

i) **Carboxylic acid-**

A carboxylic acid is an organic acid that contains a carboxyl group attached to an R-group.

General Formula - General formula of a carboxylic acid is R–COOH, with R referring to the alkyl group.

Ex.- Acetic acid (CH_3COOH)

j) **Amines-**

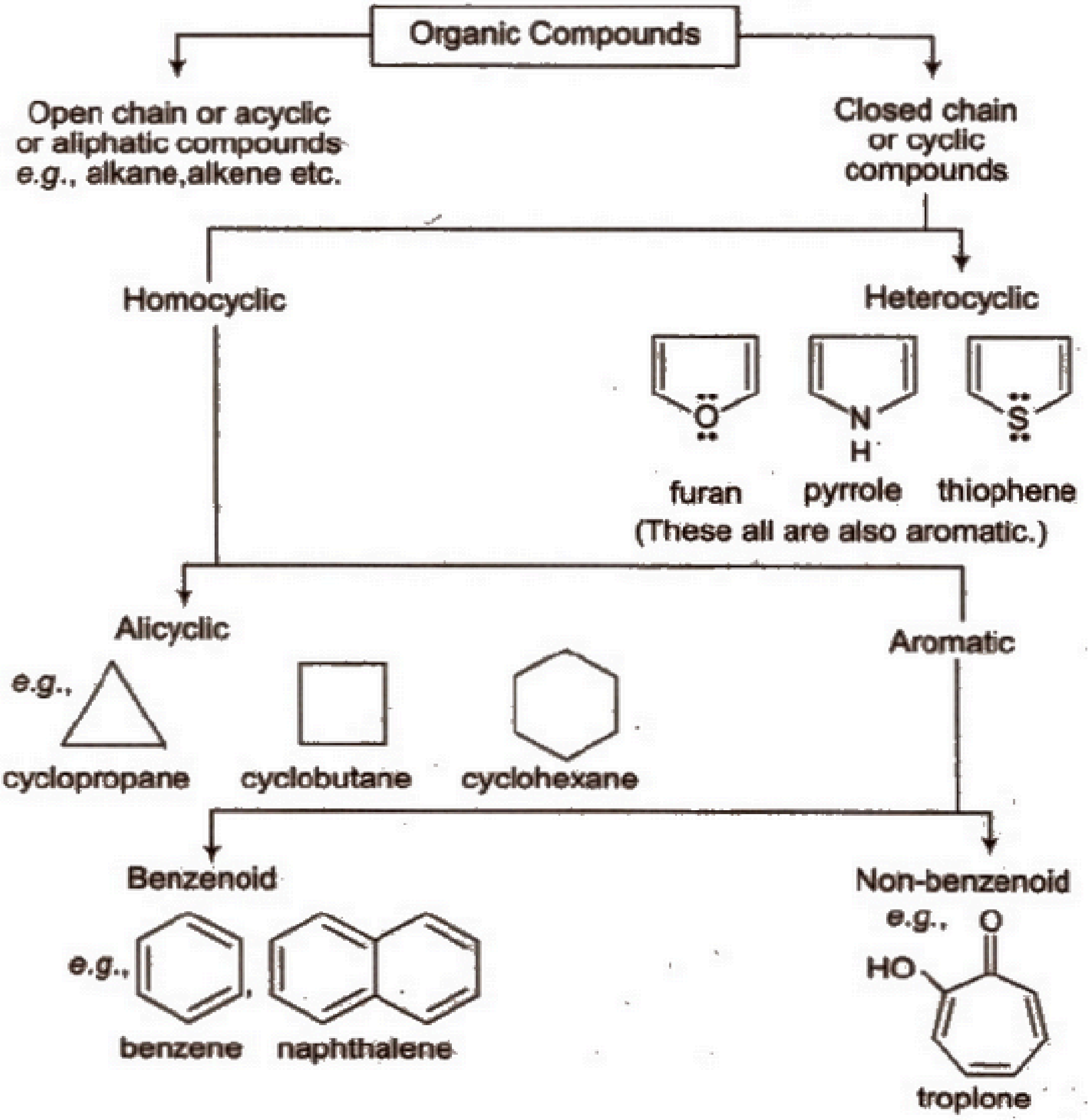
Amines are compounds and functional groups that contain a basic nitrogen atom with a lone pair.

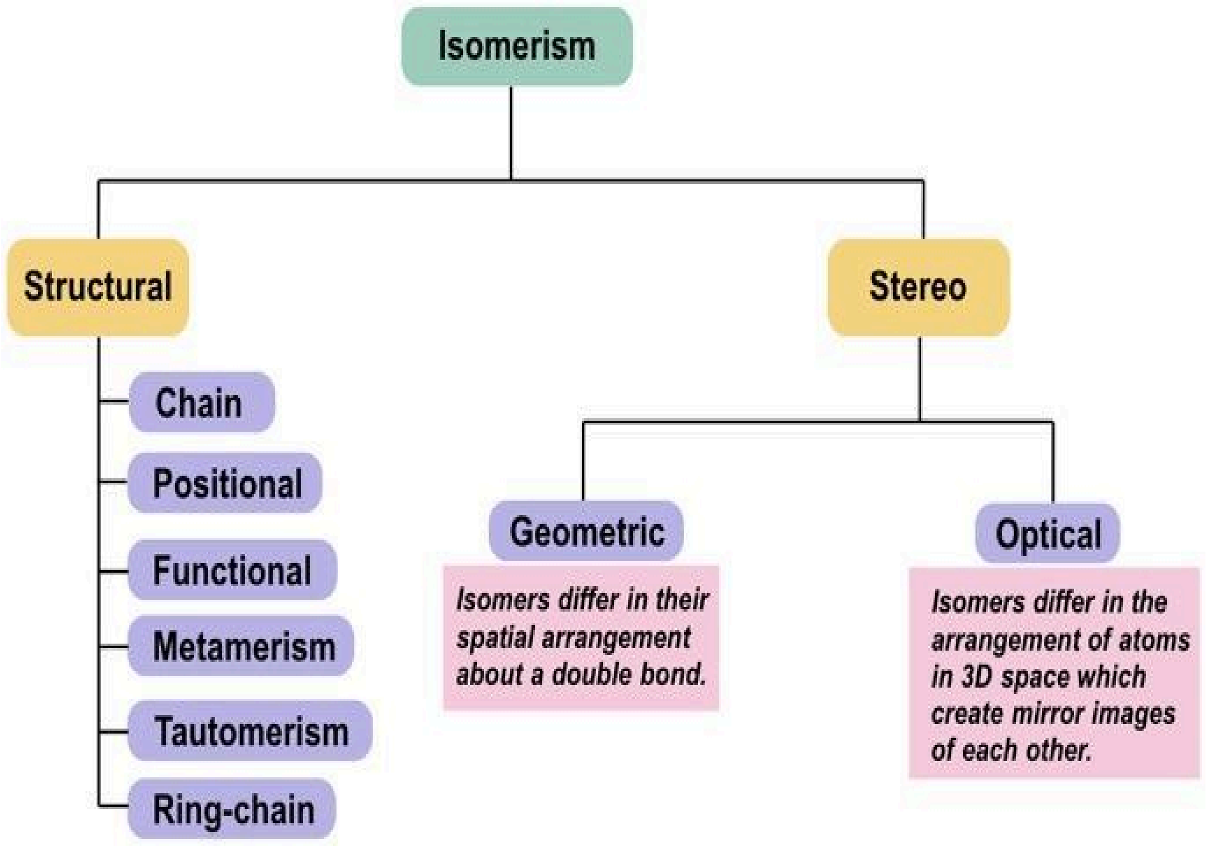
Amines are formally derivatives of ammonia, wherein one or more hydrogen atoms have been replaced by a substituent such as an alkyl or aryl group.

General Formula - RNH_2, R_2NH, and R_3N

Ex.- Ethyl Amine ($C_2H_5NH_2$)

Classification of Organic Compounds


Organic Compounds
Open chain or acyclic or aliphatic compounds e.g., alkane,alkene etc.
Closed chain or cyclic compounds
Homocyclic
Heterocyclic
Ö
N
H
S
furan
pyrrole
thiophene
(These all are also aromatic.)
Alicyclic
e.g.,
cyclopropane
cyclobutane
cyclohexane
Aromatic
Benzenoid
e.g.,
benzene
naphthalene
Non-benzenoid
e.g.,
O
HO
troplone



Aromatic Compounds

Aromatic" meanings related to odor, aroma compound.

An aroma compound, also known as an **odorant, aroma, fragrance, or flavor, is a chemical compound that has a smell or odor.**

Examples-

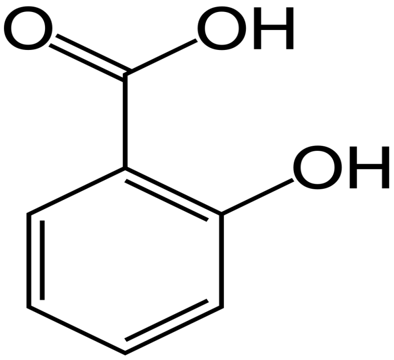
Benzene- Benzene is an organic chemical compound with the molecular formula C6H6. The benzene molecule is composed of six carbon atoms joined in a planar ring with one hydrogen atom attached to each. As it contains only carbon and hydrogen atoms, benzene is classed as a hydrocarbon.

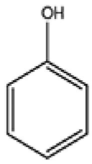
Phenols- In organic chemistry, phenols, sometimes called phenolics, are a class of chemical compounds consisting of one or more hydroxyl groups (—OH) bonded directly to an aromatic hydrocarbon group.

Aromatic Amines- An aromatic amine is an organic compound consisting of an aromatic ring attached to an amine.

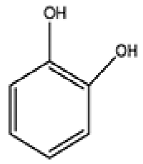
Aromatic acids - Aromatic acids include compounds that contain a -COOH group bonded to an aromatic ring. The simplest aromatic acid is benzoic acid.

Note- Salicylic acid is both a carboxylic acid and a phenol.

