

BP402T. MEDICINAL CHEMISTRY – I (Theory)

UNIT – ONE



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UNIT- I 10 Hours

Introduction to Medicinal Chemistry

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 TO MEDICINAL CHEMISTRY

The subject of medicinal chemistry explains the design and production of compounds that can be used for the prevention, treatment or cure of human and animal diseases. Medicinal chemistry includes the study of already existing drugs, of their biological properties and their structure activity relationships.

Medicinal chemistry was defined by IUPAC specified commission as, "it concerns the discovery, the development, the identification and the interpretation of the mode of action of biologically active compounds at the molecular level".

Medicinal chemistry covers the following stages (i) In the first stage new active substances or drugs are identified and prepared from

natural sources, organic chemical reactions or biotechnological processes. They are known as lead molecules.

(ii) The second stage is optimization of lead structure to improve potency, selectivity

and lessen toxicity.

(iii) Third stage is development stage involves optimization of synthetic route for bulk production and modification of pharmacokinetic and pharmaceutical properties of active substance to render it chemically useful.

Medicinal chemistry is the application of chemical research techniques to the synthesis of pharmaceuticals. During the early stages of medicinal chemistry development, scientists were primarily concerned with the isolation of medicinal agents found in plants. Today, scientists in this field are also equally concerned with the creation of new synthetic drug compounds. Medicinal chemistry is almost always geared towards drug discovery and development.

Medicinal chemists apply their chemistry training to the process of synthesizing new pharmaceuticals. They also work on improving the process by which other pharmaceuticals are made. Most chemists work with a team of scientists from different disciplines, including biologists, toxicologists, pharmacologists, theoretical chemists, microbiologists, and biopharmacists. Together this team uses sophisticated analytical techniques to synthesize and test new drug products and to develop the most cost-effective and environmentally friendly means of production.

HISTORY AND DEVELOPMENT OF MEDICINAL CHEMISTRY

8000 BC: Prehistoric medicine

It is difficult to imagine anything other than modern medical treatments but for thousands of years humans have become ill and for the same amount of time people have tried to cure them. Our ideas about medicines in prehistoric times come from archaeologists who have excavated and explored ancient sites. Their findings reveal a very different world to the one we experience today. Cave paintings and symbolic artefacts found by archaeologists suggest the earliest humans believed in spirits and supernatural forces. One form of primitive surgery seems quite shocking. Ancient skulls have been found with a hole bored into them. This appears to have been a deliberate operation and carried out whilst the person was still alive. We can only speculate as to the reason for this operation, called trepanning, but it may have been to allow the evil spirits to leave a sick person.

2000 BC: Egyptian medicines

The ancient Egyptians built pyramids to bury their Pharaohs and worshipped gods who ruled every aspect of their lives. The goddess Sekhmet was believed to cause or cure diseases and priests played a large part in Egyptian medicine. Archaeologists have found documents, written on a type of paper called papyrus, that describe medical techniques similar to those used today. The Egyptians used compression on a wound to stop bleeding and had specialists in obstetrics and gynecology who were the forerunners of modern midwives.

Their Pharmacist prepared prescriptions of ointments, lotions, inhalers and pills by processing plant materials that were used to treat specific illnesses. Records show that they used many preparations including opium, cannabis, linseed oil and senna. Many modern drugs have originated from the study and isolation of active ingredients from plants with healing properties.

450 BC to 300 AD: Greeks and Romans

Greece was home to one of the earliest civilizations. Writing, mathematics, philosophy and the arts all flourished. The Greeks believed in many different gods but they also tried to understand their world in a much more scientific way.

Possibly the most famous name in medicine belongs to the Greek philosopher Hippocrates. He is seen as the father of modern medicine and gives his name to the hippocratic oath that doctors take.

The Romans realized that there was a link between dirt and disease. To improve public health, they built aqueducts to supply clean drinking water and sewers to remove wastes safely. Improved personal hygiene helped to reduce disease and Roman baths were places to socialize as well as stay clean.

500 - 1400 AD: The Middle Ages

The fall of the Roman Empire meant that many of their public hygiene practices were soon lost. The middle ages in Europe saw most people without access to clean drinking water, regular bathing or a sewage system. This meant that health conditions were often worse than during the Roman occupation of earlier centuries. Most people were farmers and food was not as plentiful as today. Starvation and disease were common.

Medicine in the middle ages was dominated by religion. Sickness was believed to be a punishment from God for sins committed and the only way to cure someone was to pray for their forgiveness. Doctors in the middle ages were usually priests or other religious scholars. Hospitals often sprang up in monasteries and other religious establishments. The patients were given food and comforted by religious nursing staff but little else was done to cure their illness.

