Semester-IV

Sub Name-medicinal chemistry-I (sub code-BP-402T)

Objective

Medicinal Chemistry

· Introduction, History and development of medicinal chemistry.

Physicochemical properties in relation to biological action

· Ionization, Solubility, Partition Coefficient, Hydrogen bonding, Protein binding,

Chelation, Bioisosterism , Optical and Geometrical isomerism.

Drug metabolism

· Drug metabolism principles- Phase I and Phase II.

· Factors affecting drug metabolism including stereo chemical aspects.

Introduction

Medicinal chemistry and pharmaceutical chemistry are disciplines at the intersection of chemistry, especially synthetic organic chemistry, and pharmacology and various other biological specialties, where they are involved with design, chemical synthesis and development for market of pharmaceutical agents, or bio-active molecules (drugs).

Compounds used as medicines are most often organic compounds, which are often divided into the broad classes of small organic molecules (e.g., atorvastatin, fluticasone, clopidogrel) and "biologics" (infliximab, erythropoietin, insulin glargine), the latter of which are most often medicinal preparations of proteins (natural and recombinant antibodies, hormones, etc.). Inorganic and organometallic compounds are also useful as drugs (e.g., lithium and platinum-based agents such as lithium carbonate and cisplatin as well as gallium).

In particular, medicinal chemistry in its most common practice—focusing on small organic molecules—encompasses synthetic organic chemistry and aspects of natural products and computational chemistry in close combination with chemical biology, enzymology and structural biology, together aiming at the discovery and development of new therapeutic agents. Practically speaking, it involves chemical aspects of identification, and then systematic, thorough synthetic alteration 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 in development in relation to their bioactivities (biological activities and properties), i.e., understanding their structure-activity relationships (SAR). Pharmaceutical chemistry is focused on quality aspects of medicines and aims to assure fitness for purpose of medicinal products.

At the biological interface, medicinal chemistry combines to form a set of highly interdisciplinary sciences, setting its organic, physical, and computational emphases alongside biological areas such as biochemistry, molecular biology, pharmacognosy and pharmacology, toxicology and veterinary and human medicine; these, with project management, statistics, and pharmaceutical business practices, systematically

oversee altering identified chemical agents such that after pharmaceutical formulation, they are safe and efficacious, and therefore suitable for use in treatment of disease.

History

Medicinal chemistry's roots can be found in the fertile mix of ancient folk medicine and early natural product cizemistn;, and hence its name. As appreciation for the links between chemical structure and observed biological activity grew, medicinal chemistry began to emerge about 150 years ago as a distinct discipline intending to explore these relationships via chemical modification and structural mimicry of nature's materials,)particularly with an eye toward enhancing the efficacy of substances thought to be of therapeutic value.

Just as in all fields of science, the history of medicinal chemistry is comprised of the ideas, knowledge, md available tools that have advanced contemnor knowledge. The spectacular advances in medicinal chemistry over the years are no exception. Burger3 stated that" the great advances of medicinal chemistry have been achieved by two types of investigators: those with the genius of prophetic logic, who have opened a new field by interpreting correctly a few well-placed experiments, whether they pertained to the design or the mechanism of action of drugs; and those who have varied patiently the chemical structures of physiologically active compounds until a useful drug could be evolved as a tool in medicine.

The nineteenth century age of innovation and chemistry the nineteenth century saw a great expansion 111 the knowledge of chemistry, which greatly extended the herbal ph, llmacopeia that had preViously been established. Building on the work of Lavoisier, chemists throughout Europe refined and extended the techniques of chemical analysis. The synthesis of acetic acid by Kolbe in 1845 and of methane by Berthelot in 1856 set the stage for organic chemically. The emphasis was shifted from finding new medicaments from the vast world of plants to the finding of active ingredients that accowlted for their pharmacologic properties. The isolation of morphine by Sertiirner in 1803, of emetine from ipecacuanha by Pelletier in 1816, and his purification of caffeine, quinine, and colchicines in 1820 all contributed to the increased use of "pure" substances as therapeutic agents. The nineteenth century also contributed to the use of digitalis by William Withering, the English physician and botanist, for the treatment of dropsy. Niemen isolated cocaine in 1860 and the active ingredient, Physotigmine, from the Calabar bean in 1864.

