Unit 1

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Content

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.

CHEMISTRY

What is Chemistry?

- Chemistry is known

as the **central of science.**

- **It is a branch of physical science that studies the composition, structure, properties and changes of matter.**
- MATTER = Solid / Liquid/ Gas.

BRANCHES OF CHEMISTRY

PHYSICAL CHEMISTRY

- the branch of chemistry concerned with the application of the techniques and theories of physics to the study of chemical systems.
- Branches : chemical Kinetics, Electrochemistry, spectroscopy, photochemistry.

INORGANIC CHEMISTRY

- deals with the synthesis and behaviour of **inorganic** and organometallic compounds
- Branches :Bioinorganic, Cluster, Material & Nuclear Chemistry

ORGANIC CHEMISTRY

- study of the structure, properties, and reactions of **organic** compounds and **organic** materials, i.e., matter in its various forms that contain carbon atoms.
- Branches : Biochemistry, biophysical, Biorganic, P'ceutical, Medicinal

WHAT IS MEDICINAL CHEMISTRY

- It is a discipline or intersection of chemistry especially synthetic organic chemistry & pharmacology.

OR

- Medicinal chemistry involves discovery, development, identification & interpretation of Mode of action of biologically active compounds at molecular level

- Medicinal chemistry is best to be defined as an interdisciplinary research area incorporating different branches of chemistry and biology in the research for better and new drugs (Drug Discovery).
- In other words, medicinal chemistry is the science, which deals with the discovery and design of new and better therapeutic chemicals and development of these chemicals into new medicines and drugs.

- Generally Medicinal Chemists can:
  - Make new compounds
  - Determine their effect on biological processes.
  - Alter the structure of the compound for optimum effect and minimum side effects.
  - Study uptake, distribution, metabolism and excretion of drugs

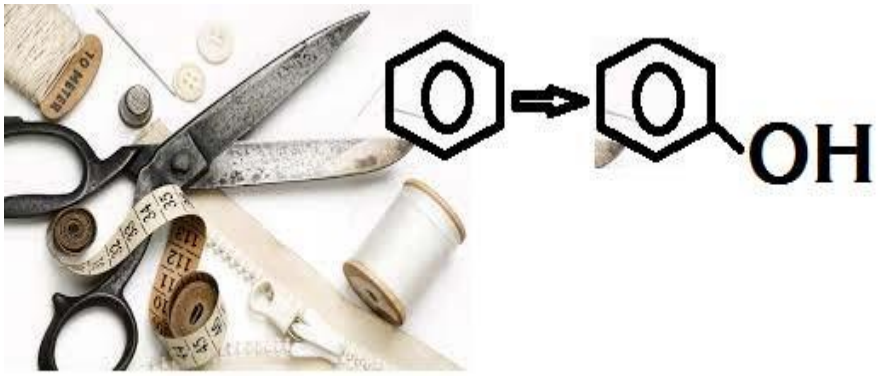
Finally medicinal chemistry ….

- Medicinal chemistry includes synthetic & computational aspects of the study of existing drugs and agents in development in relation to their bioactivities i.e., understandings a **SAR**s (Structure Activity Relationships).

OR

- It is a tailoring

of drugs



Origins of Medicinal Chemistry

3500 BC - Sumerians report use of opium

3000 BC - Chinese report use of ma huang (ephedra)

Greek culture:

Hippocrates- followed the teachings of Aristotle; focus is on the soul.

Galen- followed the teachings of Plato; focus is on experiment- believed the whole could be explained by the parts

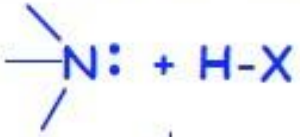
Renaissance period:

Doctors were humanists- followers of Hippocrates- treat the soul and the body will heal. Initially, there were no relationships with alchemy.

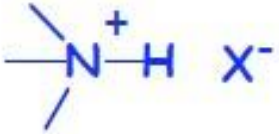
In 1793, Faureroy & Vauquehin split from the monarchy-controlled bodies and establish the Ecole Supurieure de Pharmacie- 1st to incorporate chemistry into the pharmacy curriculum. Develop research to find the active principles in plant-based drugs.

1803 - Derosome isolates a crystalline salt from opium

1817 - Sertürner publishes work demonstrating that the narcotic principle of opium is basic (alkaline) and, thus, it will form salts with acids- names the principle "morpheus"



Gay-Lussac predicts that other alkaline plant extracts will have useful medical properties- changes name of morpheus to morphine



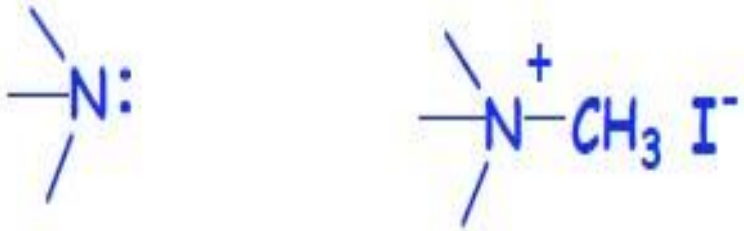
1818 - Meissner proposes the general term alkaloids

1853 - Henry How proposes that there are "functional groups" that can be chemically modified to alter reactivities….