Traditional cures, using herbal remedies and potions were seen as witchcraft and medicine. Schools and universities began to educate wealthy individuals in religion, the arts, law and medicine. Generally men, and occasionally a few women, were trained and allowed to become physicians. As universities developed, more and more came from a non-religious background and eventually it was not necessary to be a cleric to practice medicine.

Surgery was a crude practice during the middle ages but operations such as amputations, setting broken bones, replacing dislocations and binding wounds were relatively common. Opium was sometimes used as an anesthetic while wounds were cleaned with wine to prevent infections. During the middle ages, the only treatments were superstitious remedies, prayer, herbal medicines and recipes for clearing the air of miasma or poison. The plague was considered to be a punishment from God and so public health was not considered to be important.

700 - 1500 AD: Arabic medicines

For many centuries after the fall of the Roman Empire, the Arabic world was the centre of scientific and medical knowledge. Texts from Greece and Rome were translated into Arabic and studied by Islamic scholars. They developed and refined Hippocrates's theories and Islamic physicians began to use the regulation of diet, exercise and the prescription of medicinal herbs in the treatment of their patients. Arabic pharmacists became skilled in the formulation of medicines from plants and minerals. Even though they did not know about microbes, they used alcohol to clean wounds which healed better and did not become infected.

Records show that Arabic doctors performed many different surgical operations including the removal of varicose veins, kidney stones and the replacement of dislocated limbs. They used sponges soaked in narcotic drugs which were placed over the patient's nose as early anesthetics.

1700 - 1900: Eighteenth and Nineteenth centuries

The industrial revolution of the eighteenth and nineteenth centuries saw a massive change in the way people lived and how this affected their health. People moved from small villages and an agricultural lifestyle to live in towns and cities that sprang up around the new factories, where they could work. People lived in dirty, overcrowded conditions with poor sanitation and dirty drinking water. Many died from diseases such as cholera, tuberculosis, measles and pneumonia infections that could spread quickly and easily in these conditions. Two of the big medical advances of this time were: vaccinations, X rays.

Edward Jenner pioneered the earliest vaccinations and discoveries by Louis Pasteur and Robert Koch led to the understanding that infections were caused by certain bacteria or germs. The study of microbes, or microbiology, was born and the increased knowledge of pathogenic microbes led to the development of new medicines to tackle infectious diseases. The pharmaceutical industry was born.

The ideas of an earlier physician, Thomas Sydenham, were applied and this led to a great advance in the treatment of patients. He recognized the importance of detailed observation, record-keeping and the influence of the environment on the health of the patient.

1900 - 2000: The Twentieth century

In 1901, the average life expectancy in the United Kingdom was 47 years. By the year 2000 it had risen to 77 years. New medicines, improved air quality and better public hygiene has contributed to this 64 percent increase in the life-expectancy. The twentieth century has seen some major advances in healthcare. These have included the development of:

Penicillin: The discovery and development of antibiotics by Fleming, Florey and Chain

Insulin: Banting and Best's work to show that insulin can be used to treat diabetes.

Other Medicines : Pharmaceutical laboratories around the world are constantly producing new treatments for diseases.

PHYSIOCHEMICAL PROPERTIES

- The ability of chemical compounds to elicit a pharmacological or therapeutic effect is related to influence of various physical and chemical properties of the chemical substances on the biomolecules that interact with
- Physiochemical properties of organic medicinal agents that influence pharmacological action are
 - Solubility
 - partition coefficient
 - dissociation constant
 - hydrogen bonding
 - chelation
 - molar refractivity
 - Ionisation
 - surface activity

- protein binding
- bioisosterism - optical and geometrical

SOLUBILITY

- Because a significant percentage of all living structures consist of water, all biochemical reactions are based on small molecules dissolved in an aqueous phase or on macromolecules dispersed in this phase. The non-aqueous structures of cells such as plasma membranes or membranes of organelles, are of lipid nature, and can dissolve polar or non-polar hydrophobic molecules. In either case, a highly significant physical property of all physiologically and pharmacologically important small molecules is their solubility, because only in solution they can interact with cellular and subcellular structures that carry drug receptors, thus triggering pharmacological action.
- The solubility of a substance at given temperature is defined as the concentration of dissolved solute, which is in equilibrium with the solid solute. The atoms and molecules of all organic substances are held together by several types of bonds (e.g. hydrogen bond, dipole-dipole, Vander Waals). These forces are involved in solubility because it is the solvent-solvent, solute-solute and solvent-solute interactions that govern solubility.