The twentieth century and the pharmaceutical industry Diseases of protozoal and spirochetes origin responded to synthetic chemotherapeutic agents. Interest in synthetic chemicals that could inhibit the rapid reproduction of pathogenic bacteria and enable the host organism to cope with invasive bacteria was dramatically increased when Domagk reported that the red dyestuff 2,-!-diaminoazobenzene-4' -sulfonamide (Prontosil) dramatically cured dangerous, systemic Cr,ll11-positive bacterial infections in man and animals. The observation by Woods and Fildes in 1940 that the bacteriostatic action of sulfon,lmide-like drugs was antagonized by p-aminobenzoic acid, was one of the early examples in which a balance of stimulatory and inhibitory properties depended on the structural analogies of chemicals.

Drug Metabolism

The human body is an example of an exquisitely designed, extremely complex machine that functions day-in and day-out to allow for survival of the organism in response to a never-ending onslaught of external challenges. When one considers the enormous variety of environmental stressors to which the body is continually subjected, it is not surprising to anticipate the existence of a multitude of checks and balances associated with its physiological and biochemical systems. Humans are exposed throughout their lifetime to a large variety of drugs and nonessential exogenous (foreign) compolmds (collectively termed "xenobiotics") that may pose health hazards. Most drugs and other xenobiotics are metabolized by enzymes normally associated with the metabolism of endogenous constituents (e.g., steroids and biogenic amines). The liver is the major site of drug metabolism, although other xenobiotic-metabolizing enzymes are fowl in nervous tissue, kidney, lung, plasma, and the gastrointestinal tract. Among the more active extra hepatic tissues capable of metabolizing drugs are the intestinal mucosa, kidney, and lung. The ability of the liver and extra hepatic tissues to metabolize substances to either pharmacologically inactive or bioactive metabolites before reaching systemic blood levels is termed" first-pass metabolism.

Phase I reactions (Biotransformations)

This type includes oxidation, hydroxylation, reduction, and hydrolysis. In these enzymatic reactions, a new functional group is introduced into the substrate molecule, an existing functional group is modified, or a functional group or acceptor site for Phase II transfer reactions is exposed, making the xenobiotic more polar and, therefore, more readily excreted.

Phase II reactions (Conjugation)

These reactions are enzymatic syntheses whereby a functional group, such as alcohol, phenol, or amine, is masked by the addition of a new group, such as acetyl, sulfate, glucuronic acid, or certain amino acids, which further increases the polarity of the drug or xenobiotic. Most substances undergo both Phase I and Phase II reactions sequentially.

Physicochemical properties in relation to biological action

- ✓ **Ionization**

  Ionization or ionisation is the process by which an atom or a molecule acquires a negative or positive charge by gaining or losing electrons, often in conjunction with other chemical changes. The resulting electrically charged atom or molecule is called an ion. Ionization can result from the loss of an electron after collisions with subatomic particles, collisions with other atoms, molecules and ions, or through the interaction with electromagnetic radiation. Heterotypic bond cleavage and heterolysis substitution reactions can result in the formation of ion pairs. Ionization can occur through radioactive decay by the internal conversion process, in which an excited nucleus transfers its energy to one of the inner-shell electrons causing it to be ejected.

Production of ions

Negatively charged ions are produced when a free electron collides with an atom and is subsequently trapped inside the electric potential barrier, releasing any excess energy. The process is known as electron capture ionization.

Positively charged ions are produced by transferring an amount of energy to a bound electron in a collision with charged particles (e.g. ions, electrons or positrons) or with photons. The threshold amount of the required energy is known as ionization potential. The study of such collisions is of fundamental importance with regard to the few-body problem, which is one of the major unsolved problems in physics. Kinematic ally complete experiments,[1] i.e. experiments in which the complete momentum vector of all collision fragments (the scattered projectile, the recoiling target-ion, and the ejected electron) are determined, have contributed to major advances in the theoretical understanding of the few-body problem in recent years.

Adiabatic ionization is a form of ionization in which an electron is removed from or added to an atom or molecule in its lowest energy state to form an ion in its lowest energy state.

The Townsend discharge is a good example of the creation of positive ions and free electrons due to ion impact. It is a cascade reaction involving electrons in a region with a sufficiently high electric field in a gaseous medium that can be ionized, such as air. Following an original ionization event, due to such as ionizing radiation, the positive ion drifts towards the cathode, while the free electron drifts towards the anode of the device. If the electric field is strong enough, the free electron gains sufficient energy to liberate a further electron when it next collides with another molecule. The two free electrons then travel towards the anode and gain sufficient energy from the electric field to cause impact ionization when the next collisions occur; and so on. This is effectively a chain reaction of electron generation, and is dependent on the free electrons gaining sufficient energy between collisions to sustain the avalanche.

