Medicinal Chemistry I

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Course Description:

The aim of this course is to introduce the basic concepts of medicinal chemistry. Study of drug physicochemical properties, distribution, metabolism and excretion. In addition to understand the concept of structure-activity relationship (SAR). Beginning to study drugs used for the treatment of some diseases.

Course objectives:

- Study the relation between the drug chemical structure and its biological activity in the body.
- The importance of organic functional groups in determining the physicochemical properties of the drug.
- Understand the interactions drug-protein, drug-enzyme, drug-receptor.
- How the body interact and make changes on the chemical structure of the drug.
- Introduce various classes of therapeutic agents with the emphasis on their structure activity relationship (SAR).

- ***Knowledge and understanding:***

a.1 Recognise and identify drug receptor, drug enzyme, drug protein interactions

a.2 Be familiar with the main classification of drugs

a.3 Describe the physicochemical properties of drugs and its roll in drugs absorption to blood circulation and crossing of system barriers

a.4 Identify The Henderson-Hasselbalch Equation in calculating the drug ionization and its effect on drug absorption

a.5 Describe importance of water solubility of drug and relate it to its chemical structure.

a.6 Define the biological factors that affect the drug metabolism

a.7 Define the different phases of drug metabolism in the body (phase I and phase II) with their different chemical modifications.

a.8 Describe the SAR of different types and classes of drugs

- ***Intellectual Skills:***

b.1 Differentiate between drug as an enzyme substrate and its action on a cell receptor

b.2 Differentiate between ionisable and non ionisable drug functional group

b.3 Recognise the hydrophilic and lipophilic properties of the drug chemical structure.

b.4 Differentiate between the general chemical reaction involved in Phase I and Phase II drug metabolism.

b.5 Recognise the medicinal action of chemical compounds according to their structure.

- ***Professional and practical skills:***

c.1 Be able to propose new drug chemical structure to modify drug activity

c.2 Be able to resolve problems related to drug solubility and absorbtivity in mammalian system

c.3 Be able propose chemical modifications to different types of drug formulations

Text Books:

1. **An Introduction to Medicinal Chemistry. Graham L. Patrick. 5th ed**
2. **Foye's principles of medicinal chemistry. 6th ed**
3. **wilson and gisvold's textbook of organic and pharmaceutical chemistry 12th ed**

Medicinal chemistry course-
Dr.Mohyeddin Assali

❖ Course outlines

Topic 1: Introduction of medicinal chemistry

Topic 2: Introduction of drug targets

Topic 3: Protein as drug targets

Topic 4: Enzymes as drug target

Topic 5: Receptors as drug target

Topic 6: Drug Functional groups

Topic 7: Pharmacokinetics

Topic 8: Anti-infective agents

Topic 9: Antibacterial agents

Topic 10: Antiviral agents

Topic 11: Nonsteroidal anti-Inflammatory Drugs "NSAIDs"

Topic 1: Introduction to medicinal chemistry

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DRUG DESIGN AND DEVELOPMENT

Stages

1) Identify target disease
2) Identify drug target
3) Establish testing procedures
4) Find a lead compound
5) Structure Activity Relationships (SAR)
6) Identify a pharmacophore
7) Drug design- optimising target interactions
8) Drug design - optimising pharmacokinetic properties
9) Preclinical trials
10) Chemical development and process development
11) Patenting and regulatory affairs
12) Clinical trials

Note: Stages 9-11 are usually carried out in parallel

1. The Lead Compound

- **A compound demonstrating a property likely to be therapeutically useful**

- **The level of activity and target selectivity are not crucial**

- **Used as the starting point for drug design and development**

- **Found by design (molecular modelling or NMR) or by screening compounds (natural or synthetic)**

- **Need to identify a suitable test in order to find a lead compound**

- **Active Principle - a compound that is isolated from a natural extract and which is principally responsible for the extract's pharmacological activity. Often used as a lead compound.**