Methods to improve solubility:

- Structural modification
- Use of co-solvents
- Employing surfactants
- Complexation

PARTITION COEFFICIENT

- The ability of a drug to dissolve liquid phase is referred as lipophilicity.
- Highly water soluble drugs cannot penetrate organs rich in lipid such as brain and other neural tissue on the other hand compound that is very lipophilic will be trapped in the first site of loss like fat tissue and will be unable to leave this site quickly to reach the target.
- Partition coefficient is one of the several physiochemical parameter influencing the drug transport and distribution, the way in which the drug transport and distribution, the way in which the drug reach the site of action.
- Partition coefficient can be defined as equilibrium constant of drug concentration for a molecule in two phases.
- Since partition coefficient are difficult to measure in living system . They are usually determined invitro using 1-octanol as a lipid phase and phosphate buffer of pH 7.4 as the aqueous phase. The partition coefficient P is dimensionless and its logarithm log P is widely used as the measure of lipophilicity.

DISSOCIATION CONSTANT

- The dissociation constant is one of the most important characteristics of a pharmaceutical compound
- The pKa or dissociation constant is a measure of the strength of an acid or a base and is sometimes called the acidity constant or ionization constant.
- It is a numerical representative of the relative proton transfer for that substance or donating a proton
- For almost all the drugs, the dissociation constants are reported as pka, regardless of whether the drug is a weak acid or a weak base. For acids, Ka refers to the ability of the acid to give out the proton. Therefore, the higher the tendency of an acid to give out the proton, the stronger is the acid (or the lower the pKa value). For bases, Ka refers to the ability of the conjugated acid form of the base to give out the proton. Therefore, the higher the conjugated acid's (of the base) tendency to give out the proton (the lower the pKa value), the weaker the original base.

Ionization

- Ionized form imparts good water solubility to the drug which is essential for good binding interactions of drug with its receptor, while non-ionized form helps the drug to cross cell membranes. Hence, a good balance of ionized, non-ionized form is essential for better pharmacodynamic and pharmacokinetic features

HYDROGEN BONDING

- The hydrogen bond is a special type of dipole-dipole interaction between the hydrogen atom in a polar bond such as N-H, O-H, or F-H and an electronegative atom O, N, or F atom. This interaction is written as A-H... B. A and B represent O, N or F. A-H is one molecule (or) part of a molecule and B is a part of another molecule; and the dotted line represents the hydrogen bond. These three atoms usually lie along a straight line, but the angle AHB can deviate as much as 20° from linearity. Ex: Hydrogen bonding in NH₃, H₂O and HF.
- Generally, the hydrogen bonding is classified into 2 types:
 - A. Intermolecular hydrogen bonding
 - B. Intramolecular hydrogen bonding
- (A) Intermolecular hydrogen bonding

In this type, hydrogen bonding occurs between two or more than two molecules of the same compound and results in the formation of polymeric aggregate. Intermolecular hydrogen bonding increases the boiling point of the compound and its solubility in water. The molecules that can develop intermolecular hydrogen bonding improve their solubility by the formation of intermolecular hydrogen bonding with water. Eg; Ethanol shows higher boiling point and higher solubility in water than dimethyl ether even though both have the same molecular weight

- (B) Intramolecular hydrogen bonding

In this type, hydrogen bonding occurs within two atoms of the same molecule. This type of hydrogen bonding is commonly known as chelation and frequently occurs in organic compounds. Sometimes intramolecular hydrogen bonding develops a six or 5-membered ring. Intramolecular hydrogen bonding decreases the boiling point of the compound and its solubility in water. This is because the chelation between the ortho substituted groups restricts the possibility of intermolecular hydrogen bonding with water and thus prevents association of the molecules, which would have raised the melting point, boiling point.

PROTEIN BINDING

- Depending upon whether the drug is weak or strong acid or base, or is neutral, it can, bind to a single blood protein, to multiple proteins.
- The most significant protein involved in the binding of drugs is **albumin** which comprises half of all blood proteins.
- Protein binding values are normally given as the percentage of the total plasma concentration of drug that is bound to all plasma proteins. The extent to which a drug is bound to plasma proteins can affect the distribution of the drug in several ways.
- The drug-protein complex does not permeate through phospholipids bilayers, including capillary membranes, glomerular membranes in nephron, and blood brain barrier.
- Bound drugs are also less available to enzymes involved in first pass metabolism. After metabolic and excretory processes have cleared much of free drug, the reversible drug protein complex serves as a depot to replenish the concentration in vivo.
- For these reasons, drugs with high protein binding activity values tend to have a greater half life compared to those with lower values. The prolonged activity resulting from these factors may be desirable or may promote the emergence of undesirable side effects.

CHELATION

- The compounds that are obtained by donating electrons to metal ion with the formation of a ring structure are called chelates.
- The compound capable of forming a ring structure with metal ion termed as ligands.
- Most of the metals can form chelates or complexes, but the chelating property is restricted to atoms like N, S and O which are electron donating.
- The phenomenon of chelation is significantly involved in biological system and to some extent in explaining drug action.
- Penicillamine is an effective antidote for the treatment of copper poisoning because it forms a water soluble chelate with copper and other metal ions.