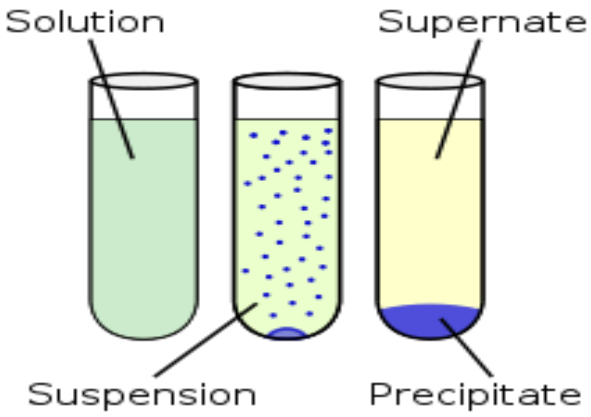
Ionization efficiency is the ratio of the number of ions formed to the number of electrons or photons used.

Types of ionization

There are many **types** of **ionization** methods are used in mass spectrometry methods. The classic methods that most chemists are familiar with are electron impact (EI) and Fast Atom Bombardment (FAB). These techniques are not used much with modern mass spectrometry except EI for environmental work using GC-MS.

Solubility

Solubility is the property of a solid, liquid or gaseous chemical substance called *solute* to dissolve in a solid, liquid or gaseous solvent. The solubility of a substance fundamentally depends on the physical and chemical properties of the solute and solvent as well as on temperature, pressure and presence of other chemicals (including changes to the pH) of the solution. The extent of the solubility of a substance in a specific solvent is measured as the saturation concentration, where adding more solute does not increase the concentration of the solution and begins to precipitate the excess amount of solute.



Factors affecting solubility

Temperature

The solubility of a given solute in a given solvent typically depends on temperature. Depending on the nature of the solute the solubility may increase or decrease with temperature. For most solids and liquids, their solubility increases with temperature. In liquid water at high temperatures, (e.g. that approaching the critical temperature), the solubility of ionic solutes tends to decrease due to the change of properties and structure of liquid water; the lower dielectric constant results in a less polar solvent.

Gaseous solutes exhibit more complex behavior with temperature. As the temperature is raised, gases usually become less soluble in water (to minimum, which is below 120 °C for most permanent gases), but more soluble in organic solvents.

Pressure

For condensed phases (solids and liquids), the pressure dependence of solubility is typically weak and usually neglected in practice. The pressure dependence of solubility does occasionally have practical significance. For example, precipitation fouling of oil fields and wells by calcium sulfate (which decreases its solubility with decreasing pressure) can result in decreased productivity with time.

Solubility of gases

Henry's law is used to quantify the solubility of gases in solvents. The solubility of a gas in a solvent is directly proportional to the partial pressure of that gas above the solvent. The solubility of gases is sometimes also quantified using Bunsen solubility coefficient.

In the presence of small bubbles, the solubility of the gas does not depend on the bubble radius in any other way than through the effect of the radius on pressure (i.e. the solubility of gas in the liquid in contact with small bubbles is increased due to pressure increase by $\Delta p = 2\gamma/r$; see Young–Laplace equation).

Polarity

A popular aphorism used for predicting solubility is "*like dissolves like*" also expressed in the *Latin* language as "*Similia similibus solventur*". This statement indicates that a solute will dissolve best in a solvent that has a similar chemical structure to itself. This view is simplistic, but it is a useful rule of thumb. The overall salvation capacity of a solvent depends primarily on its polarity. For example, a very polar (hydrophilic) solute such as urea is very soluble in highly polar water, less soluble in fairly polar methanol, and practically insoluble in non-polar solvents such as benzene. In contrast, a non-polar or lipophilic solute such as naphthalene is insoluble in water, fairly soluble in methanol, and highly soluble in non-polar benzene.

Rate of dissolution

Dissolution is not an instantaneous process. The rate of solubilization (in kg/s) is related to the solubility product and the surface area of the material. The speed at which a solid dissolves may depend on its crystalline or lack thereof in the case of amorphous solids and the surface area (crystallite size) and the presence of polymorphism. Many practical systems illustrate this effect, for example in designing methods for controlled drug delivery. In some cases, solubility equilibrium can take a long time to establish (hours, days, months, or many years; depending on the nature of the solute and other factors).

