Lecture 5.

- **Initial evaluation of a compound as a potential drug.**
- **What properties make a compound "Drug-like"?**
  - Likely to be **a**bsorbed and become bio-available?
  - Likely to be **d**istributed and transported to the required organs in the body?
  - **M**etabolized?
  - **E**xcreted?

Lipinski rule of 5.

In order to have a reasonable chance of becoming a drug and meet the required ADME characteristics, a compound should

Have a MW less than 500

Have a logP of less than 5

Have fewer than 5 H-bond donors

Have fewer than 5 H-bond receptors.

Not all successful drugs fit all of these requirements

Almost all are consistent with three of the four!

*****

New and “improved variation.

- Have a MW less than 500
  - Small enough to be readily absorbed via the intestines

- Have a logP of less than 5
  - logP = log of the solubility of the compound in octanol / divided by the solubility in water.
    - If a compound is completely insoluble in biological media –mainly aqueous then it is not likely to be transported and distributed.

-Have fewer than 5 H-bond donors

Have fewer than 5 H-bond receptors.

Hydrogen bonding and Drugs

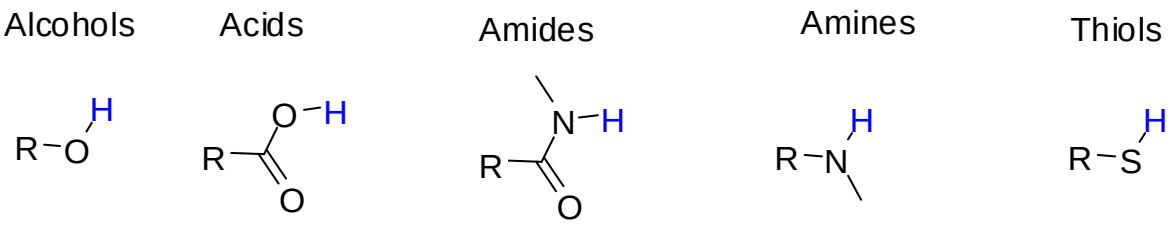
- Water is an excellent H-bond donor and an H bond acceptor.
- Molecules that have many H-bond donor or H-bond acceptor positions interact very strongly with water. H-bond strength is up to 5 Kcal/mol
- **Much energy is required for the drug molecule to be desolvated from the water { water removed} before it can bind to { interact with} a receptor site-Unfavourable!!!**

Takes a large amount of energy.

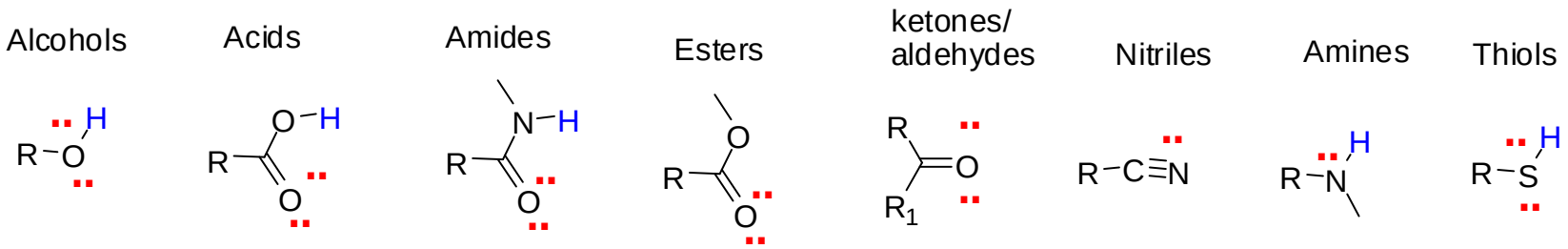
Receptor site tends to be non polar.

Lipinski rule of 5

- Have fewer than five hydrogen bond donors and fewer than five hydrogen bond acceptors
- H-bond donor unit is one in which a H is bonded to an electronegative element such as oxygen > nitrogen > sulfur



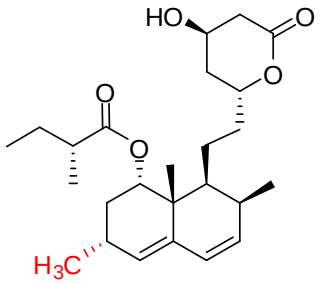
- Hydrogen bond accepting unit is one which has an atom which has a lone pair such as nitrogen, oxygen, sulfur



Resonance involved due to lone pairs.