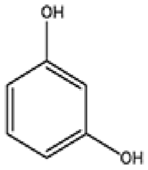




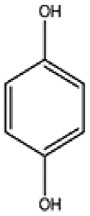
phenol



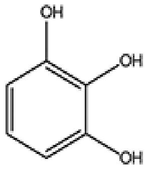
pyrocatechol



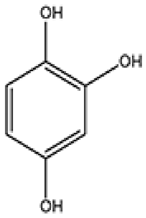
resorcinol



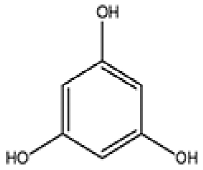
hydroquinone



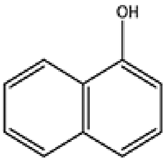
pyrogallol



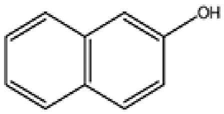
hydroxyhydroquinone



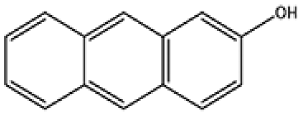
phloroglucitol



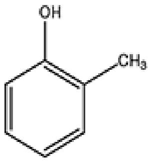
1-naphthol



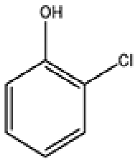
2-naphthol



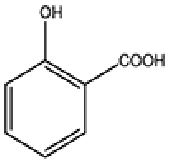
2-hydroxyanthracene



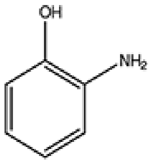
o-cresol



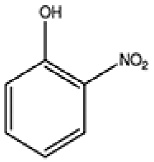
o-chlorophenol



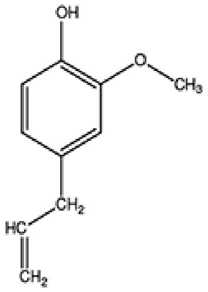
salicylic acid



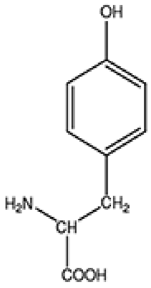
o-aminophenol



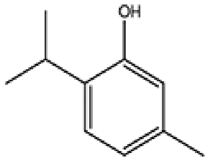
o-nitrophenol



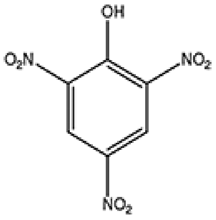
eugenol



tyrosine

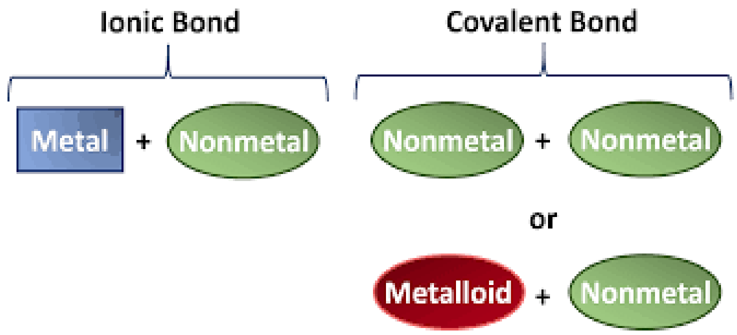


thymol



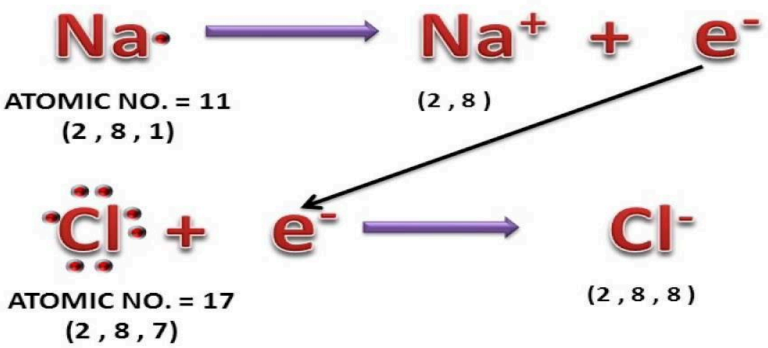
picric acid

REACTION MECHANISM

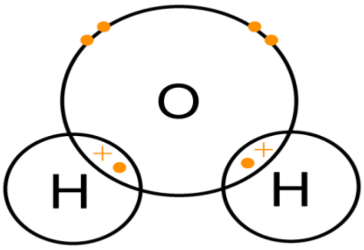


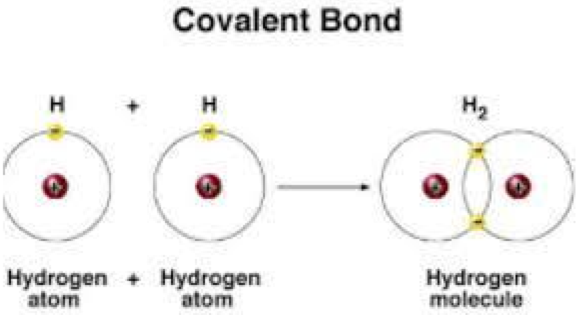
- **Metal** is an element that readily forms positive ions (Cations) and has metallic bonds.
- **Nonmetal** is a chemical element that mostly lacks the characteristics of a metal. Elements which easily form negative ions by accepting electrons.
- A **metalloid** is an element that has properties that are intermediate between those of metals and nonmetals. **Metalloids** can also be called semimetals. **Examples-** Silicon; Boron; Arsenic; Antimony

- **Ionic bond,** also called **electrovalent bond**, type of linkage formed from the electrostatic attraction between oppositely charged ions in a chemical compound. Such a **bond** forms when the valence (outermost) electrons of one atom are transferred permanently to another atom.

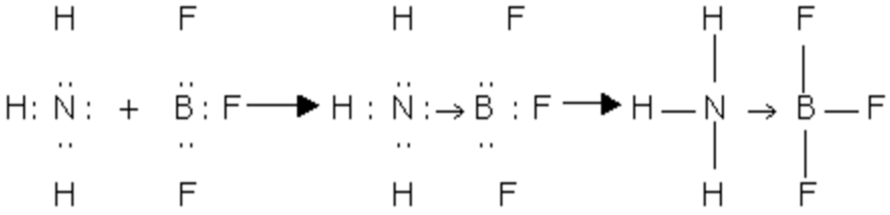


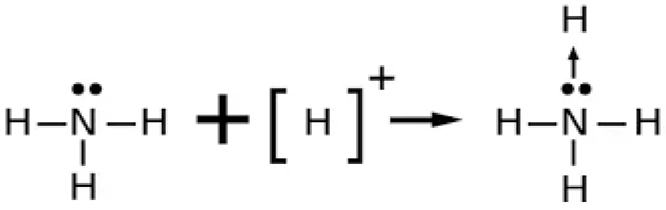
- A covalent bond is a chemical bond that involves the sharing of electron pairs between atoms.

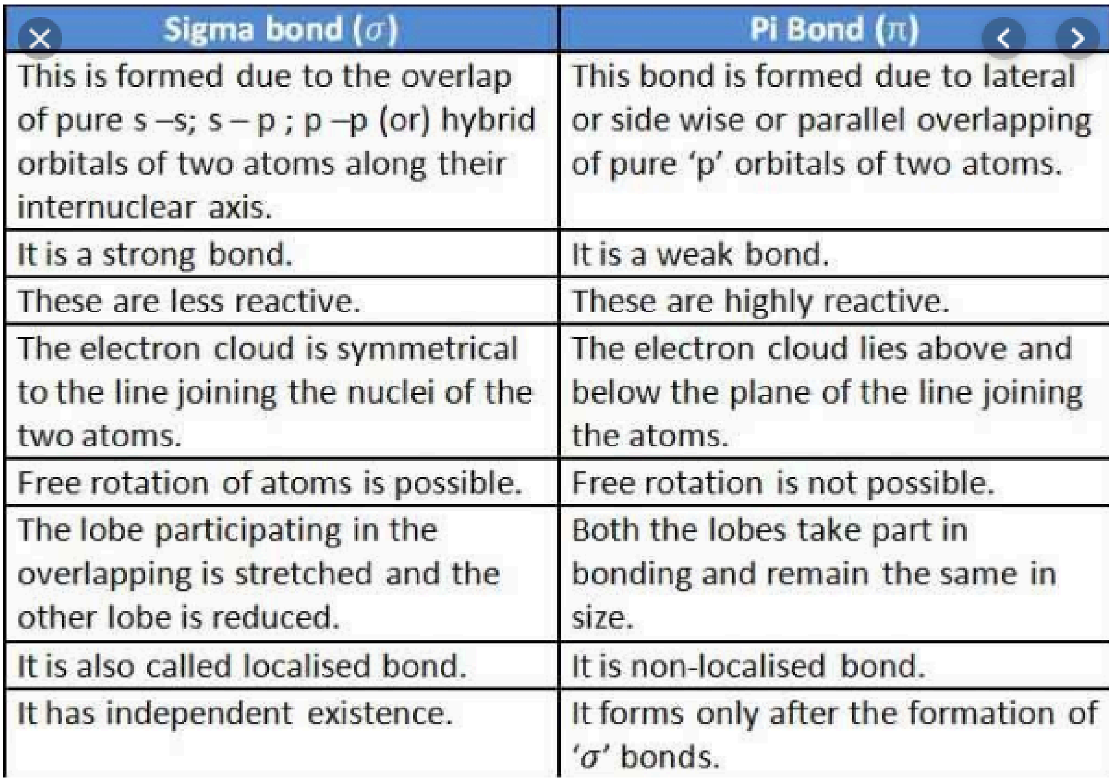




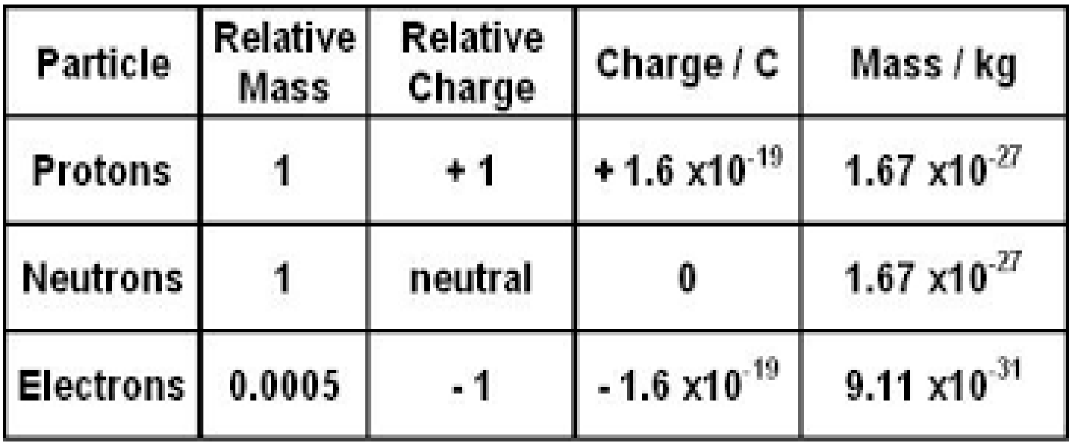
- A **coordinate bond** (also called a dative covalent **bond**) is a covalent **bond** (a shared pair of electrons) in which both electrons come from the same atom.