BIOISOSTERISM

- The concept of isosterism to modify biological activity has been rise to term bioisosterism. Bioisosteres are chemical substituents or groups with similar physical or chemical properties which produce broadly similar biological properties to another chemical compound. The purpose of exchanging one bioisostere for another is to enhance the desired biological or physical properties of a compound without making significant changes in chemical structure. 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 bioisosteres :

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.

- Non-classical bioisosteres : Non-classical bioisosteres may differ in a multitude of ways from classical bioisosteres but retain the focus on providing similar steric and electronic profile to the original functional group. Whereas classical bioisosteres commonly conserve much of the same structural properties, nonclassical bioisosteres 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.

OPTICAL AND GEOMETRICAL ISOMERISM

- Physicochemical properties of a molecule are not only dependent upon what functional groups are present in molecule, but also the special arrangement of these groups. This become an especially crucial factor when a molecule is subjected to an asymmetric environment such as the human body.
- Optical isomerism: Optical isomers may be defined simply as compounds that differ only in their ability to rotate the plane polarized light. The differences in biological activity between optical isomers depends on their ability to react selectively at an asymmetrical centre in the biological system
- Geometric isomerism: The term geometric isomerism indicates a type of diastereoisomer that occur as a result of restricted rotation around a bond as in olefinic compounds. Geometric isomerism does not necessarily impart optical isomerism to the compound. If the structure is asymmetric (or dissymmetric), however, geometric isomers may exhibit optical activity.
- Unlike enantiomers, it may be difficult to correlate the differences in biologic activity solely with the difference in special arrangement of isomers. The observed differences in biological activity

of geometric isomers may be due in part to differences in the interatomic distance of groups essential for the elicitation of response. The classic example is diethylstilboestrol, a drug synthesized to mimic natural estrogenic hormone estradiol. The trans isomer of diethylstilboestrol, has 14 times the estrogenic activity of the cis compound

DRUG METABOLISM

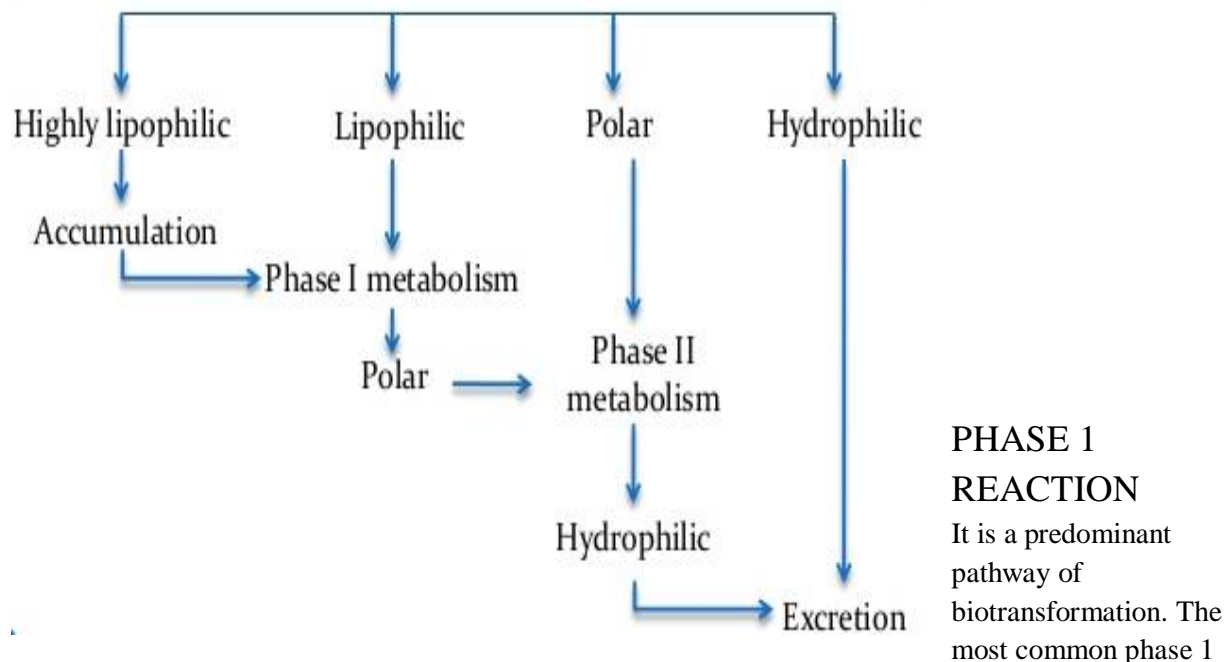
Drug metabolism is the process which describes biotransformation of drugs or nonessential exogenous compounds in body so that they can be easily eliminated. It is basically a process of introduction of hydrophilic moiety into drug molecule to facilitated excretion.