Applications

Solubility is of fundamental importance in a large number of scientific disciplines and practical applications, ranging from ore processing and nuclear reprocessing to the use of medicines, and the transport of pollutants.

Solubility is often said to be one of the "characteristic properties of a substance", which means that solubility is commonly used to describe the substance, to indicate a substance's polarity, to help to distinguish it from other substances, and as a guide to applications of the substance. For example, indigo is described as "insoluble in water, alcohol, or ether but soluble in chloroform, nitrobenzene, or concentrated sulfuric acid.

Solubility of a substance is useful when separating mixtures. For example, a mixture of salt (sodium chloride) and silica may be separated by dissolving the salt in water, and filtering off the undissolved silica. The synthesis of chemical compounds, by the milligram in a laboratory, or by the ton in industry, both make use of the relative solubilities of the desired product, as well as unreacted starting materials, byproducts, and side products to achieve separation.

Another example of this is the synthesis of benzoic acid from phenyl magnesium bromide and dry ice. Benzoic acid is more soluble in an organic solvent such as dichloromethane or diethyl ether, and when shaken with this organic solvent in a separatory funnel, will preferentially dissolve in the organic layer. The other reaction products, including the magnesium bromide, will remain in the aqueous layer, clearly showing that separation based on solubility is achieved. This process, known as liquid–liquid extraction, is an important technique in synthetic chemistry. Recycling is used to ensure maximum extraction.

Partition Coefficient

Partition coefficient (*P*) or distribution coefficient (*D*) is the ratio of concentrations of a compound in a mixture of two immiscible solvents at equilibrium. This ratio is therefore a comparison of the solubilities of the solute in these two liquids. The partition coefficient generally refers to the concentration ratio of un-ionized species of compound, whereas the distribution coefficient refers to the concentration ratio of all species of the compound (ionized plus un-ionized).

Nomenclature

Partition coefficient and log P

The partition coefficient, abbreviated *P*, is defined as a particular ratio of the concentrations of a solute between the two solvents (a biphase of liquid phases), specifically for un-ionized solutes, and the logarithm of the ratio is thus log *P*. When one of the solvents is water and the other is a non-polar solvent, then the log *P* value is a measure of lipophilicity or hydrophobicity. The defined precedent is for the lipophilic and hydrophilic phase types to always be in the numerator and denominator respectively; for example, in a biphasic system of *n*-octanol (hereafter simply "octanol") and water.

Distribution coefficient and log D

The distribution coefficient, log *D*, is the ratio of the sum of the concentrations of all forms of the compound (ionized plus un-ionized) in each of the two phases, one essentially always aqueous; as such, it depends on the pH of the aqueous phase, and log *D* = log *P* for non-ionizable compounds at any pH. For measurements of distribution coefficients, the pH of the aqueous phase is buffered to a specific value such that the pH is not significantly perturbed by the introduction of the compound. The value of each log *D* is then determined as the logarithm of a ratio—of the sum of the experimentally measured concentrations of the solute's various forms in one solvent, to the sum of such concentrations of its forms in the other solvent.

Application

Pharmacology

A drug's distribution coefficient strongly affects how easily the drug can reach its intended target in the body, how strong an effect it will have once it reaches its target, and how long it will remain in the body in an active form. Hence, the log *P* of a molecule is one criterion used in decision-making by medicinal chemists in pre-clinical drug discovery, for example, in the assessment of druglikeness of drug candidates.

Pharmacokinetics

In the context of pharmacokinetics (what the body does to a drug), the distribution coefficient has a strong influence on ADME properties of the drug. Hence the hydrophobicity of a compound (as measured by its distribution coefficient) is a major determinant of how drug-like it is. More specifically, for a drug to be orally absorbed, it normally must first pass through lipid bilayers in the intestinal epithelium (a process known as transcellular transport). For efficient transport, the drug must be hydrophobic enough to partition into the lipid bilayer, but not so hydrophobic, that once it is in the bilayer, it will not partition out again.

Pharmacodynamics

In the context of pharmacodynamics (what a drug does to the body), the hydrophobic effect is the major driving force for the binding of drugs to their receptor targets. On the other hand, hydrophobic drugs tend to be more toxic because they, in general, are retained longer, have a wider distribution within the body (e.g., intracellular), are somewhat less selective in their binding to proteins, and finally are often extensively metabolized. In some cases the metabolites may be chemically reactive. Hence it is advisable to make the drug as hydrophilic as possible while it still retains adequate binding affinity to the therapeutic protein target. For cases where a drug reaches its target locations through passive mechanisms (i.e., diffusion through membranes), the ideal distribution coefficient for the drug is typically intermediate in value (neither too lipophilic, nor too hydrophilic); in cases where molecules reach their targets otherwise, no such generalization applies.