Sigma bond (σ)	Pi Bond (π)
This is formed due to the overlap of pure s –s; s – p ; p –p (or) hybrid orbitals of two atoms along their internuclear axis.	This bond is formed due to lateral or side wise or parallel overlapping of pure 'p' orbitals of two atoms.
It is a strong bond.	It is a weak bond.
These are less reactive.	These are highly reactive.
The electron cloud is symmetrical to the line joining the nuclei of the two atoms.	The electron cloud lies above and below the plane of the line joining the atoms.
Free rotation of atoms is possible.	Free rotation is not possible.
The lobe participating in the overlapping is stretched and the other lobe is reduced.	Both the lobes take part in bonding and remain the same in size.
It is also called localised bond.	It is non-localised bond.
It has independent existence.	It forms only after the formation of 'σ' bonds.

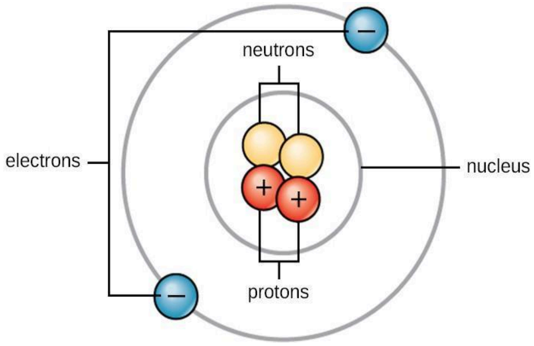


Particle	Relative Mass	Relative Charge	Charge / C	Mass / kg
Protons	1	+ 1	$+ 1.6\ \mathrm{x}10^{-19}$	$1.67\ \mathrm{x}10^{-27}$
Neutrons	1	neutral	0	$1.67\ \mathrm{x}10^{-27}$
Electrons	0.0005	- 1	$- 1.6\ \mathrm{x}10^{-19}$	$9.11\ \mathrm{x}10^{-31}$

- **Electron configuration**- spectral lines as "sharp", "principal", "diffuse" and "fundamental".

The **electron configuration is the distribution of electrons of an atom or molecule in atomic or molecular orbitals.*

- An atom is the smallest unit of ordinary matter that forms a chemical element. Every solid, liquid, gas, and plasma is composed of neutral or ionized atoms. Atoms are extremely small, typically around 100 picometers across. (1 angstrom = 100 picometer).
- So, Atom size - 10^{-10} m (one ten-billionth of a meter or 0.1 nanometers).



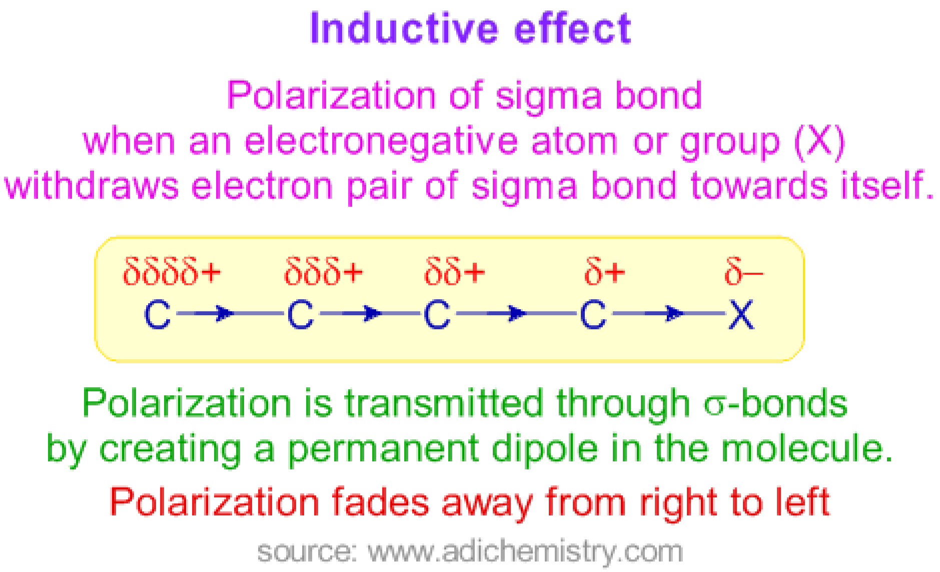
- A molecule is an electrically neutral group of two or more atoms held together by chemical bonds.

Inductive effect -

*The polarization of a σ bond due to electron withdrawing or electron donating effect of adjacent groups or atoms is referred to as **inductive effect**.*

A sigma bond between two atoms, which differ in their electronegativity, is polarized due to displacement of bond pair towards the more electronegative atom. In this process, the electronegative atom gets partial negative charge while the other atom gets partial positive charge. Thus induced polarity is transmitted through the sigma bonds in the molecule by creating a permanent dipole. This phenomenon is referred to as inductive effect.

It is represented by an arrow pointing towards the more electronegative atom carrying partial negative charge.



Inductive effect

Polarization of sigma bond
when an electronegative atom or group (X)
withdraws electron pair of sigma bond towards itself.

Polarization is transmitted through σ-bonds
by creating a permanent dipole in the molecule.

Polarization fades away from right to left

source: www.adichemistry.com

Salient features of inductive effect

* It arises due to electronegativity difference between two atoms forming a sigma bond.

* It is transmitted through the **sigma bonds**. No pi bonds are involved.

* The magnitude of inductive effect decreases while moving away from the groups causing it.

* It is a **permanent** effect. It may create permanent dipole in the molecule.

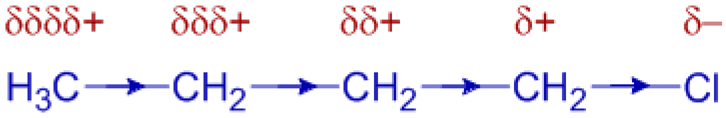
* In general, the inductive effect is relatively weak and is overshadowed by other electronic effects like resonance effect, hyperconjugation etc.

* It influences the chemical and physical properties of compounds.

EXAMPLE OF INDUCTIVE EFFECT

The C-Cl bond in the butyl chloride, CH_3-CH_2-CH_2-CH_2-Cl is polarized due to electronegativity difference. The electrons are withdrawn by the chlorine atom. Thus the first carbon atom gets partial positive charge. In turn, this carbon atom drags electron density partially from the next carbon, which also gets partial positive charge.

This will continue further and is how the inductive effect is transmitted through the carbon chain.



$$\overset{\delta\delta\delta\delta+}{H_3C} \rightarrow \overset{\delta\delta\delta+}{CH_2} \rightarrow \overset{\delta\delta+}{CH_2} \rightarrow \overset{\delta+}{CH_2} \rightarrow \overset{\delta-}{Cl}$$

One must note that the *inductive effect weakens away along the chain* and is not that much significant beyond the 3rd carbon atom.

Also note that inductive effect is a permanent effect and is inherent to the molecule, while the electromeric effect is a temporary effect is only created in the presence of attacking electrophilic or nucleophilic reagents.

TYPES OF INDUCTIVE EFFECT

The inductive effect is divided into two types based on the electron withdrawing or electron releasing nature of atom/group inducing it. The strength of inductive effect is measured by comparing with that of hydrogen.

1) Negative inductive effect (-I):

The electron withdrawing nature of groups or atoms is called as negative inductive effect. It is indicated by -I. Following are the examples of groups in the decreasing order of their -I effect:

$NH_3^+ > NO_2 > CN > SO_3H > CHO > CO > COOH > COCl > CONH_2 > F > Cl > Br > I > OH > OR > NH_2 > C_6H_5 > H$

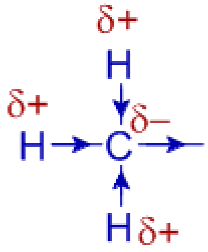
2) Positive inductive effect (+I):

It refers to the electron releasing nature of the groups or atoms and is denoted by +I. Following are the examples of groups in the decreasing order of their +I effect.

$C(CH_3)_3 > CH(CH_3)_2 > CH_2CH_3 > CH_3 > H$

Why alkyl groups are showing positive inductive effect?

Though the C-H bond is practically considered as non-polar, there is partial positive charge on hydrogen atom and partial negative charge on carbon atom. Therefore each hydrogen atom acts as electron donating group. This cumulative donation turns the alkyl moiety into an electron donating group.



APPLICATIONS OF INDUCTIVE EFFECT

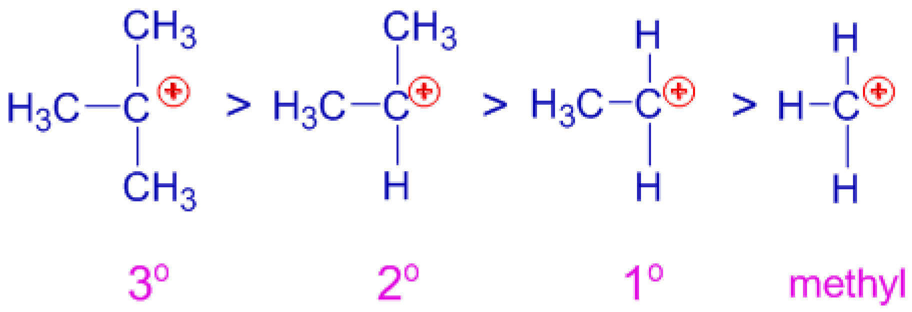
Stability of carbocations (carbonium ions):

The stability of carbocations increase when +I groups like alkyl groups are present adjacent to positively charged carbon. The +I groups reduce the positive charge on the carbon by donating negative charge density through positive inductive effect. This results in greater stability of carbocation.

Whereas, the -I groups destabilize the carbocations as they increase the positive charge by withdrawing electron density.