Lipinski rule illustrations

- **Lovostatin**



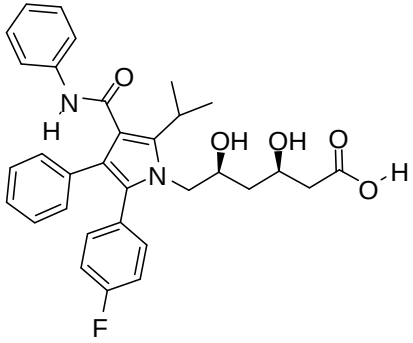
Mw = 418

Log P: 4.22

H- bond donors = 1

H-bond accpetors = 3

- **Lipitor**



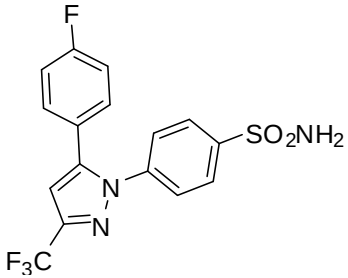
MW = 544

Log P: 4.94

H-bond donor sites : 4

H-bond accpetor sites - 4

- **Celebrex**



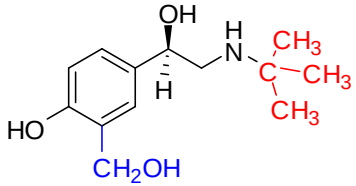
Mw= 239

Log P = 4.0

H-bond donors = 1

H-bond acceptors = 3

Salbutamol



Mw= 239

Log P = 1.0

H-bond donors = 4

H-bond acceptors = 4

Metabolism

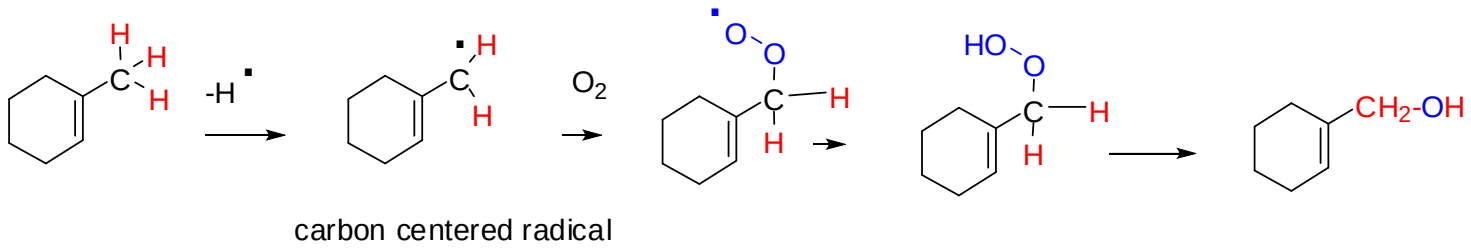
- Mainly by liver enzymes belonging to the cyctochrome P-450 family
- Almost a dozen variations have been identified in humans. The most important are **CYP3A4** and **CYP2C19**
  - 50% of metabolism of drugs.
  - Liver enzymes.
  - ~50%
- These enzymes accept compounds with widely different shapes and sizes of
  - Introduce oxygen into the molecule using molecular oxygen.
    - oxygen gets further transformed so the compound can be eliminated.
- Mechanism

all animals have developed this in order to remove toxic materials, not just drugs. all foods contain naturally toxic materials. we need these enzymes to prevent the build up of xenophobic (toxic) materials.

Metabolism

2 kinds of mechanisms, depends on if youre introducing oxygen to a double bond or saturated carbon (sp3 hybridized)

- Introduction of an OH group at a saturated carbon atom
- Mechanism:
  - 1. Abstraction of a hydrogen atom, preferred from a relatively weak C-H bond, thereby forming a relatively stable carbon centered radical
  - 2. Reaction with molecular oxygen to form a hydroperoxy radial
  - 3. Abstraction of a hydogen atom from another molecule giving a hydroperoxide
  - 4. Reduction of the hydroperoxide to an alcohol.