1.1 Sources of Lead Compounds

A) The Natural World

Plantlife (flowers, trees, bushes)
Micro-organisms (bacteria, fungi)
Animal life (frogs, snakes, scorpions)
Biochemicals (Neurotransmitters, hormones)
Marine chemistry (corals, bacteria, fish etc)

B) The Synthetic World

Chemical synthesis (traditional)
Combinatorial & parallel synthesis

C) The Virtual World

Computer aided drug design

2. Structure Activity Relationships (SAR)

Aim - Identify which functional groups are important for binding and/or activity

Method

- **Alter, remove or mask a functional group**

- **Test the analogue for activity**

- **Conclusions depend on the method of testing**

***in vitro* - tests for binding interactions with target**

***in vivo*- tests for target binding interactions and/or pharmacokinetics**

- **If *in vitro* activity drops, it implies group is important for binding**

- **If *in vitro* activity is unaffected, it implies group is not important**

Notes on analogues

- **Modifications may disrupt binding by electronic / steric effects**

- **Easiest analogues to make are those made from the lead compound**

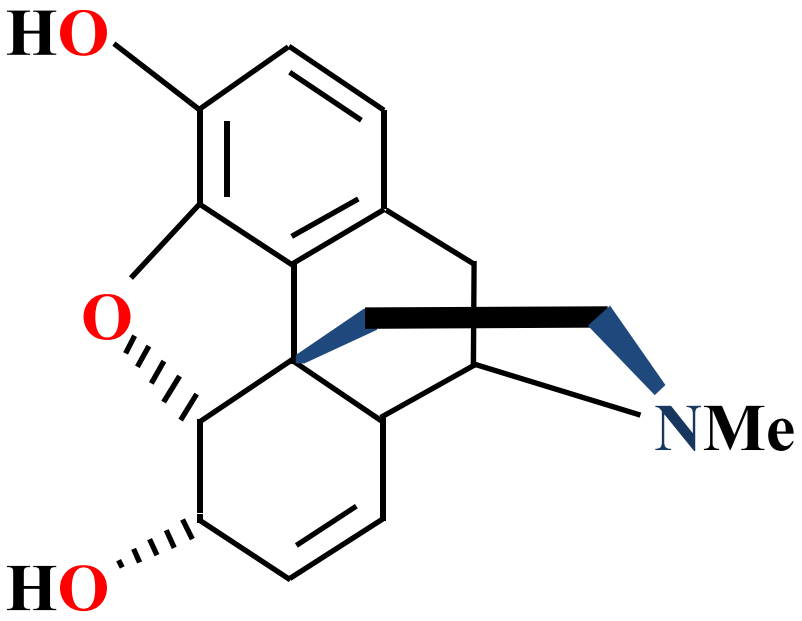
- **Possible modifications may depend on other groups present**

- **Some analogues may have to be made by a full synthesis**
  (e.g. replacing an aromatic ring with a cyclohexane ring)

- **Allows identification of important groups involved in binding**

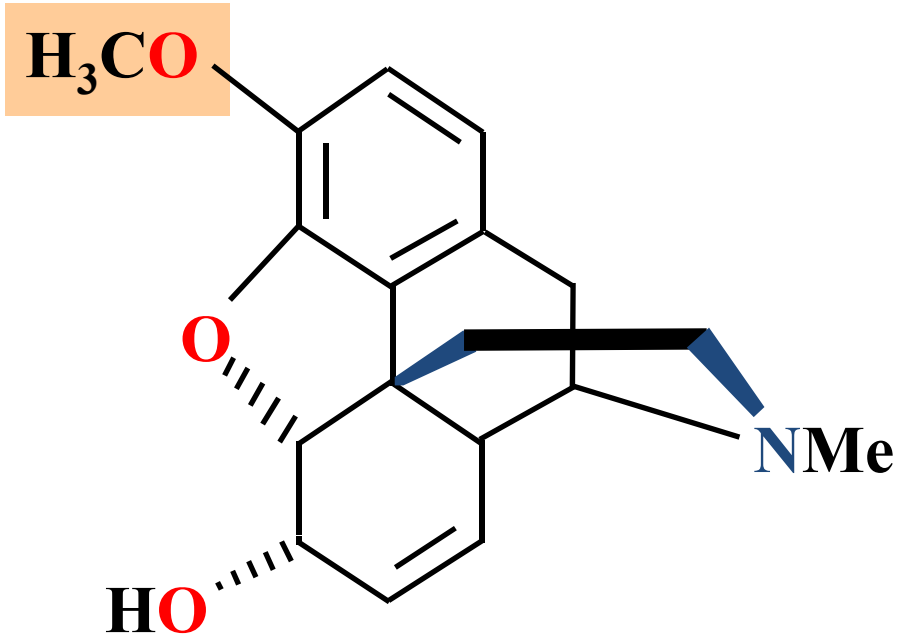
- **Allows identification of the pharmacophore**