Note that any factor that increases the charge (either negative or positive) on an ion results in destabilization while any factor that reduces the charge results in stabilization of that ion.

For example, the order of stability of a few carbocations containing alkyl groups is as follows:

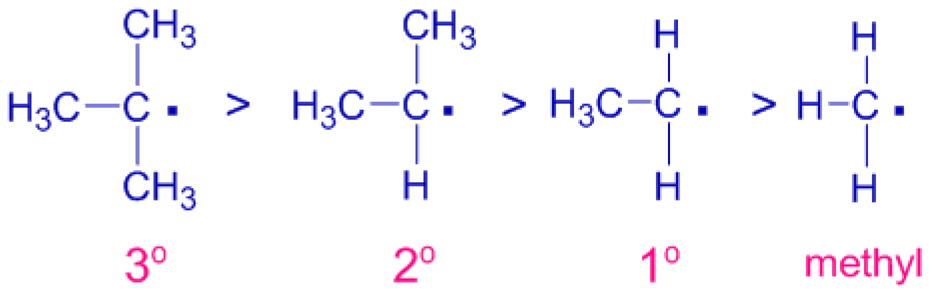


The tertiary carbocation containing three alkyl groups is more stable than the secondary carbocation with two alkyl groups and which in turn is more stable than the primary carbocation. Methyl carbocation is the least stable among the given.

Stability of free radicals:

In the same way the stability of free radicals increases with increase in the number of alkyl groups.

Thus the stability of different free radicals is:

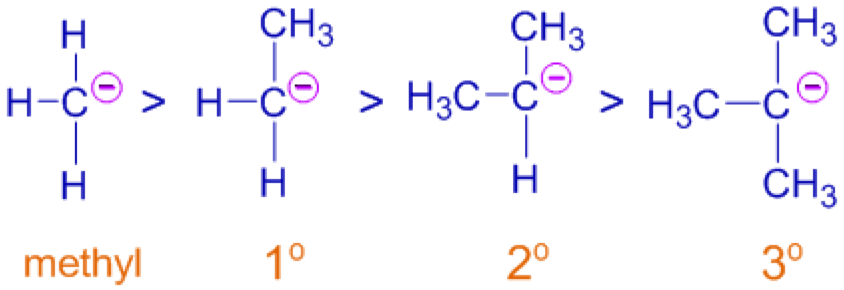


Stability of carbanions:

However, the +I groups decrease the stability of carbanions while the -I groups increases their stability.

For example, the alkyl groups (+I) donate electron density to the negatively charged carbon resulting in destabilization of carbanion.

Thus the order of stability of following carbanions is:



Now the order is reversed. The tertiary carbanion is least stable while the methyl carbanion is most stable among the given.

Acidic strength of carboxylic acids and phenols:

A protonic acid is always in equilibrium with its conjugate base that is formed by loss of a proton. Any factor that stabilizes the negatively charged conjugate base favors greater ionization of acid. i.e increases the acidic strength.

The electron withdrawing groups showing negative inductive effect (-I) reduce the negative charge on the conjugate base (like carboxylate ion) by pulling the electron density and thus by stabilizing it. Hence the acidic strength increases when -I groups are present.

On the contrary, the +I groups decrease the acidic strength as they destabilize the conjugate base of acid (anionic) by releasing electron density which in turn increases the negative charge on the anion and thus destabilizing it.

E.g.

i) The acidic strength increases with increase in the number of electron withdrawing Fluorine atoms as shown below.

$CH_3COOH < CH_2FCOOH < CHF_2COOH < CF_3COOH$

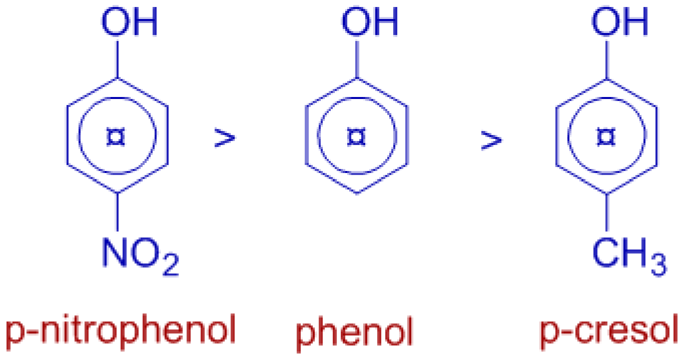
ii) Formic acid is stronger acid than acetic acid since the $–CH_3$ group destabilizes the carboxylate ion.

On the same lines, the acidic strength of phenols increases when -I groups are present on the ring.

E.g.

The p-nitrophenol is stronger acid than phenol since the $-NO_2$ group is a -I group that withdraws electron density. Whereas, the para-cresol is weaker acid than phenol, since the $-CH_3$ group shows positive inductive effect (+I).

For example, the order of acidic strength following phenols is:



Basic strength of amines:

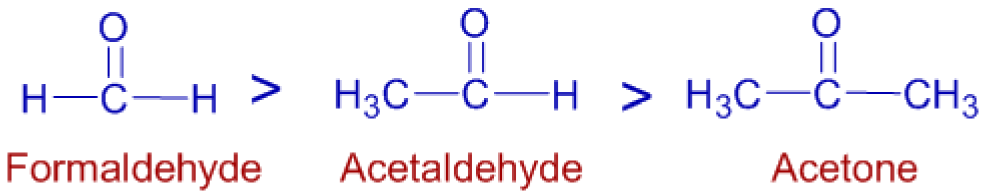
The electron donating groups like alkyl groups increase the basic strength of amines whereas the electron withdrawing groups like aryl groups decrease the basic nature. Therefore alkyl amines are stronger Lewis bases than ammonia, whereas aryl amines are weaker than ammonia.

Thus the order of basic strength of alkyl and aryl amines with respect to ammonia is :$CH_3NH_2 > NH_3 > C_6H_5NH_2$

Reactivity of carbonyl compounds:

The +I groups increase the electron density at carbonyl carbon. Hence their reactivity towards nucleophiles decreases. Thus formaldehyde is more reactive than acetaldehyde and acetone towards nucleophilic addition reactions.

Thus the order of reactivity follows:



Inductive effect vs Resonance effect

In general, the inductive effect is **less** influencing than other effects like resonance effect and hyperconjugation.

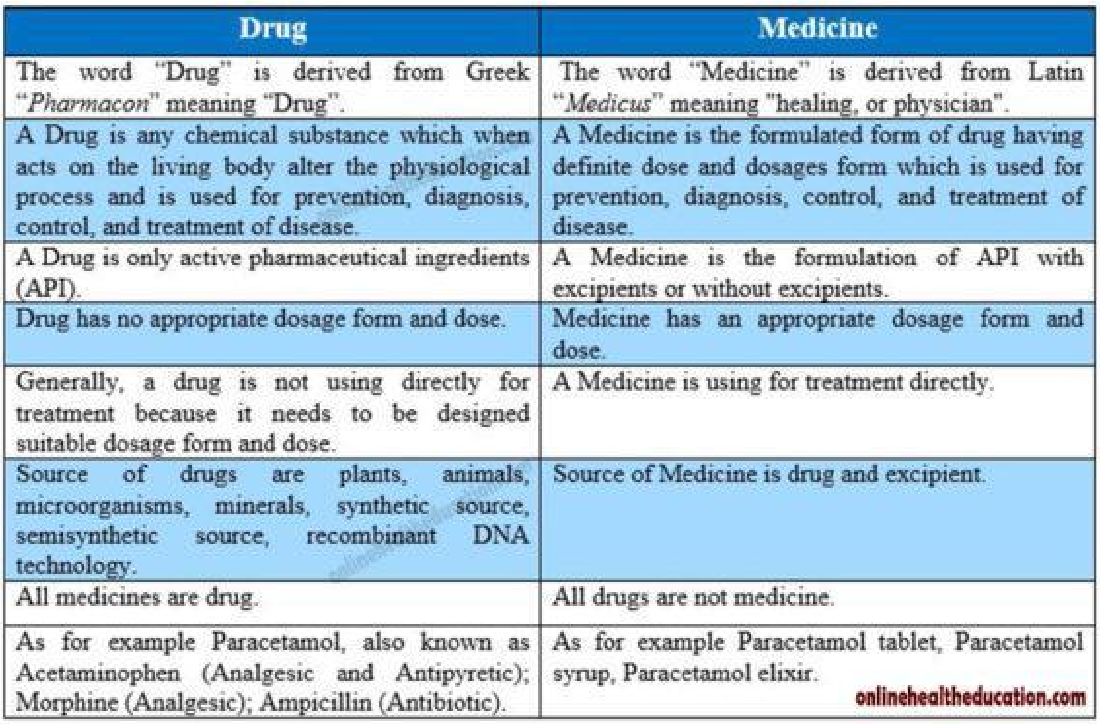
E.g. The electron withdrawing nature of nitro group, $-NO_2$ is mostly due to resonance effect rather than the inductive effect.

But there are exceptions. For example, in the cases of halogens, the negative inductive effect is more dominating than positive resonance effect.

Drug desgin

What is a Drug?

A drug is "a chemical substance used in the treatment, cure, prevention, or diagnosis of disease or used to otherwise enhance physical or mental well-being ".



Drug	Medicine
The word "Drug" is derived from Greek "*Pharmacon*" meaning "Drug".	The word "Medicine" is derived from Latin "*Medicus*" meaning "healing, or physician".
A Drug is any chemical substance which when acts on the living body alter the physiological process and is used for prevention, diagnosis, control, and treatment of disease.	A Medicine is the formulated form of drug having definite dose and dosages form which is used for prevention, diagnosis, control, and treatment of disease.
A Drug is only active pharmaceutical ingredients (API).	A Medicine is the formulation of API with excipients or without excipients.
Drug has no appropriate dosage form and dose.	Medicine has an appropriate dosage form and dose.
Generally, a drug is not using directly for treatment because it needs to be designed suitable dosage form and dose.	A Medicine is using for treatment directly.
Source of drugs are plants, animals, microorganisms, minerals, synthetic source, semisynthetic source, recombinant DNA technology.	Source of Medicine is drug and excipient.
All medicines are drug.	All drugs are not medicine.
As for example Paracetamol, also known as Acetaminophen (Analgesic and Antipyretic); Morphine (Analgesic); Ampicillin (Antibiotic).	As for example Paracetamol tablet, Paracetamol syrup, Paracetamol elixir.