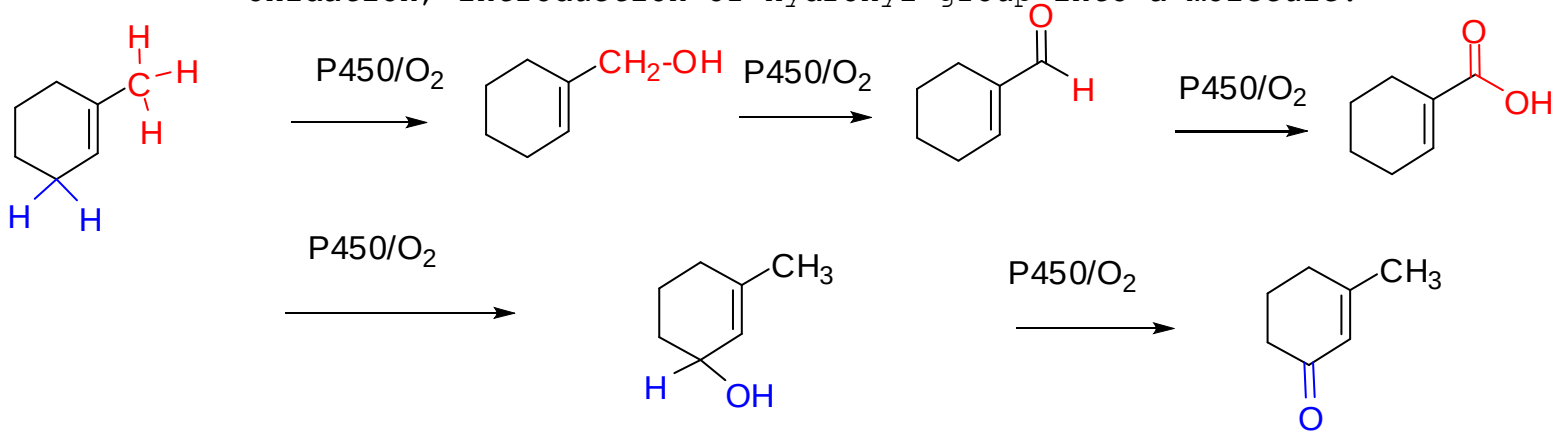
carbon centered radical

active site of enzyme, involving iron, extracts 1 of the Hs
tends to extract the Hs from the weakest CH bond -> forms most stable carbon radical
then forms a radical, reactive species

Metabolism: P450 Oxidation at a saturated carbon

- Oxidation can occur at different sites, and several times at the same site
  - CH3 groups -> CH2OH -> CH=O -> CO2H
  - -CH2- groups -> -CH(OH)- -> -C(=O)-

oxidation, introduction of hydroxyl group into a molecule.



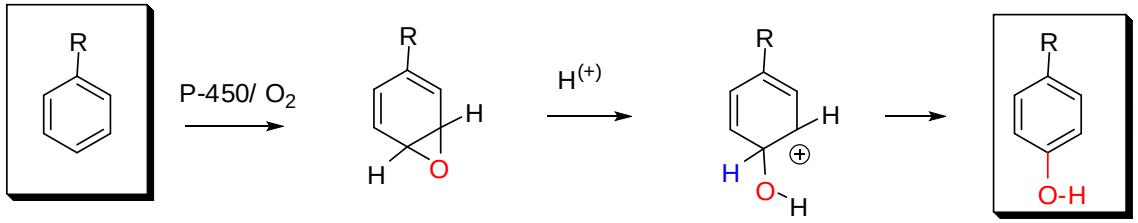
hydroxyl grp can join something very polar, then the cytochrome enzyme in the liver can remove it.

Metabolism: Introduction of OH groups into of aromatic rings

- Mechanism involves formation of an epoxide followed by rearrangement

high e- density in the benzene ring is easier,
low e- density makes it more difficult.

- Electrophilic attack on the benzene ring



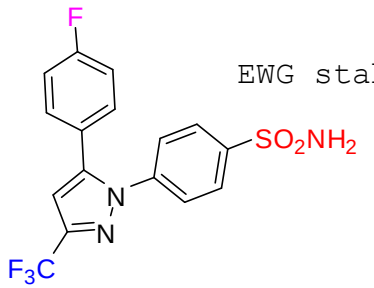
- Helps explains why substituents such as F, Cl, CF3, and SO2CH3 slow down the metabolism of drugs containing these groups on an aromatic ring in the drug.
  - These substituents are electron withdrawing groups (EWG).
  - They remove electron density from the aromatic ring making the epoxide reaction less favourable.

another method is to create a 3 membered ring epoxide, ring will swing open, and be able to form new bonds.

EWG groups reduce the rate of metabolism drugs containing a benzene ring.