2.1. Structure Activity Relationships (SAR)



MORPHINE

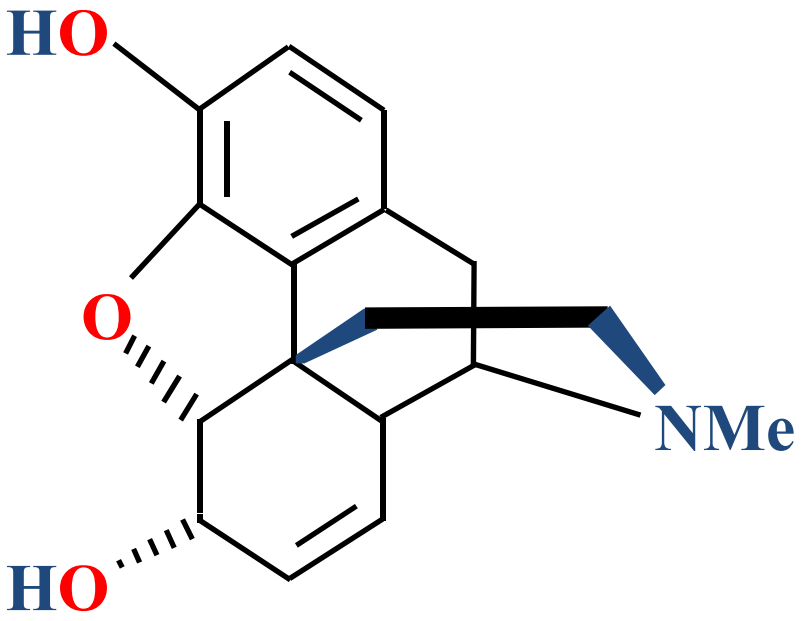
2.1. Structure Activity Relationships (SAR)



CODEINE

ACTIVITY DROPS

2.1. Structure Activity Relationships (SAR)



MORPHINE

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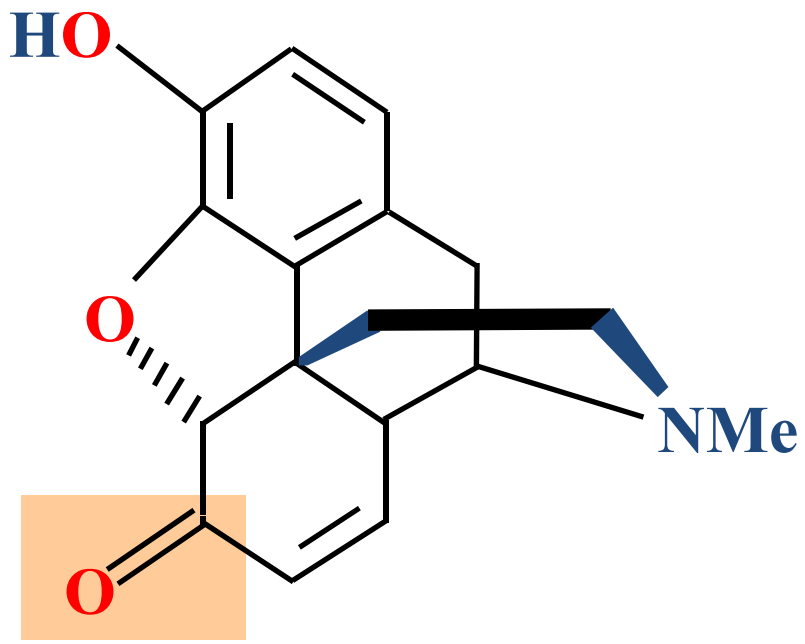