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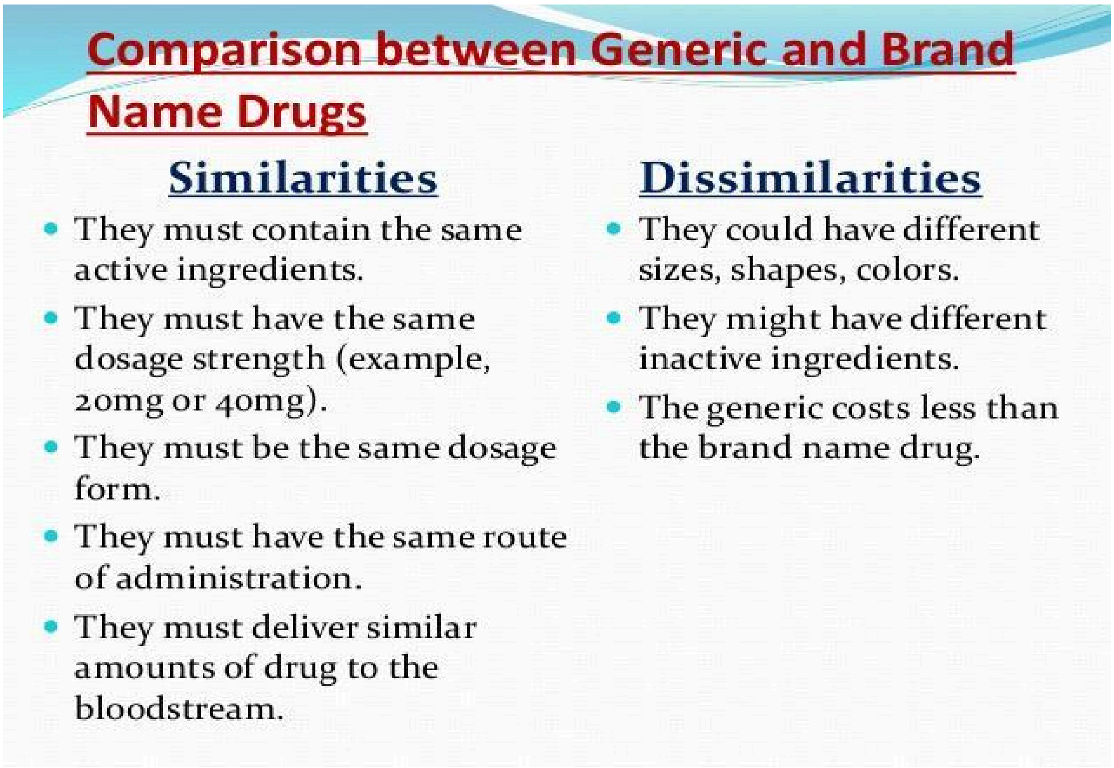


Comparison between Generic and Brand Name Drugs

Similarities

- They must contain the same active ingredients.
- They must have the same dosage strength (example, 20mg or 40mg).
- They must be the same dosage form.
- They must have the same route of administration.
- They must deliver similar amounts of drug to the bloodstream.

Dissimilarities

- They could have different sizes, shapes, colors.
- They might have different inactive ingredients.
- The generic costs less than the brand name drug.

Chemical Name	Non proprietary	Trade Name
Acetyl Salicyclic acid	**ASPIRIN**	**Disprin (India)** **Bayer's Asprin (USA)** **Ecospirin (India)**

Source of Drugs

- Natural
  - Plants
  - Animal
  - Micro organisms
  - Mineral
- Synthetic
  - Semi synthetic
  - Synthetic

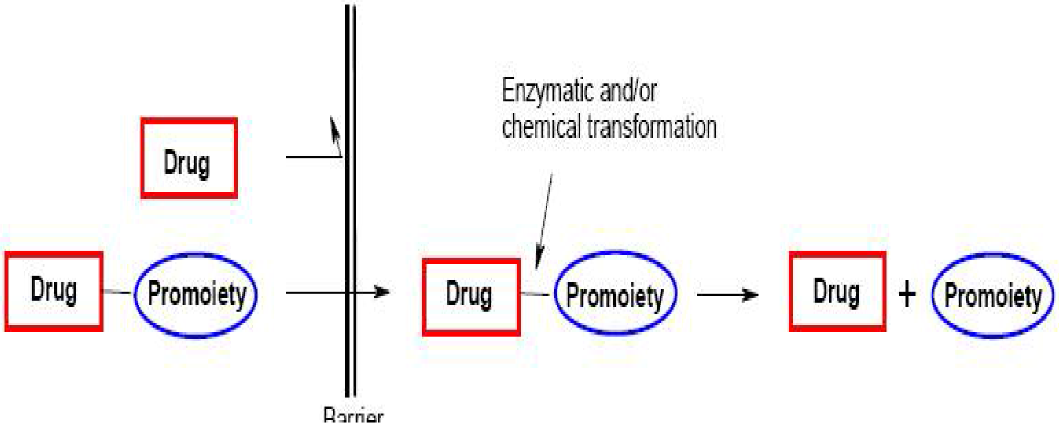
What is Drug Design?

It is the innovative process of finding new medications based on the knowledge of a biological target.

- **Prodrug Concept**

  The concept of "prodrug" was first introduced by Adrian Albert in 1958 to describe compounds that undergo biotransformation prior to eliciting their pharmacological effect.
- A prodrug is defined as a biologically inactive derivative of a parent drug molecule that usually requires a chemical or enzymatic transformation within the body to release the active drug, and possess improved delivery properties over the parent molecule.
- The development of prodrugs is now well established as a strategy to improve the physicochemical, biopharmaceutical or pharmacokinetic properties of pharmacologically potent compounds, and thereby increase usefulness of a potential drug.

SCHEMATIC ILLUSTRATION OF THE PRODRUG CONCEPT



History and the Present of Prodrug Design

1899

- **Methenamine**
- **First intentional Prodrug**

1935

- **Protonsil**
- **Antibiotic**

1958

- **Adrien Albert First introduced the term “pro-drug”**

1960

- **An explosive increase in the use of prodrugs in drug discovery and development.**

2009

- **15% of the 100 best selling drugs were Prodrugs**

Rationale for prodrug design

- **A. Improving formulation and administration**
- **B. Enhancing permeability and absorption**
- **C. Changing the distribution profile**
- **D. Protecting from rapid metabolism**
- **E. Overcoming toxicity problems**

Properties of ideal prodrug

1.Pharmacological Inertness

2.Properties of ideal prodrug.

- **Rapid transformation, chemically or enzymatically, into the active form at the target site**

3.Non-toxic metabolic fragments followed by their rapid elimination

Classification of Prodrugs

- **Prodrugs**
- **Carrier linked prodrug**
- **Bipartite prodrug**
- **Tripartite prodrug**
- **Mutual Prodrugs**
- **Bioprecursors**
- **Classification of Prodrugs**

A) Carrier linked prodrug

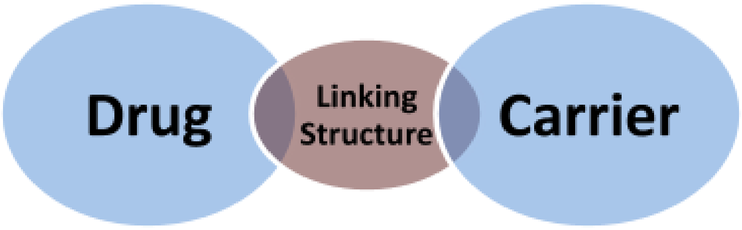
Carrier linked prodrug consists of the attachment of a carrier group to the active drug to alter its physicochemical properties.

The subsequent enzymatic or non-enzymatic mechanism releases the active drug moiety.

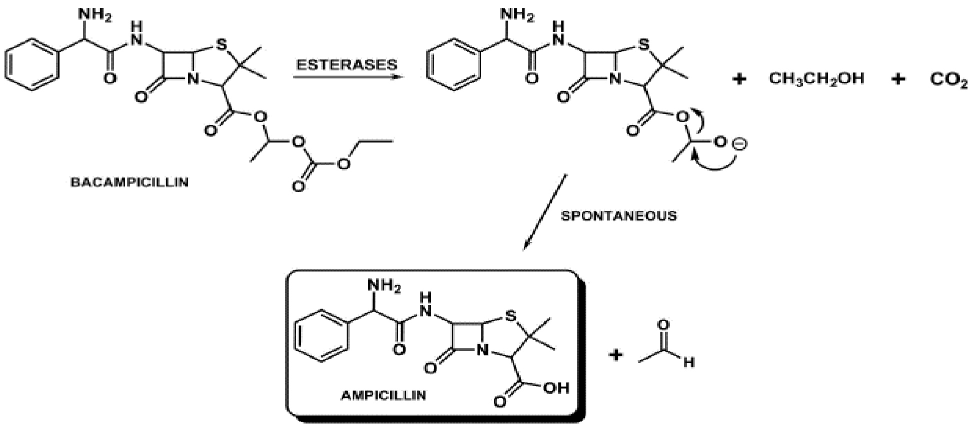
1.Bipartite Prodrug

- It is composed of one carrier (group) attached to the drugs.
- Such prodrugs have greatly modified lipophilicity due to the attached carrier. The active drug is released by hydrolytic cleavage either chemically or enzymatically.
- E.g. Tolmetin-glycine prodrug.
- Tolmetin- Nonsteroidal anti-inflammatory drug

2. Tripartite Prodrug



The carrier group is attached via linker to drug.



3. Mutual Prodrugs

- A mutual prodrug consists of two pharmacologically active agents coupled together so that each acts as a promoiety for the other agent and vice versa.
- A mutual prodrug is a bipartite or tripartite prodrug in which the carrier is a synergistic drug with the drug to which it is linked.
- Benorylate is a mutual prodrug aspirin and paracetamol.
- Sultamicillin, which on hydrolysis by an esterase produces ampicillin & sulbactum.

B) Bioprecursors

Bio- precursor prodrugs produce their effects after in vivo chemical modification of their inactive form.

Bioprecursor prodrugs rely on oxidative or reductive activation reactions unlike the hydrolytic activation of carrier-linked prodrugs.