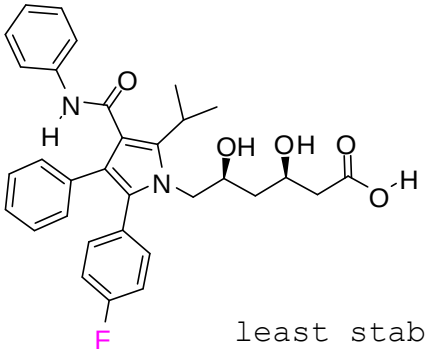
- Many drugs with aromatic rings have such substituents in order to slow down their rate of metabolism and increase their half-life in the body. (Other effect of F and Cl: increase in lipophilicity [logP]) storing within the fat in the body - liphophilicity.

Celebrex



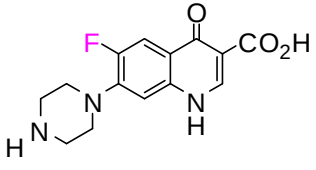
EWG stabilizes

Lipotor

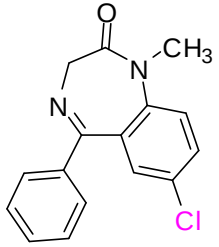


least stable, only one EWG.

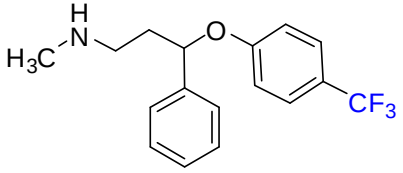
Ciprofloxacin



Valium

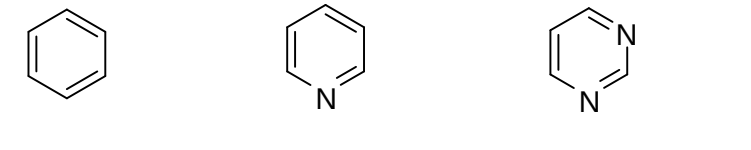


Prozac



Metabolism at aromatic rings other than benzene

- Electron poor aromatic rings tend to be metabolically more stable than a benzene ring

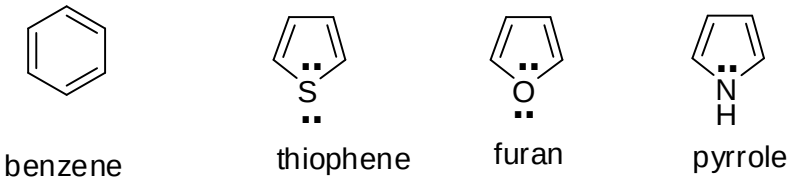


decreases electronegativity because of electronegative elements.

Decreasing electron density

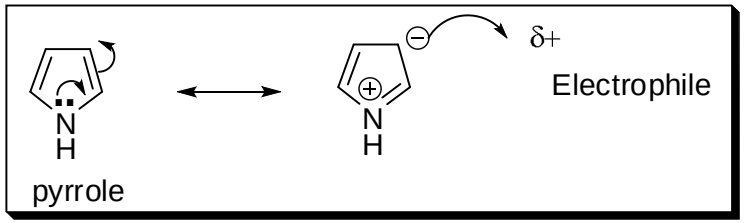
Increasing metabolic stability

changes the property of the drug, right now we're only concerned with stability.



Increasing electron density in the double bonds
Increases the rate of epoxide formation
(Increase rate of metabolism

Explanation



l.p involved in resonance. can result in excess e- density, which causes an electrophilic attack.

Drug-Drug Interactions, some compounds (drugs, natural health compounds) inhibit the key CYP enzmyes and reduce the rate of metabolism of the prescribed drug.
the result may be desirable or undesirable, even tragic.
need to be aware of the: metabolism (enzyme involved), degree of inhibition, therapeutic index [TI]
therefore, one drug causing inhibition could result in elevated levels of another drug, causing toxicity.

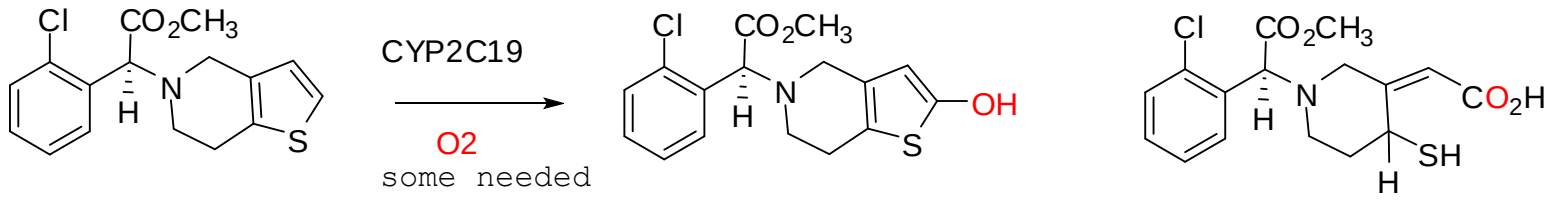
low TI is bad, high is good (difference between efficacy and toxicity).
TI, toxic dosage for 50% of patients, therapeutic dosage for 50% of the patients.
TD50/ED50, ideally a large number, if less than 5 it gives a narrow window & a small margin of error