Environmental science

The hydrophobicity of a compound can give scientists an indication of how easily a compound might be taken up in groundwater to pollute waterways, and its toxicity to animals and aquatic life. Partition coefficient can also be used to predict the mobility of radionuclides in groundwater. In the field of hydrogeology, the octanol–water partition coefficient K_{ow} is used to predict and model the migration of dissolved hydrophobic organic compounds in soil and groundwater.

Agrochemical research

Hydrophobic insecticides and herbicides tend to be more active. Hydrophobic agrochemicals in general have longer half-lives and therefore display increased risk of adverse environmental impact.

Metallurgy

In metallurgy, the partition coefficient is an important factor in determining how different impurities are distributed between molten and solidified metal. It is a critical parameter for purification using zone melting, and determines how effectively an impurity can be removed using directional solidification, described by the Scheil equation.

Hydrogen bonding

A hydrogen bond (often informally abbreviated H-bond) is a partial intermolecular bonding interaction between a lone pair on an electron rich donor atom, particularly the second-row elements nitrogen (N), oxygen (O), or fluorine (F), and the antibonding orbital of a bond between hydrogen (H) and a more electronegative atom or group. Such an interacting system is

generally denoted Dn–H···Ac, where the solid line denotes a polar covalent bond, and the dotted or dashed line indicates the hydrogen bond. The use of three centered dots for the hydrogen bond is specifically recommended by the IUPAC. While hydrogen bonding has both covalent and electrostatic contributions, and the degrees to which they contribute are currently debated, the present evidence strongly implies that the primary contribution is covalent.

Types of Hydrogen Bonding

There are two types of hydrogen bonding

1. Intermolecular Hydrogen Bonding: This occurs when the hydrogen bonding is between H-atom of one molecule and an atom of the electronegative element of another molecule. For example. (i) Hydrogen bond between the molecules of hydrogen fluoride. (ii) Hydrogen bond in alcohol or water molecules.
2. Intramolecular hydrogen bonds are those which occur within one single molecule. This occurs when two functional groups of a molecule can form hydrogen bonds with each other.

Protein binding

Plasma protein binding refers to the degree to which medications attach to proteins within the blood. A drug's efficiency may be affected by the degree to which it binds. The less bound a drug is, the more efficiently it can traverse cell membranes or diffuse. Common blood proteins that drugs bind to are human serum albumin, lipoprotein, glycoprotein, and α, β, and γ globulins.

Binding (Drug Distribution)

A drug in blood exists in two forms: bound and unbound. Depending on a specific drug's affinity for plasma protein, a proportion of the drug may become bound to plasma proteins, with the remainder being unbound. If the protein binding is reversible, then a chemical equilibrium will exist between the bound and unbound states, such that:

Protein + drug ⇌ Protein-drug complex

Notably, it is the unbound fraction which exhibits pharmacologic effects. It is also the fraction that may be metabolized and/or excreted. For example, the "fraction bound" of the anticoagulant warfarin is 97%. This means that of the amount of warfarin in the blood, 97% is bound to plasma proteins. The remaining 3% (the fraction unbound) is the fraction that is actually active and may be excreted.

Protein binding can influence the drug's biological half-life. The bound portion may act as a reservoir or depot from which the drug is slowly released as the unbound form. Since the unbound form is being metabolized and/or excreted from the body, the bound fraction will be released in order to maintain equilibrium.

Since albumin is alkalotic, acidic and neutral drugs will primarily bind to albumin. If albumin becomes saturated, then these drugs will bind to lipoprotein. Basic drugs will bind to the acidic alpha-1 acid glycoprotein. This is significant because various medical conditions may affect the levels of albumin, alpha-1 acid glycoprotein, and lipoproteins.