SITES FOR METABOLISM

Liver is the major site for metabolism. Liver contains many necessary enzymes required for metabolism of drugs and foreign compound (collectively referred as xenobiotics). Liver disease should have important effects on metabolism of drugs and the duration of drugs Liver disease affects elimination half- life of some drugs.

Although liver is primary site for metabolism, all tissue cells have some metabolic activities. Other organs having significant metabolic activities are gastrointestinal tract kidney lungs skin, plasma, and nervous tissue.

DRUG METABOLISM PATHWAYS

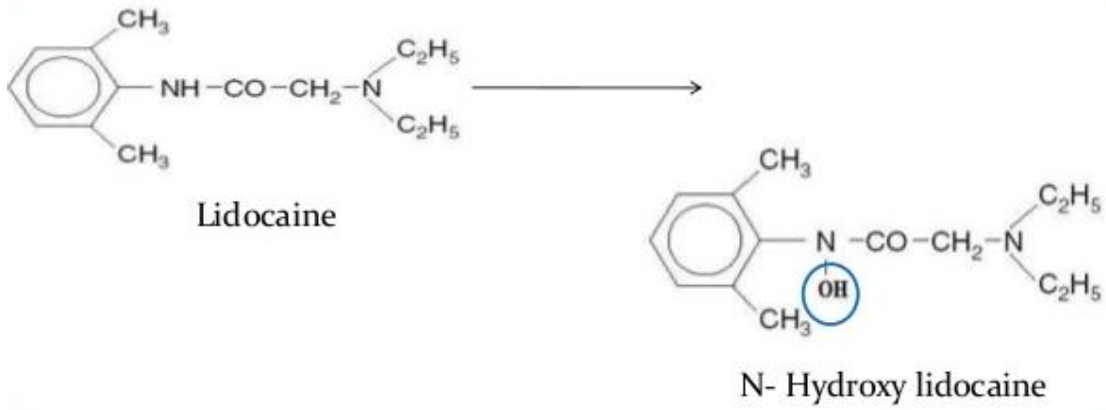


PHASE 1 REACTION

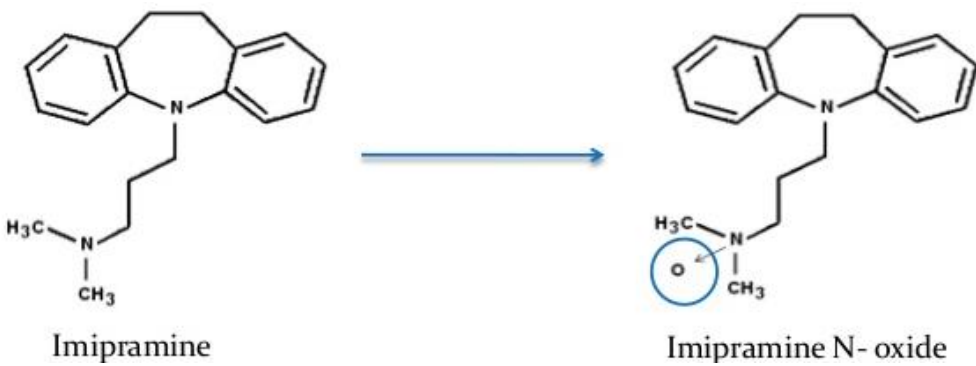
It is a predominant pathway of biotransformation. The most common phase 1

reactions are oxidative processes (aromatic and aliphatic hydroxylation, N-, O-, S-dealkylation, N-hydroxylation, N-oxidation, sulfoxidation, deamination and dehalogenation), reduction (azodye reduction and nitro reduction) and hydrolytic reactions.

