

Alkaloids

Presented by

Ku. Kavita G. More

M.Sc. - II / Sem- - III (. Natural Product)

Alkaloid

The course discuss the organic chemistry of important classes of drugs and bioactive natural products.

Synthesis / biosynthesis, mode of action, bioavailability and stability for chosen drug classes.

Structure activity and structure optimisation

- 
- 
- **Natural Products**
 - **Drug Design**
 - **Receptors - Drug Action**
 - **Drug Metabolism**

- **Antibiotics/Antimicrobial Agents**
- **Antiparasitic Agents**
- **Antifungal Agents**
- **Antimycobacterial Agents**
- **Anticancer Agents**
- **Antiviral Agents**

Origin of Drugs / Bioactive Compounds

- **Natural Products / Natural Product Derivatives**
- **Random testing, serendipity***
- **Screening of Libraries**
- **(Rational) Drug Design** (1. mentioned SciFinder 1970, most papers after 1990)

• **Screening/Design/Serendipity**

• **Lead compound -**

• **Design/Structure Optimisation**

• **Actual Drug**



• **Activity**

• **Toxicity**

• **Bioavailability**

• **Metabolism**

in vitro

in vivo animals

in vivo humans

Why new drugs?

Resistance

New diseases (Aging, life style)

Less tolerance for side effects

***Fortunate discovery by accident**

“The three princes of Serendip” Persian Fairy tale

Serendip=Sri Lanka

Origin of Drugs / Bioactive Compounds: History

Before 1800: Plants, plant extracts, inorganic material

1805: Morphine isolated from opium (structure proposed 1828, proved by synth. 1852)

1828: First organic synthesis (urea)

1840-1850: First synthesized org. compds used in medicine: CHCl_3 , Et_2O (anesthetics)

Ex of early synthetic drugs:

Chloral hydrate (sleeping pill) 1869

Acetyl salicylic acid synth 1853, clin trials 1893

Phenazone synth 1884

Benzocaine 1902

Prontosil 1932

Ex of early isolated nat. prod.

Quinine ca 1825

Digitoxin 1841 (structure 1928)

Salicylic acid, antipyretic 1875

Cocaine isol. 1860, local anesthetic 1884

Benzylpenicillin 1941

Traditional medicine

Screening

Serendipity

Natural Products

- Only source of drugs before last part of 19th century
- Antibiotics 1940 - 1960
- Cyclosporin (immunomodulator) isolated from soil fungus *Hardangervidda* 1971
- Taxol isolated 1960s, approved drug USA 1992

• Lead compounds

Natural Products

Sources

- **Microorganisms (bacteria, fungus) - Antibiotics**
- **Higher plants, ex. morphine, quinine, taxol**
- **Sponges (polycellular “animals”, no real organs or cell tissue) ex. agelasines**
- **Higher animals, fewer examples, epibatidine from South American tree frog**

Microorganisms, sponges, plants

No immune system, produce their own antibiotics as defence

Secondary metabolites with great structural diversity, stereochemistry!

Secondary metabolites have no known metabolic role in cells

Three main classes: **alkaloids, terpenoids, phenolics**

Alkaloid Natural Products

- **Largest class of secondary metabolites, >6500 compds known**
- **Contains N, most compds basic (alkaline)**
- **Often highly toxic**
- **Found in certain higher plants (seldom in bacteria)**
- **Little is known regarding why alkaloids are produced**
- **Biosynthesis from amino acids**

Alkaloid Natural Products

Amino alkaloids: N as amine / amide (not in heterocycle)

Source *Ephedra sinica*



Sub types cholinerge reseptors

Acetylcholine

Muscarinerge

Nicotinerge

Source
Amanita muscaria



**Nicotine from
*Nicotiana tabacum***



KJM5230 - H06

Alkaloid Natural Products

Amino alkaloids

Source

Lophophora williamsi



Pyridine / piperidine alkaloids

Source

Erythroxylon coca

Cocaine



KJM5230 - H06

Pyridine / piperidine alkaloids

**Parasympatolytika
(Antikolinergika)**

Tropanalkaloids

Source *Atropa belladonna* og *Hyoscamus niger*



Atropa belladonna

Muscle relax (guts, eye)



Hyoscamus niger
(bulmeurt)

Scopolamin

Alkaloid Natural Products

Isoquinoline alkaloids

Curare - Poison - Southamerican indians

Mixt. of alkaloids

Several sources *i.e.* *Chondodendron tomentosum*



Ex. *Mivacurium klorid*

Muscle relax, anesthesia

***Suksametonium*, Curacit® “Nesset”**

Alkaloid Natural Products

Isoquinoline alkaloids

Morfin isolert fra opium 1803 (Morpheus: gresk søvngud)



Morfinanalogs, binds to opiopeptide (endorfin / enkefalin) reseptors

Naturally occurring and semisynth analgetic opioides

Morphine

Codeine

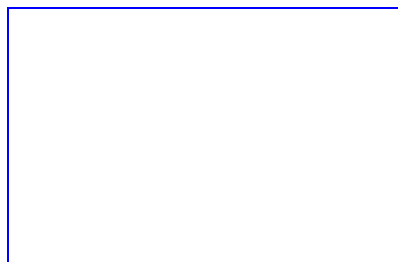
**also against cough
slow metabol. to morphine**

Small amounts in opium, semisynth from morphine

Total synthetic analgetic opioides

SAR - morphine

Model of morphine bound to μ -reseptor



Petidin (Meperidin)

Ketodur®, **Ketorax®**

Fentanyl

Fentanyl®, **Leptanal®**
(anestetica)

Ketobemidon

Ketodur®, **Ketorax®**
Ketogan®

Moscow theatre

KJM5230 - H06

Dekstropropoksyfen

Aporex®

Metadon

Buprenorfin

Temgesic®, Subutex®

(+) most active
less addict. than M.