6-OXYMORPHINE

ACTIVITY UNAFFECTED

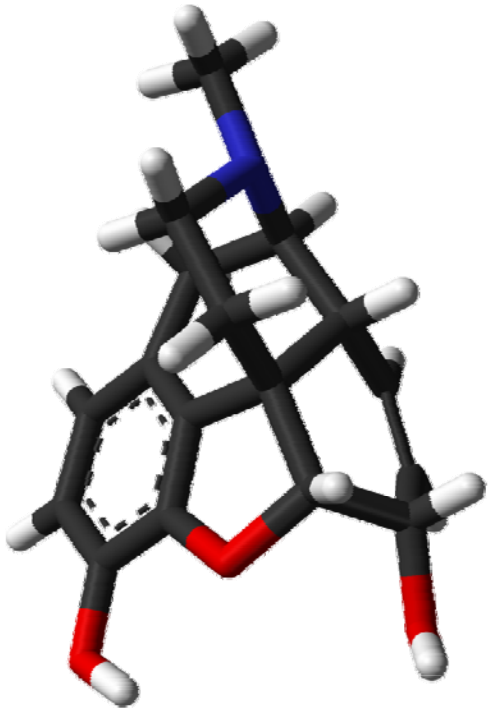
- the **theory of receptors** has become one of the fundamental concepts of medicinal chemistry.

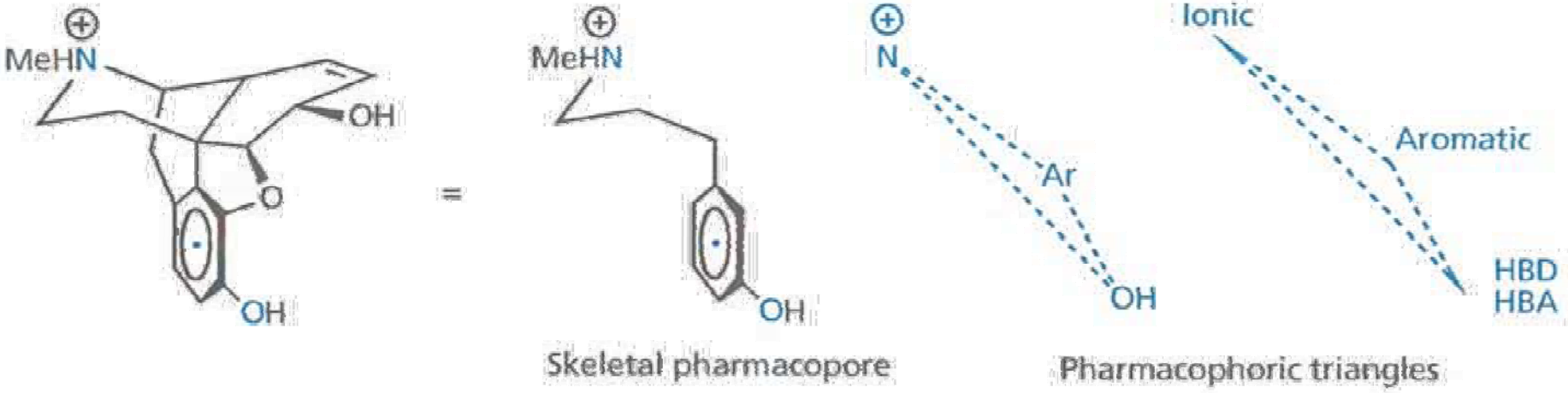
- **Receptor sites** usually take the form of pockets, grooves or other cavities in the surface of certain proteins and glycoproteins in the living organism.

- They should not be confused with active sites, which are the regions of enzymes where metabolic chemical reactions occur.