They metabolized into a new compound that may itself be active or further metabolized to an active metabolite

Applications of prodrugs

Pharmaceutical Applications

- Masking Taste & Odor
- Minimizing Pain at Site of Injection
- Alteration of Drug Solubility
- Enhancement of Chemical Stability
- Reduction of G.I. irritation
- Change of physical form of the drug

Pharmacokinetic Applications

- Enhancement of bioavailability (Lipophilicity)
- Prevention of Pre-systemic Metabolism
- Prolongation of duration of action
- Reduction of toxicity
- Site specific drug delivery

DRUG-

- **A drug** is a chemical substance, typically of known structure, which, when administered to a living organism, produces a biological effect. A pharmaceutical **drug**, also called a medication or medicine, is a chemical substance used to treat, cure, prevent, or diagnose a disease or to promote well-being.

DRUG DESIGN-

- **Drug design**, also known as rational **drug design**, is the inventive process of finding new medications based on the knowledge of a biological target. **Drug design** defines the **design** of molecules that are complementary in shape and charge to the bimolecular target with which they interact and therefore will bind to it.

DRUG DISCOVERY-

- In the fields of medicine, biotechnology and pharmacology, **drug discovery** is the process by which new candidate medications are discovered. Historically, **drugs** were discovered by identifying the active ingredient from traditional remedies or by serendipitous **discovery**, as with penicillin.

DRUG DEVELOPMENT -

- **Drug development** is the process of bringing a new **pharmaceutical drug** to the market once a lead compound has been identified through the process of **drug discovery**.

- **Drug design**, often referred to as **rational drug design** or simply rational design, is the inventive process of finding new medications based on the knowledge of a biological target.
- The drug is most commonly an organic small molecule that activates or inhibits the function of a biomolecule such as a protein, which in turn results in a therapeutic benefit to the patient.
- In the most basic sense, drug design involves the design of molecules that are complementary in shape and charge to the biomolecular target with which they interact and therefore will bind to it. Drug design frequently but not necessarily relies on computer modeling techniques.

- This type of modeling is sometimes referred to as **computer-aided drug design**. Finally, drug design that relies on the knowledge of the three-dimensional structure of the biomolecular target is known as **structure-based drug design**.
- In addition to small molecules, biopharmaceuticals including peptides and especially therapeutic antibodies are an increasingly important class of drugs and computational methods for improving the affinity, selectivity, and stability of these protein-based therapeutics have also been developed.
- The phrase "drug design" is to some extent a misnomer. A more accurate term is ligand design (i.e., design of a molecule that will bind tightly to its target).[6] Although design techniques for prediction of binding affinity are reasonably successful, there are many other properties, such as bioavailability, metabolic half-life, side effects, etc., that first must be optimized before a ligand can become a safe and efficacious drug. These other characteristics are often difficult to predict with rational design techniques. Nevertheless, due to high attrition rates, especially during clinical phases of drug development, more attention is being focused early in the drug design process on selecting candidate drugs whose physicochemical properties are predicted to result in fewer complications during development and hence more likely to lead to an approved, marketed drug.
- Furthermore, in vitro experiments complemented with computation methods are increasingly used in early drug discovery to select compounds with more favorable ADME (absorption, distribution, metabolism, and excretion) and toxicological profiles

Drug targets

A biomolecular target (most commonly a protein or a nucleic acid) is a key molecule involved in a particular metabolic or signaling pathway that is associated with a specific disease condition or pathology or to the infectivity or survival of a microbial pathogen. Potential drug targets are not necessarily disease causing but must by definition be disease modifying.

In some cases, small molecules will be designed to enhance or inhibit the target function in the specific disease modifying pathway. Small molecules (for example

receptor agonists, antagonists, inverse agonists, or modulators;
enzyme activators or inhibitors; or ion channel openers or blockers) will be designed that are complementary to the binding site of target.

Small molecules (drugs) can be designed so as not to affect any other important "off-target" molecules (often referred to as antitargets) since drug interactions with off-target molecules may lead to undesirable side effects. Due to similarities in binding sites, closely related targets identified through sequence homology have the highest chance of cross reactivity and hence highest side effect potential.

Most commonly, drugs are organic small molecules produced through chemical synthesis, but biopolymer-based drugs (also known as biopharmaceuticals) produced through biological processes are becoming increasingly more common.

In addition, mRNA-based gene silencing technologies may have therapeutic applications

Rational drug discovery

In contrast to traditional methods of drug discovery (known as forward pharmacology), which rely on trial-and-error testing of chemical substances on cultured cells or animals, and matching the apparent effects to treatments, rational drug design (also called reverse pharmacology) begins with a hypothesis that modulation of a specific biological target may have therapeutic value. In order for a biomolecule to be selected as a drug target, two essential pieces of information are required. The first is evidence that modulation of the target will be disease modifying. This knowledge may come from, for example, disease linkage studies that show an association between mutations in the biological target and certain disease states.

The second is that the target is "druggable". This means that it is capable of binding to a small molecule and that its activity can be modulated by the small molecule.

Once a suitable target has been identified, the target is
normally cloned and produced and purified. The purified protein is then used to establish a screening assay. In addition, the three-dimensional structure of the target may be determined.

The search for small molecules that bind to the target is begun by screening libraries of potential drug compounds. This may be done by using the screening assay (a "wet screen"). In addition, if the structure of the target is available, a virtual screen may be performed of candidate drugs. Ideally the candidate drug compounds should be "drug-like", that is they should possess properties that are predicted to lead to oral bioavailability, adequate chemical and metabolic stability, and minimal toxic effects.

Several methods are available to estimate druglikeness such as Lipinski's Rule of Five and a range of scoring methods such as lipophilic efficiency.

Several methods for predicting drug metabolism have also been proposed in the scientific literature

Due to the large number of drug properties that must be simultaneously optimized during the design process, multi-objective optimization techniques are sometimes employed.

Finally because of the limitations in the current methods for prediction of activity, drug design is still very much reliant on serendipity and bounded rationality.

Computer-aided drug design

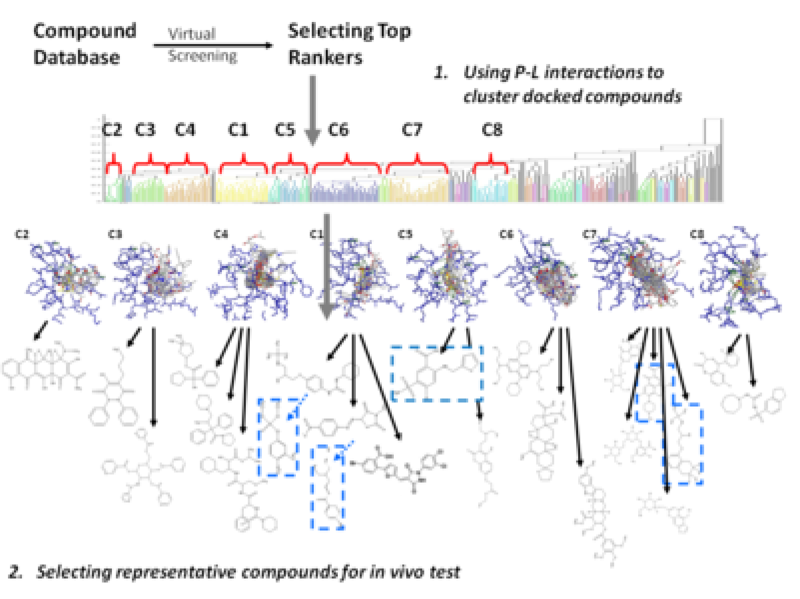
The most fundamental goal in drug design is to predict whether a given molecule will bind to a target and if so how strongly. Molecular mechanics or molecular dynamics is most often used to estimate the strength of the intermolecular interaction between the small molecule and its biological target. These methods are also used to predict the conformation of the small molecule and to model conformational changes in the target that may occur when the small molecule binds to it.Semi-empirical, ab initio quantum chemistry methods, or density functional theory are often used to provide optimized parameters for the molecular mechanics calculations and also provide an estimate of the electronic properties (electrostatic potential, polarizability, etc.) of the drug candidate that will influence binding affinity.

Molecular mechanics methods may also be used to provide semi-quantitative prediction of the binding affinity. Also, knowledge-based scoring function may be used to provide binding affinity estimates. These methods use linear regression, machine learning, neural nets or other statistical techniques to derive predictive binding affinity equations by fitting experimental affinities to computationally derived interaction energies between the small molecule and the target.

Ideally, the computational method will be able to predict affinity before a compound is synthesized and hence in theory only one compound needs to be synthesized, saving enormous time and cost. The reality is that present computational methods are imperfect and provide, at best, only qualitatively accurate estimates of affinity. In practice it still takes several iterations of design, synthesis, and testing before an optimal drug is discovered. Computational methods have accelerated discovery by reducing the number of iterations required and have often provided novel structures.

Drug design with the help of computers may be used at any of the following stages of drug discovery:

1. hit identification using virtual screening (structure- or ligand-based design)
2. hit-to-lead optimization of affinity and selectivity (structure-based design, QSAR, etc.)
3. lead optimization of other pharmaceutical properties while maintaining affinity

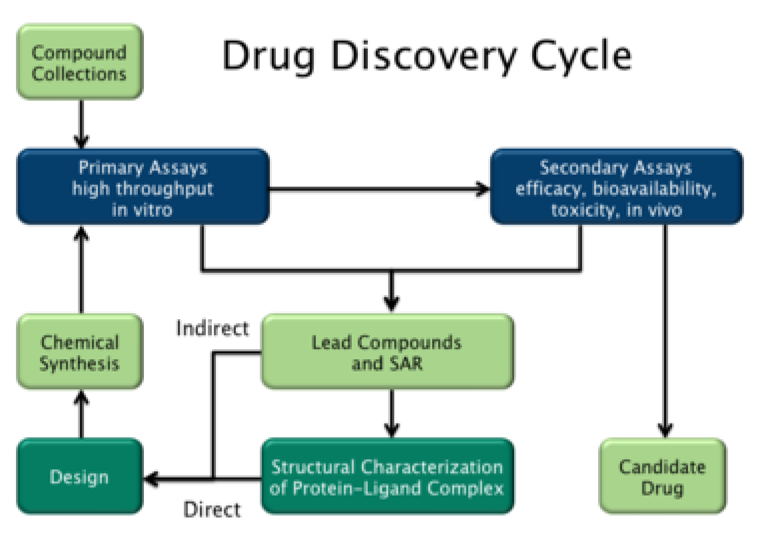


Flowchart of a Usual Clustering Analysis for Structure-Based Drug Design

In order to overcome the insufficient prediction of binding affinity calculated by recent scoring functions, the protein-ligand interaction and compound 3D structure information are used for analysis. For structure-based drug design, several post-screening analyses focusing on protein-ligand interaction have been developed for improving enrichment and effectively mining potential candidates:

- Consensus scoring
    - Selecting candidates by voting of multiple scoring functions
    - May lose the relationship between protein-ligand structural information and scoring criterion
- Cluster analysis
    - Represent and cluster candidates according to protein-ligand 3D information
    - Needs meaningful representation of protein-ligand interactions.