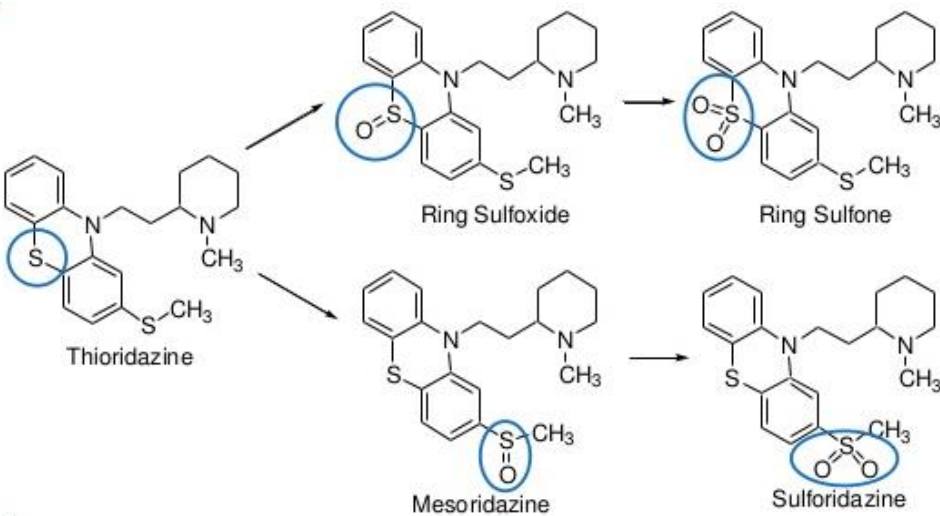
N HYDROXYLATION



NOXIDATION



S-OXIDATION



N-DEALKYLATION

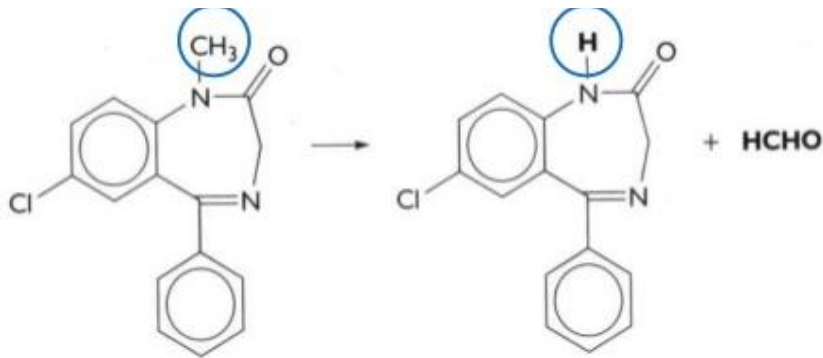
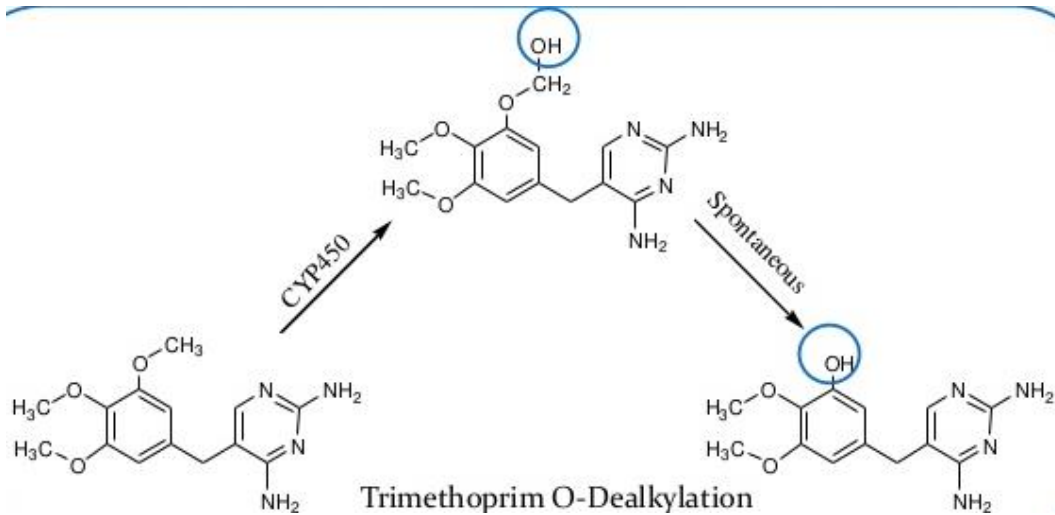


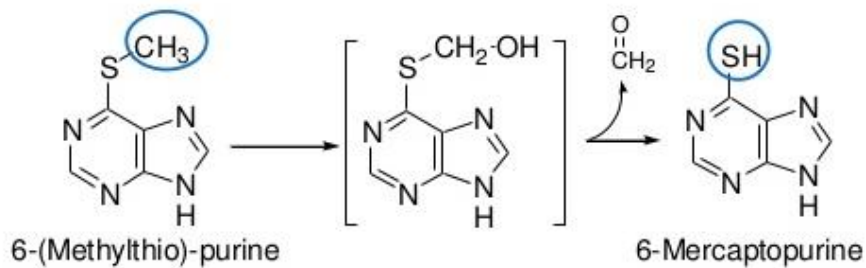
Figure 1.4 The N-demethylation of diazepam.