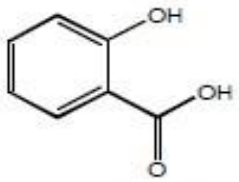
morphine R = H

codeine R = CH_3

morphine $\xrightarrow{CH_3I}$ quaternary salt

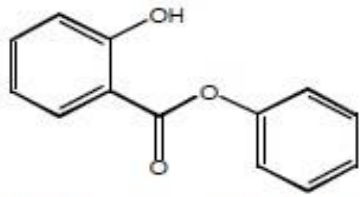


Fraser and Brown make quaternary salts of many different alkaloids (i.e, morphine, strychnine, nicotine) and find that all exhibit curare-paralyzing activities- propose that quaternary salts have curariform activity



salicylic acid

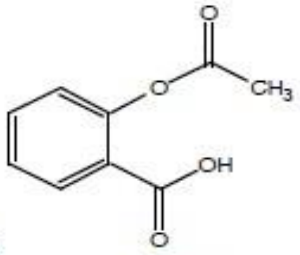
1875- Carl Buss isolates salicylic acid from *Spirea ulmaria* and shows that it is an effective antipyretic- however, it is unpalatable and causes gastric distress.



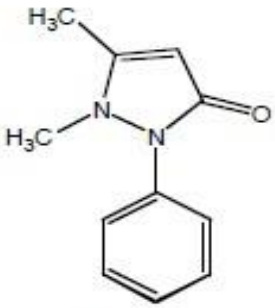
salol (phenyl salicylate)

1883- von Nencki makes a salicylate ester with phenol, salol- it has very poor solubility but it is better tolerated. It is hydrolyzed slowly in the small intestine to give salicylic acid- the first sustained release drug

1890s - Hoffman at Bayer tests acetyl salicylic acid and finds it to be better tolerated- names it aspirin as in "a" for acetyl and "spirin" for *Spirea*. It is rapidly hydrolyzed in the gut to give active salicylic acid- it is a "pro-drug"



acetyl salicylic acid



phenazone

Phenazone was synthesized in 1884 and was the most popular drug world-wide until it was taken over by aspirin in the early 1900s- in addition to being an antipyretic, it also cured headaches- a new market was born...

There is a long history of plants being used to treat various diseases.

The therapeutic properties of plants were described by the Ancient Greeks and by the Romans and are recorded in the writings of Hippocrates, Dioscorides, Pliny and Galenus.

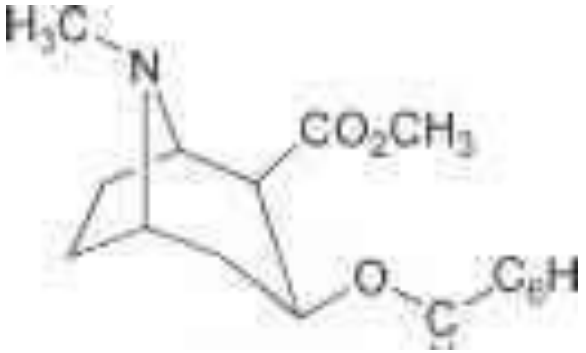
Some metals and metal salts were also used at this time.

In the Middle Ages various 'Materia Medica and pharmacopeas brought together traditional uses of plants.

- The nineteenth century saw the beginnings of modern organic chemistry and consequently of medicinal chemistry.
- The isolation of a number of alkaloids including morphine (1805), quinine (1823) and atropine (1834) from crude medicinal plant extracts was part of the analytical effort to standardize drug preparations and overcome fraud.
- General anaesthetics were introduced in surgery from 1842 onwards (diethyl ether (1842), nitrous oxide (1845) and chloroform (1847)). Antiseptics such as iodine (1839) and phenol (1860) also made an important contribution to the success of surgery. The hypnotic activity of chloral (trichloroethanal) (1869) was also reported.

- The use of willow bark as a pain-killer was known to the herbalists, the analgesic activity of its constituent salicin and of salicylic acid were developed in the 1860s and 1870s.
- p-Hydroxyacetanilide (paracetamol) and phenacetin (1886) were also recognized as pain-killers.
- Acetylation of salicylic acid to reduce its deleterious effect on the stomach led to the introduction of aspirin in 1899.

- The local anaesthetic action of cocaine was reported in 1884 although its structure was not known at the time.
- Various modifications of the dialkylamino esters of aromatic acids modelled on part of the structure of cocaine led to benzocaine (1892) and procaine (1905). The barbiturates, veronal (1903) and phenobarbital (1911) were introduced as sleeping tablets.



- The 1920s and 1930s saw the recognition of vitamin deficiency diseases and the elucidation of the structure of various vitamins.
- It was also a period in which there was exposure of many Europeans to tropical diseases. The iodinated quinolines such as entero-vioform were introduced to combat amoebic dysentary and complex dyestuff derivatives such as suramin and germanin were developed in the 1920s to treat sleeping sickness.
- Synthetic anti-malarials such as pamaquine (1926), mepacrine (1932) and later chloroquine (1943) and paludrine (1946) were introduced as quinine replacements.

- In 1935 Domagk observed the anti-bacterial action of the sulfonamide dyestuff, prontosil red , from which the important family of sulfonamide anti-bacterial agents were developed.
- With the onset of the Second World War, there was a need for new antibiotics. In 1929 Fleming had observed that a strain of Penicillium notatum inhibited the growth of a Staphylococcus. In 1940-1941 Chain, Florey and Heaton isolated benzylpenicillin
- . After considerable chemical work, the b-lactam structure for the penicillins was established. The relatively easy bio-assays for anti-bacterial and anti-fungal activity led to the isolation of a number of antibiotics including streptomycin (1944), chloramphenicol (1949) and the tetracyclines such as aureomycin (1949).

- A number of developments took place in the 1960s, which changed medicinal chemistry.
- It was found that a drug, thalidomide, which had been introduced as a sedative, when used by pregnant women, led to the birth of deformed children. The consequences of this teratogenic effect brought about a major tightening of the regulations regarding drug registration and the safety of medicines.
- The logical development during the 1960s of histamine antagonists for the treatment of peptic ulcers led to cimetidine (1976) and then ranitidine (1981). The reasoning behind this work had a major impact on the development of medicinal chemistry.