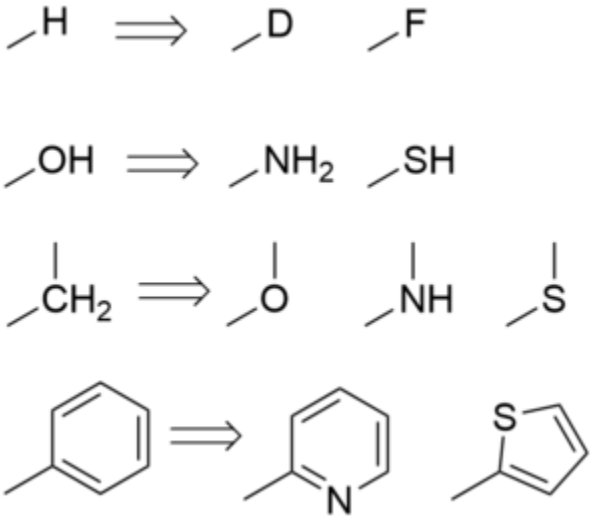
Chelation

Chelation is a type of bonding of ions and molecules to metal ions. It involves the formation or presence of two or more separate coordinate bonds between a polydentate (multiple bonded) ligand and a single central atom. These ligands are called chelants, chelators, chelating agents, or sequestering agents. They are usually organic compounds. Chelation is useful in applications such as providing nutritional supplements, in Chelation therapy to remove toxic metals from the body, as contrast agents in MRI scanning, in manufacturing using homogeneous catalysts, in chemical water treatment to assist in the removal of metals, and in fertilizers.

Bioisosterism

In medicinal chemistry, Bioisosterism are chemical substituents or groups with similar physical or chemical properties which produce broadly similar biological properties to another chemical compound. In drug design, the purpose of exchanging one Bioisosterism for another is to enhance the desired biological or physical properties of a compound without making significant changes in chemical structure. The main use of this term and its techniques are related to pharmaceutical sciences. Bioisosterism is used to reduce toxicity, change bioavailability, or modify the activity of the lead compound, and may alter the metabolism of the lead.

Classical Bioisosterism



Classical Bioisosterism was originally formulated by James Moir and refined by Irving Langmuir as a response to the observation that different atoms with the same valence electron structure had similar biological properties.

For example, the replacement of a hydrogen atom with a fluorine atom at a site of metabolic oxidation in a drug candidate may prevent such metabolism from taking place. Because the fluorine atom is similar in size to the hydrogen atom the overall topology of the molecule is not significantly affected, leaving the desired biological activity unaffected. However, with a blocked pathway for metabolism, the drug candidate may have a longer half-life.

- Procainamide, an amide, has a longer duration of action than Procaine, an ester, because of the isosteric replacement of the ester oxygen with a nitrogen atom. Procainamide is a

classical Bioisosterism because the valence electron structure of a disubstituted oxygen atom is the same as a trisubstituted nitrogen atom, as Langmuir showed.

Non-classical Bioisosterism

Non-classical Bioisosterism may differ in a multitude of ways from classical Bioisosterism, but retain the focus on providing similar steric and electronic profile to the original functional group. Whereas classical Bioisosterism commonly conserve much of the same structural properties, nonclassical Bioisosterism are much more dependent on the specific binding needs of the ligand in question and may substitute a linear functional group for a cyclic moiety, an alkyl group for a complex heteroatom moiety, or other changes that go far beyond a simple atom-for-atom switch.

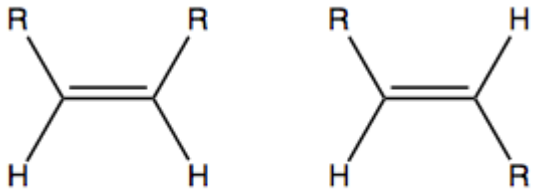
For example, a chlorine -Cl group may often be replaced by a trifluoromethyl $-CF_3$ group, or by a cyano -C≡N group, but depending on the particular molecule used the substitution may result in little change in activity, or either increase or decrease affinity or efficacy depending on what factors are important for ligand binding to the target protein. Another example is aromatic rings, a phenyl $-C_6H_5$ ring can often be replaced by a different aromatic ring such as thiophene or naphthalene which may improve efficacy, change specificity of binding, or reduce metabolically labile sites on the molecule, resulting in better pharmacokinetic properties.

Optical isomerism

Optical isomers are two compounds which contain the same number and kinds of atoms, and bonds (i.e., the connectivity between atoms is the same), and different spatial arrangements of the atoms, but which have non-super imposable mirror images. Each non-super imposable mirror image structure is called an enatiomer.

Geometrical Isomerism

Geometric isomers are chemical species with the same type and quantity of atoms as another species, yet having a different geometric structure. Atoms or groups exhibit different spatial arrangements on either side of a chemical bond or ring structure.



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Learning Outcomes

- Understand the Introduction, History ,Physicochemical properties & Drug metabolism of Medicinal chemistry.