Types



Drug discovery cycle highlighting both ligand-based (indirect) and structure-based (direct) drug design strategies.

There are two major types of drug design. The first is referred to as **ligand-based drug design** and the second, **structure-based drug design**.

Ligand-based

Ligand-based drug design (or **indirect drug design**) relies on knowledge of other molecules that bind to the biological target of interest. These other molecules may be used to derive a pharmacophore model that defines the minimum necessary structural characteristics a molecule must possess in order to bind to the target.In other words, a model of the biological target may be built based on the knowledge of what binds to it, and this model in turn may be used to design new molecular entities that interact with the target. Alternatively, a quantitative structure-activity relationship (QSAR), in which a correlation between calculated properties of molecules and their experimentally determined biological activity, may be derived. These QSAR relationships in turn may be used to predict the activity of new analogs.

Structure-based drug design (or **direct drug design**) relies on knowledge of the three dimensional structure of the biological target obtained through methods such as x-ray crystallography or NMR spectroscopy.If an experimental structure of a target is not available, it may be possible to create a homology model of the target based on the experimental structure of a related protein. Using the structure of the biological target, candidate drugs that are predicted to bind with high affinity and selectivity to the target may be designed using interactive graphics and the intuition of a medicinal chemist. Alternatively various automated computational procedures may be used to suggest new drug candidates.

Current methods for structure-based drug design can be divided roughly into three main categories.The first method is identification of new ligands for a given receptor by searching large databases of 3D structures of small molecules to find those fitting the binding pocket of the receptor using fast approximate docking programs. This method is known as virtual screening. A second category is de novo design of new ligands. In this method, ligand molecules are built up within the constraints of the binding pocket by assembling small pieces in a stepwise manner. These pieces can be either individual atoms or molecular fragments. The key advantage of such a method is that novel structures, not contained in any database, can be suggested.[37][38][39] A third method is the optimization of known ligands by evaluating proposed analogs within the binding cavity.

Binding site identification is the first step in structure based design.
If the structure of the target or a sufficiently similar homolog is determined in the presence of a bound ligand, then the ligand should be observable in the structure in which case location of the binding site is trivial. However, there may be unoccupied allosteric binding sites that may be of interest. Furthermore, it may be that only apoprotein (protein without ligand) structures are available and the reliable identification of unoccupied sites that have the potential to bind ligands with high affinity is non-trivial. In brief, binding site identification usually relies on identification of concave surfaces on the protein that can accommodate drug sized molecules that also possess appropriate "hot spots" (hydrophobic surfaces, hydrogen bonding sites, etc.) that drive ligand binding.

Structure-based drug design attempts to use the structure of proteins as a basis for designing new ligands by applying the principles of molecular recognition. Selective high affinity binding to the target is generally desirable since it leads to more efficacious drugs with fewer side effects. Thus, one of the most important principles for designing or obtaining potential new ligands is to predict the binding affinity of a certain ligand to its target (and known antitargets) and use the predicted affinity as a criterion for selection.

One early general-purposed empirical scoring function to describe the binding energy of ligands to receptors was developed by Böhm.
This empirical scoring function took the form:

where:

- ΔG_0 – empirically derived offset that in part corresponds to the overall loss of translational and rotational entropy of the ligand upon binding.
- ΔG_{hb} – contribution from hydrogen bonding
- ΔG_{ionic} – contribution from ionic interactions
- ΔG_{lip} – contribution from lipophilic interactions where $|A_{lipo}|$ is surface area of lipophilic contact between the ligand and receptor
- ΔG_{rot} – entropy penalty due to freezing a rotatable in the ligand bond upon binding

A more general thermodynamic "master" equation is as follows:

where:

- desolvation – enthalpic penalty for removing the ligand from solvent
- motion – entropic penalty for reducing the degrees of freedom when a ligand binds to its receptor
- configuration – conformational strain energy required to put the ligand in its "active" conformation
- interaction – enthalpic gain for "resolvating" the ligand with its receptor

The basic idea is that the overall binding free energy can be decomposed into independent components that are known to be important for the binding process. Each component reflects a certain kind of free energy alteration during the binding process between a ligand and its target receptor. The Master Equation is the linear combination of these components. According to Gibbs free energy equation, the relation between dissociation equilibrium constant, K_d, and the components of free energy was built.

Various computational methods are used to estimate each of the components of the master equation. For example, the change in polar surface area upon ligand binding can be used to estimate the desolvation energy. The number of rotatable bonds frozen upon ligand binding is proportional to the motion term. The configurational or strain energy can be estimated using molecular mechanics calculations. Finally the interaction energy can be estimated using methods such as the change in non polar surface, statistically derived potentials of mean force, the number of hydrogen bonds formed, etc. In practice, the components of the master equation are fit to experimental data using multiple linear regression. This can be done with a diverse training set including many types of ligands and receptors to produce a less accurate but more general "global" model or a more restricted set of ligands and receptors to produce a more accurate but less general "local" model.

Medicinal chemistry

- Medicinal chemistry is a science whose roots are interlinked in the branches of chemistry and biology. Medicinal chemistry is a chemistry-based discipline, which involves aspects of biological, medical and pharmaceutical sciences. It is concerned with the invention, discovery, design, identification, preparation of biologically active compounds, the study of their metabolism, the interpretation of their mode of action at the molecular level and the construction of structure-activity relationships (SARs). It is an important branch of chemistry which is directly related to health care with other branches of chemistry like organic, inorganic, biochemistry and analytical chemistry.
- It also contributes in designing the drug molecule. Medicinal chemistry focuses on small organic molecules including synthetic organic chemistry, chemistry of natural products and computational chemistry in combination with chemical biology, enzymology and structural biology. It helps in the discovery and development of new therapeutic agents.
- It involves identification, systematic, thorough synthetic modification of new chemical entities to make them suitable for therapeutic use. It includes synthetic and computational aspects of the study of existing drugs and agents to develop a relation to their biological activities and properties i.e. understanding their structure-activity relationships (SAR).
- According to recommendations of International Union of Pure and Applied Chemistry (IUPAC) "it concerns with the discovery, the development, the identification and the interpretation of the mode of action of biologically active compounds at the molecular level". It involves-

1. **Synthesis**
2. **SAR**
3. **Receptor Interactions**
4. **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.

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,
- Medicinal chemistry also involves the isolation, characterization and synthesis of compounds that can be used in medicine for the prevention, treatment, and cure

of disease. Medicinal chemistry, thus, provides the chemical basis for the interdisciplinary field of therapeutics. It defines the chemical structure of any drug in terms of type of compound, functional groups, bonds, bond angle, aromatic behavior within etc. Medicinal Chemistry concern with the understanding of mechanisms of action of drugs. It attempts to establish relationship between structure and activity and helps to link biodynamic behavior with chemical reactivity and physical properties. It encompasses discovery, development, identification and interpretation of mode of action at the molecular level. It is also concerned with the study, identification, and synthesis of the metabolic products of drugs and related compounds.

HISTORY AND DEVELOPMENT CAN BE SUMMARIZED AS-

- 3500 BC - Sumerians reported use of opium
- 3000 BC - Chinese reported use of ephedra (Ma Huang)
- 1793 - Faureroy and Vauquehin established the Ecole Supurieure de Pharmacie i.e. first to
- incorporate chemistry into pharmacy curriculum.
- 1803 - Derosome isolated a salt from opium

- 1817 - Serturner demonstrated the alkaline nature of opium
- 1818 - Meissner proposed the term alkaloids
- 1820 - Isolation of morphine quinine and atropine
- 1842 - onwards general anesthetics were introduced, antiseptics like iodine and phenol were used in surgery
- 1853 - Hennery proposed the relationship between the functional groups, modifiers and their reactivities.
- 1875 - Carl buss isolated salisylic acid from *Spirea ulmaria*
- 1884 - Phenazone was synthesized, local anesthetic action of cocaine was reported
  1890 - Hoffman named acetyl salicylic acid as aspirin.
- 1892 - Benzocaine was obtained by structural modification of cocaine
- 1894 - Ehrlich reported lock and key theory
- 1899 - 1901- Meyer and overton related distribution coefficient with biological activity.
- 1910 - Barger and dale examined the response of various tissues to muscarine and nicotine 1911- Barbiturates were introduced as sedative.
- 1920 -1930 - Identification of vitamin deficiency diseases and elucidation of structure of various vitamins
- 1930 - Structure of steroid hormones
- 1926-1946 - Synthetic antimalarials like chloroquine were introduced as a substitute of quinine.
- 1935 - Domagk observed antibacterial activity of sulphonamide dye stuff (Prontocil red).
- 1940 - Florey and Heaton isolated benzyl penicillin
- 1944 -1949 - Isolation of antibiotics e.g. streptomycin chloramphenicol and tetracyclines
- 1950 -1960 - Semisynthetic corticosteroids like prednisolone and betamethasone were prepared.

HIGHLIGHTS OF SOME DISCOVERED DRUGS

- Morphine was isolated from opium by the German Pharmacist Sertuner in 1806, which marked the introduction of chemically pure active constituents into modem therapeutics .
- Mydriatics base atropine introduced by Me·n, Ge·ger and Hesse in 1833.
- Davy (1778-1829) introduced nitrous oxide (laughing gas) as an inhalation anaesthetic and this was followed by the first clinical experiments with ether in the surgical amphitheater. Perhaps the most beneficial medicinal innovation of the nineteenth century was the discovery of general anesthesia.
- Inthe two decades 1880-1900-Antipyrine introduced by Knorr (1883).