μ-Agonist

analgetc, not euphoria,

Long duration

Good oral availabil.

More potent than M. (pain)

Partiell μ-agonist:

***Antagonister* high doses**

Naloxon effects (dysfori etc)

Naturally occurring and antitussiva opioides

Biosynthetic routes in *Papaver somniferum*



Noskapiin
(not analgetic,
not adiction)

Codeine

Etylmorfin
Cosylan®

Hydrokon
Hydrokon®

Folkodin
Tuxi®

KJM5230 - H06

Alkaloid Natural Products

Quinoline alkaloids

Cinchona pubescens (Kinatre) from South America



R=OMe: Quinine (Cinchonidine epimer at C-9)

R=H: Quinidine (Cinchonine epimer at C-9)

Quinidine: Antiarytmic

Quinine: Antimalaria

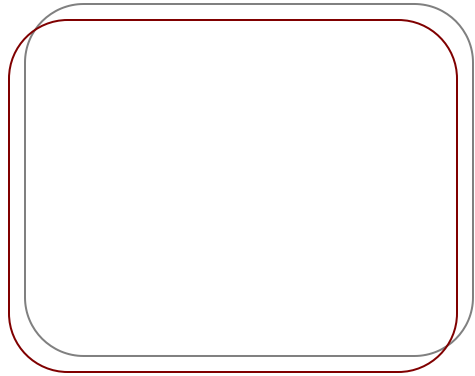
Dihydroquini(di)ne and der.

Chiral ligands

Asym. dihydroxylation (Sharpless)

Alkaloid Natural Products

Indole natural products



Indole alkaloids



KJM5230 - H06



Strychnos alkaloids - from *Strychnos nux vomica*



KJM5230 - H06

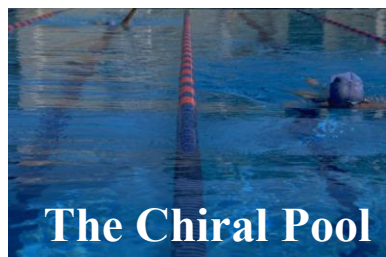
Terpenoide Natural Products

C-10: Monoterpenes
C-15: Sesquiterpenes
C-20: Diterpenes
C-25: Sesterterpenes
C-30: Triterpenes

Natures leaving group

Monoterpenes

Voilatile compds, smell, taste etc.



Cannabinoids,
from *Cannabis sativa* (Hemp)



Permetrin, Nix®

Shampoo, Lice, scabies

KJM5230 - H06

Diterpenes (C-20)

Head to tail coupling

Triterpenes (C-20)

Steroids

Cholesterol

Sex hormones

Estrogens

Progesterones

Testosteron and anabolic steroids

B / C og C / D always *trans* (animals)

Corticoids

Glucocorticosteroids

Cortison etc. etc.

Mineralcorticosteroidsr

Aldosterone

Digitalis glycosides

Fucidinic acid (antibiotic)

Brassinosteroids (Plant growth hormones)

etc. etc.

KJM5230 - H06

Sex hormones - Estrogenes

Estrogene agonists (mimics)

**Phytoestrogen
(in soya)**

Sex hormones - Progesterones (gestagens, progestrines)

Many semisynth drugs in use (better bioavailabil.)

Testosterone

Doping - Anabolic steroids

Semisynthesis sex hormones

KJM5230 - H06

Corticosteroids

Mineralcorticoid

Aldosterone

Regulation of electrolytic balance

increase re-uptake of Na (and hence H₂O)

Glucocorticoid

Effect on metabolism (karbohydrates, lipids, proteins)

Antiinflammatoric

Numerous semisynth. analogs as drugs

Various antiinflam. activity, mineralcorticoid side effects



Digitalis glycosides (cardenolides)

- Treatment of hart disease 1500 BC (Egypt)
- Increase hart contraction
- Tox.

Digitoxin

Digitoxin® R= H

Digoxin

Lanoxin® R= OH

A-B and C-D *cis* condens.

Digitalis purpurea
(foxglowe, revebjelle)

Stability

- Acid: Cleavage of sugars (acidic hydro acetals)
- Base:

Phenolic Natural Products

Biosynthesis from shikimate (- alkaloids)

From cinnamate

**Voilatile compds,
smell, taste etc.,
Not monoterpenes**

**From *Podophyllum peltatum*
May apple**

Antiviral, veneric warts

Toxic - lead for anticancer drugs

From cinnamate

Psoralenes

- Isolated from various plants
- Photochemotherapy against psoriasis
- [2+2] cycloadd. With cytosin / thymine in DNA

Dicoumarol

- Anticoagulant - Vit K antagonist
- Sweet clover disease

Warfarin - Marevan®

Aflatoxines

- From *Aspergillus flavus* (fungus)
- Attacks nuts etc.
- Carcinogenic