- **Ligand** is the chemical agent that bind to a receptor sets in motion of a series of biochemical events that result in a biological or physiological effect.

- The section of the structure of a ligand that binds to a receptor is known as its ***pharmacophore***.




MeHN
OH
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OH
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MeHN
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N
Ar
OH
Ionic
Aromatic
HBD
HBA
Skeletal pharmacopore
Pharmacophoric triangles

PATENTING AND REGULATORY AFFAIRS

Patenting "run for 20 years after the date of filling"

- Carried out as soon as a potentially useful drug is identified
- Carried out before preclinical and clinical trials
- Several years of patent protection are lost due to trials "6-10 years"
- Cannot specify the exact structure that is likely to reach market
- Patent a group of compounds rather than an individual structure
- Also patent production method

PATENTING AND REGULATORY AFFAIRS

Regulatory affairs

•Drug must be approved by regulatory bodies

-Food and Drugs Administration (FDA).... New drug application "NDA"
-European Agency for the Evaluation of Medicinal Products... Marketing Authorization application "MAA"... They are 400-700 volumes in size with each volume containing 400 pages!!!

•GLP - Good Laboratory Practice

•GMP - Good Manufacturing Practice

•GCP - Good Clinical Practice

CLINICAL TRIALS "5-7 years"

Phase 1 "1 year"

- Carried out on healthy volunteers "100-200"
- they are not intended to demonstrate whether the drug is effective or not
- Useful in establishing dose levels "determine the tolerated dose"
- Useful for studying pharmacokinetics, including drug metabolism.

- Bioavailability: the fraction of administered drug that reaches the blood supply in a set period of time.

- Bioequivalence study: is to check that the bioavailability remains the same in any alteration to the manufacturing, formulation, dosage forms or storage processes.

Phase 2 “2 years”

- Carried out on patients “20-80 patients”.
- Carried out as double blind studies
- Demonstrates whether a drug is therapeutically useful
- Establishes a dosing regimen.
- Identifies side effects

Phase 3 “ 3 years”

- Carried out on a larger number of patients & double blind studies
- Establishes statistical proof for efficacy and safety

Phase 4

- Continued after a drug reaches the market
- Studies long term effects when used chronically
- Identifies unusual side effects. E.g. Rofecoxib “VIOXX” was used to treat rheumatoid arthritis for 5 years showed that it was associated with increased risks of heart attack & stroke. “withdrawn by Merck in 2004”.

❖ Naming of drugs and medicine

- The vast majority of chemicals that are synthesized in medicinal chemistry research never reach the market so it is **impractical** to name them all.

- Research groups label them with a code which consists of **letters and numbers**.

- the **letters** are specific to the research group undertaking the work and the **number** is specific for the compound.

- Ro31-8959, ABT-538 and MK-639 were compounds prepared by Roche, Abbott, and Merck pharmaceuticals respectively.

- If the compounds concerned show promise as therapeutic drugs they are taken into development and named. E.g. the above compounds showed promise as anti-HIV drugs and were named **saquinavir, ritonavir and indinavir**, respectively.

- If the drugs prove successful and are marketed as medicines, they are given a proprietary, brand or trade name which only the company can use.

- E.g. the previous compounds were marketed as **Fortovase®, Norvir® and Crixivan®** respectively "note that brand names always start with a capital letter & have the symbol ® or ™ to indicate that they are registered brand names".

- The proprietary names are also specific for the preparation or formulation of the drug.

- E.g. Fortovase® is a preparation containing 200 mg of saquinavir in a gel filled, beige colored capsule. If the formulation is changed then a different name is used. Roche sell a different preparation of saquinavir called Invirase® which consists of a brown/green capsule containing 200 mg of saquinavir as the mesilate salt.

- When a drug's patent has expired, it is possible for any pharmaceutical company to produce and sell that drug as a generic medicine.

- It is not allowed to use the trade name used by the company that originally invented it.

- European law requires that generic medicines are given a **recommended International Non-proprietary Name** (rINN), which is usually identical to the name of the drug.