HIGHLIGHTS OF SOME DISCOVERED DRUGS

- Aspirin introduced by Dreser's in 1889.
- Barbital were innovated by Emil Fischer and Mering in 1903.
- Stolz synthesized the first hormone epinephrine (Adrenaline, 1904).
- Barger and Dale in 1909 made a fundamental study of the effect of chemical structure in the series of Sympathomimetic amines on the physiological effect of these compounds.

DRUG -RECEPTOR INTERACTION

Drug is a substance (chemical agent) that affects a biological system and is used in the prevention, diagnosis, treatment or cure of disease in man or other animals.

In India, as per drugs and cosmetics act 1940 definition of "drug" includes all medicines for internal or external use of human beings or animals and all substances intended to be used for or in the diagnosis, treatment, mitigation or prevention of any disease or disorder in human beings or animals, including preparations applied on human body for the purpose of repelling insects like mosquitoes.

The properties that makes a molecule to become a drug-like molecule are-

1. A molecule should be small enough to be transported throughout the body.

2. A molecule should be hydrophilic enough to dissolve in the blood stream.
3. . A molecule should be lipophillic enough to cross fat barriers within the body.
4. . A molecule should also contain polar groups to enable it to bind to a receptor, but not so many that it would be eliminated too quickly from the body through the urine.
5. A molecule should follow Lipinski's Rule of five which provides a good job of quantifying drug-like properties.

NATURE OF DRUG AND THEIR ADMISTRATION ROUTE TO DELIVERY

For lipophilic or hydrophilic drugs, the suitability of the route chosen also depends on the drug properties (both physical and chemical).

Some drugs (e.g., theophylline, phenobarbital , propofol) are not sufficiently aqueous soluble to be given by intravenous injection and if needed, these drug have to be formulated for better aqueous solubility (e.g., aminophylline, phenobarbital sodium) or given as an emulsion (e.g. propofol). On the other hand, most drugs are not sufficiently lipid soluble to be able to permeate the intact skin.

Therefore, only highly lipid soluble drugs such as nitroglycerin, fentanyl, scopolamine, nicotine and estrogen can be formulated for sustained release by transdermal delivery system. Organophosphate insecticides are also very lipid soluble and poisoning can occur through contact with contaminated clothes.

ROUTE OF ADMINISTRATION

- A route of administration in pharmacology and toxicology is the path by which a drug, fluid, poison, or other substance is taken into the body. - Most of the drugs can be administered by different routes.
- Drug- and patient-related factors determine the selection of routes for drug administration.

Factors for the choice of Drugs:-

- ✔ Physical and Chemical properties
- ✔ Site of action
- ✔ Rate and extent of absorption
- ✔ Rapidity of response
- ✔ Accuracy of dosage
- ✔ Condition of the patient

Definition

The ability of a chemical compound to elicit a pharmacological/ therapeutic effect is related to the influence of various physical and chemical (physicochemical) properties of the chemical substance on the bio molecule that it interacts with.

1)Physical Properties

Physical property of drug is responsible for its action .

2) Chemical Properties

The drug react extracellularly according to simple chemical reactions like neutralization, chelation, oxidation etc.

VARIOUS PHYSICO-CHEMICAL PROPERTIES ARE-

Solubility
Partition Coefficient
Hydrogen Bonding
Ionization
Complexation
Protein binding
Stereochemistry

SOLUBILITY:

- The solubility of a substance at a given temperature is defined as the concentration of the dissolved solute, which is in equilibrium with the solid solute.
- Solubility depends on the nature of solute and solvent as well as temperature , pH & pressure.
- The solubility of drug may be expressed in terms of its affinity/philicity or repulsion/phobicity for either an aqueous or organic solvent.

¯The atoms and molecules of all organic substances are held together by various types of bonds (e.g. hydrogen bond, dipole –dipole, ionic bond etc.)

¯These forces are involved in solubility because it is the solvent-solvent, solute-solute, solvent-solute interactions that governs solubility.

Methods to improve solubility of drugs

1) Structural modification (alter the structure of molecules)
2) Use of Co-solvents (Ethanol, sorbitol, PPG, PEG)
3) Employing surfactants
4) Complexation

Importance of solubility

1. Solubility concept is important to pharmacist because it govern the preparation of liquid dosage form and the drug must be in solution before it is absorbed by the body to produce the biological activity.
2. Drug must be in solution form to interact with receptors.

PARTITION COEFFICIENT

Hydrophobic character of a drug is crucial to how easily it crosses the cell membrane and may also important in receptor interactions. Hydrophobicity of a drug is measured experimentally by testing the drugs relative distribution in octanol water mixture. This relative distribution is known as partition coefficient.

Partition Coefficient P = Conc. of Drug in octanol]

[Conc. of drug in water]

FACTORS AFFECTING PARTITION CO-EFFICIENT

- pH
- Co solvents
- Surfactant
- Complexation
- Partition Co-efficient are difficult to measure in living system.
- They are usually determined in vitro 1-octanol as a lipid phase and phosphate buffer of pH 7.4 as the aqueous phase.
- 1-octanol as a lipid phase because,
  - It has polar and nonpolar region.
  - P o/w is easy to measure.
  - P o/w often correlates with many biological properties.
  - It can be predicted using computational mode.

Hydrpogen bond

- The ***hydrogen bond*** is a special dipole-dipole interaction between the hydrogen atom in a polar bond such as N-H, O-H or F-H & electronegative atom O, N, F atom.
- Dipoles result from unequal sharing of electrons between atoms within a covalent bond.

These are weak bonds and denoted as dotted lines. O-H…….O, HN-H…….O,

- The compounds that are capable, of forming hydrogen bonding is only soluble in water.
- hydrogen bonding is classified into 2 types:

1. Intermolecular
2. Intramolecular

1) INTER MOLECULAR HYDROGEN BONDING

It is occur between two or more than two molecules of the same or different compound.

Due to this increase the boiling point of the compound & increase the molecular weight of compound hence more energy is required to dissociate the molecular for vaporization.

2) INTRA MOLECULAR HYDROGEN BONDING

—H- bonding occurs within two atoms of the same molecules.

—This type of bonding is known as chelation and frequently occurs in organic compounds.

—Sometimes h-bond develop six or five member rings

—Due to decrease the boiling point.

Effect of H-bonding

All physical properties affected by H-bonding,

1. Boiling and Melting point
2. Water solubility
3. Strength of acids
4. Spectroscopic properties
5. On surface tension and viscosity
6. Biological products
7. Drug-receptor interaction

CHELATION /COMPLEXATION

¯Complex of drug molecules can’t cross the natural membrane barriers, they render the drug biological in effectively.

¯The rate of absorption is proportional to the concentration of the free drug molecules i.e. the diffusion of drug.

¯Due to reversibility of the Complexation, equilibrium between free drug and drug complex.

Drug + complexing agent Drug complex

¯Complexation reduce the rate of absorption of drug but not affect the availability of drug.

IONIZATION OF DRUG

- The rate of drug absorption is directly proportional to the concentration of the drug at absorbable form but not the concentration of the drug at the absorption site.
- Ionization form imparts good water solubility to the drug which is required of binding of drug and receptor interaction.
- Unionized form helps the drug to cross the cell membrane.
- Eg; Barbituric acid is inactive because it is strong acid.

while, 5,5 disubstituted Barbituric acid has CNS depressant action because it is weak acid.

PROTEIN BINDING

- The reversible binding of protein with non-specific and non- functional site on the body protein without showing any biological effect is called as protein binding.

Protein + drug ⇌ Protein-drug complex

- Depending on the whether the drug is a weak or strong acid, base or is neutral, it can bind to single blood proteins to multiple proteins (sereum albumin, acid-gycoprotien or lipoproteins).The most significant protein involved in the binding of drug is albumin, which comprises more than half of blood proteins.
- protein binding values are normally given as the percentage of total plasma concentration of drug that is bound to all plasma protein.

STEREOCHEMISTRY OF DRUGS

- Stereochemistry involve the study of three dimensional nature of molecules. It is study of the chiral molecules.
- Stereochemistry plays a major role in the pharmacological properties because;

1. Any change in stereo specificity of the drug will affect its pharmacological activity.
2. The isomeric pairs have different physical properties (log p, pKa etc.) and thus differ in pharmacological activity.

- The isomer which have same bond connectivity but different arrangement of groups or atoms in the space are termed stereoisomer.

CONFORMATIONAL ISOMERS

- Different arrangement of atoms that can be converted into one another by rotation about single bonds are called conformations.

¯Rotation about bonds allows inter conversion of conformers.

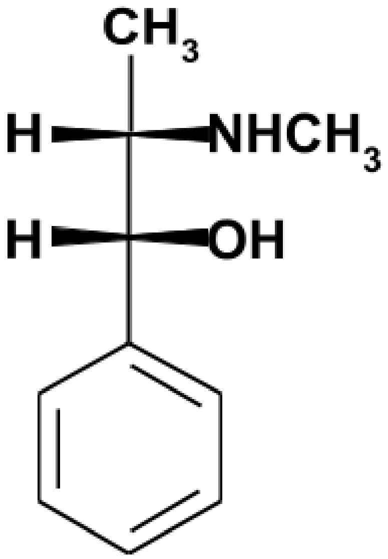
¯**OPTICAL ISOMERS**

¯Stereochemistry, enantiomers, symmetry and chirality are important concept in therapeutic and toxic effect of drug. ¯A chiral compound containing one asymmetric centre has two enantiomers. Although each enantiomer has identical chemical & physical properties, they may have different physiological activity like interaction with receptor, metabolism & protein binding.

¯A optical isomers in biological action is due to one isomer being able to achieve a three point attachment with its receptor molecule while its enantiomer would only be able to achieve a two point attachment with the same molecule

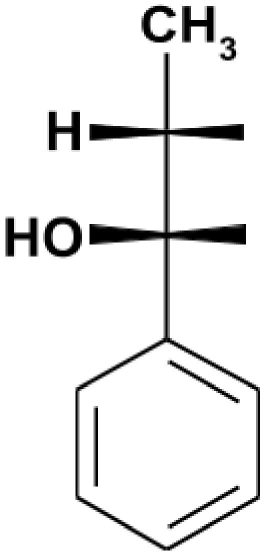
E.g. Ephedrine & Psuedoephedrine

MP = 37-39



Ephedrine

(*Erythro*)



MP = 118-120

1 gram/200 mL

Pseudoephedrine

1 gram/20 mL

(*Threo*)

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