Diazepam \longrightarrow Desmethyldiazepam + Formaldehyde

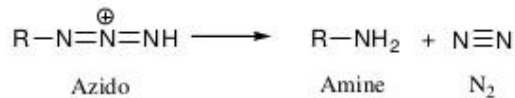
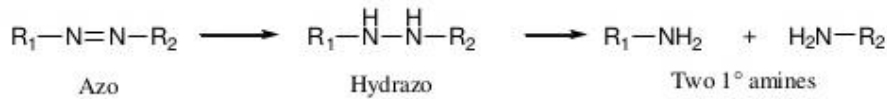
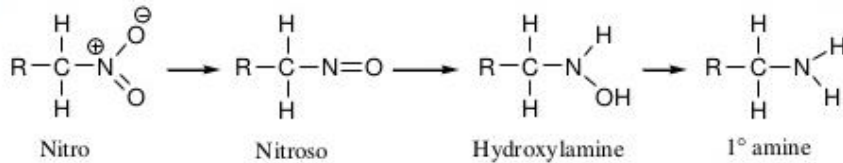
O-DEALKYLATION



S-DEALKYLATION



REDUCTION



PHASE 2 REACTIONS

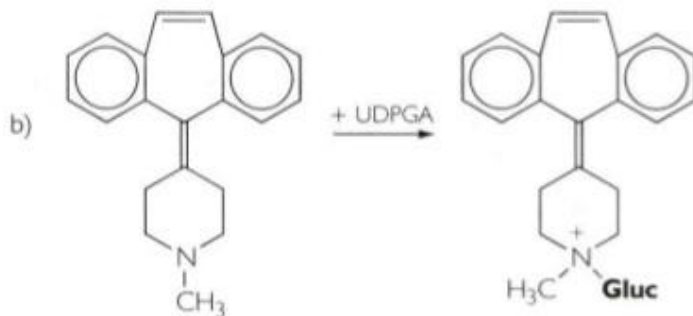
Phase II biotransformation reactions (also called 'conjugation reactions') which generally serve as a detoxifying step in metabolism of drugs and other xenobiotics as well as endogenous substrates.

On the other hand, these conjugations also play an essential role in the toxicity of many chemicals due to the metabolic formation of toxic metabolites such as reactive electrophiles.

Conjugation reactions usually involve metabolite activation by a high-energy intermediate and have been classified into two general types: type I (e.g., glucuronidation and sulfonation), in which an activated conjugating agent combines with substrate to yield the conjugated product, and type II (e.g., amino acid conjugation), in which the substrate is activated and then combined with an amino acid to yield a conjugated product.

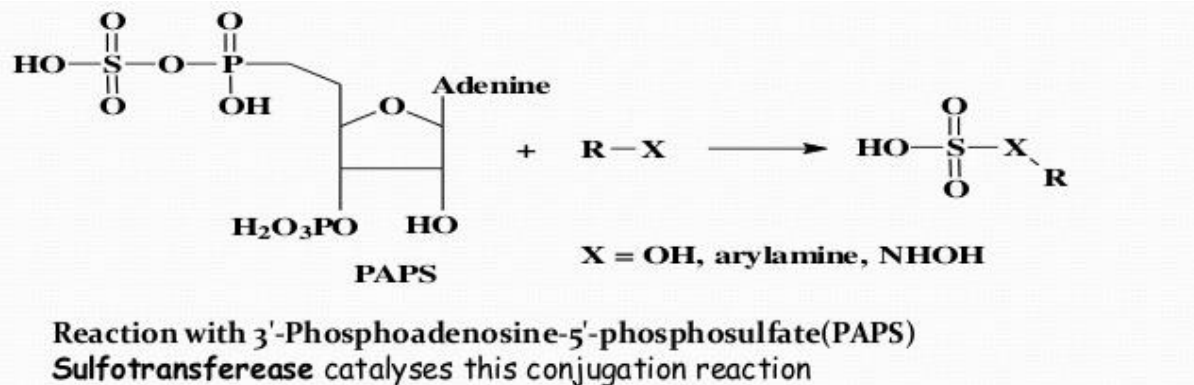
• N-glucuronidation:

- Occurs with amines (mainly aromatic)
- Occurs with amides and sulfonamides

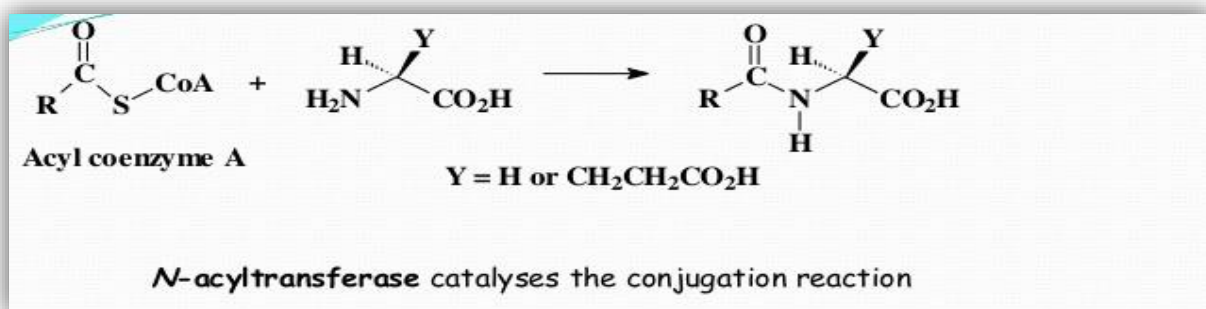


GLUCORINADATION OF SULPHANILAMIDE AND CYPROHEPTADINE

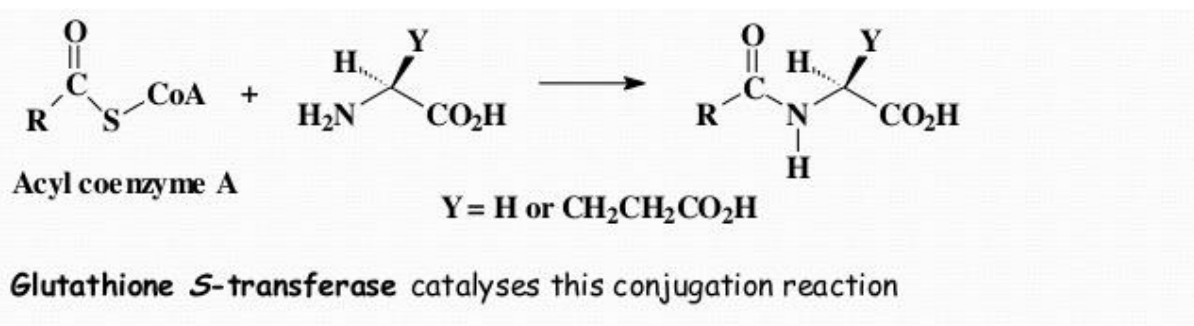
SULPHATE CONJUGATION



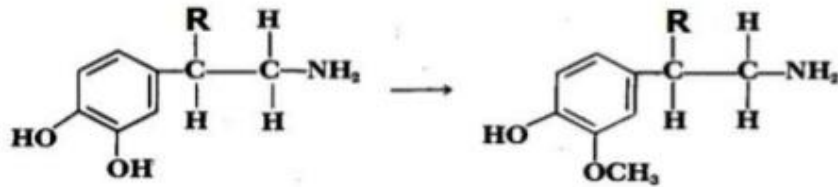
AMINO ACID CONJUGATION



GLUTATHIONE CONJUGATION



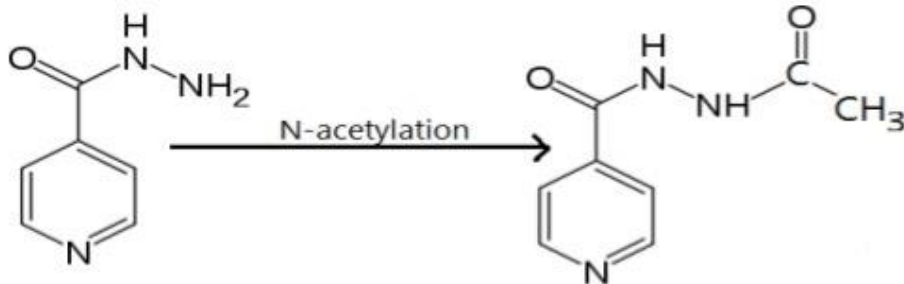
METHYLATION



R=OH (Norepinephrine)
R=H (Dopamine)

R=OH (Normetanephrine)
R=H (3 methoxy tyramine)

acetylation



FACTORS AFFECTING DRUG METABOLISM

There are many factors which influence the rate of drug metabolism These includes:

1. Genetic factors:

Species differences are seen in biotransformation and conjugation of xenobiotics Genetic differences among individuals or ethnic groups can lead to excessive or prolonged therapeutic effect or toxic overdose

2. Physiological factors:

Age is a factor because the very young and old have impaired metabolism. Harmons (including those induced by stress), sex differences, pregnancy, changes in the intestinal microflora, diseases (especially involving liver) and nutritional status can also influence xenobiotic metabolism

3. Pharmacodynamic factors:

Dose, frequency and route of administration, plus tissue distribution and protein binding of drug affect its metabolism.

4. Environmental factors:

Competition with other xenobiotics and drugs for metabolizing enzymes and poisoning of enzymes by toxic chemicals, such as carbon monoxide or pesticide synergists, alter metabolism.

5. Stereochemical factors:

Stereochemical factors generally have a dramatic influence on how the drug molecule interacts with the target receptors to elicit its pharmacological response. By the same token the preferential interaction of one stereoisomer with drugs metabolizing enzymes may lead one to anticipate differences in metabolism for the two enantiomers of a racemic mixture. Many drugs (e.g., warfarin, propranolol, hexobarbital, glutethimide, cyclophosphamide, ketamine, and ibuprofen) often are administered as racemic mixtures in humans. The two enantiomers present in a racemic mixture may differ in pharmacological activity. For example, (+)-alpha - propoxyphene (Darvon) is an analgesic, whereas (-)-alpha-propoxyphene (Novrad) is an antitussive. Usually, one enantiomer tends to be much more active than the other.