Pro-drugs are activated by metabolism

digoxin, coronary heart disease,
small TI.
acetominophen has a large TI

want low dosage, high value for toxicity.

- Famous case is Plavix.



Plavix -pro-drug

active metabolite

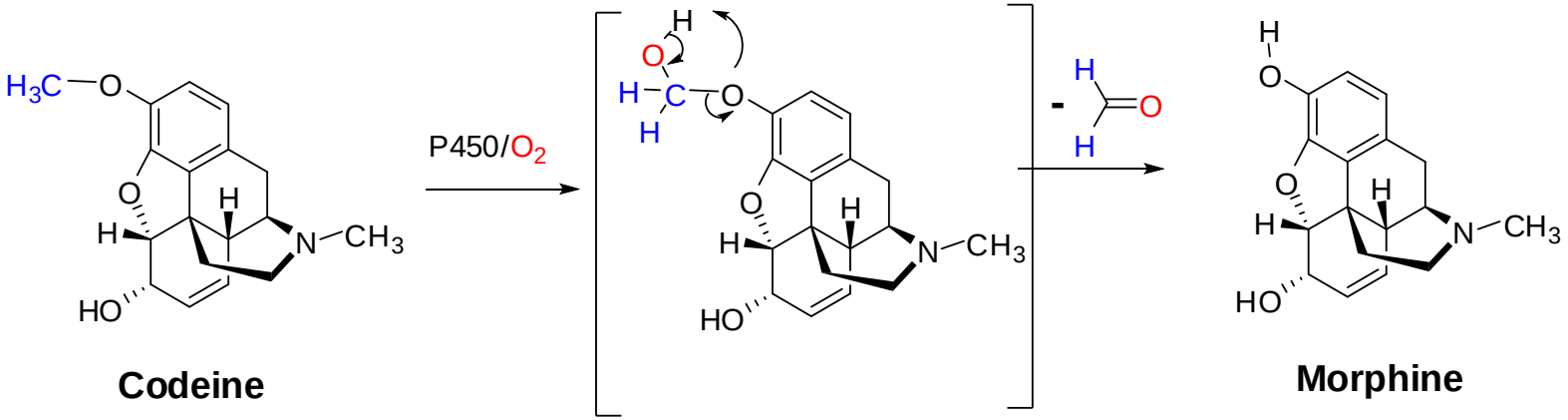
15-20% dont have the enzyme, cannot activate the drug, which is an important drug.

- antiplatelet agent used to inhibit blood clots in coronary artery disease, peripheral vascular disease, and cerebrovascular disease.
- Patients who do not have sufficient CYP2C19 have ~4 times the number of serious complications following operations

- In March 2010, the U.S. (FDA) added a boxed warning to Plavix alerting that the drug can be less effective in people who cannot metabolize the drug to convert it to its active form

Metabolism of Codeine is necessary for analgesic effect

- Metabolic conversion of O-CH3 to O-H



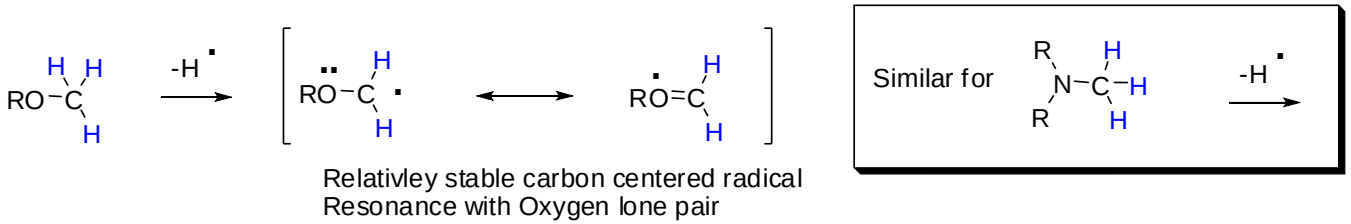
Codeine

only works for 85% of people

Morphine

a real analgesic

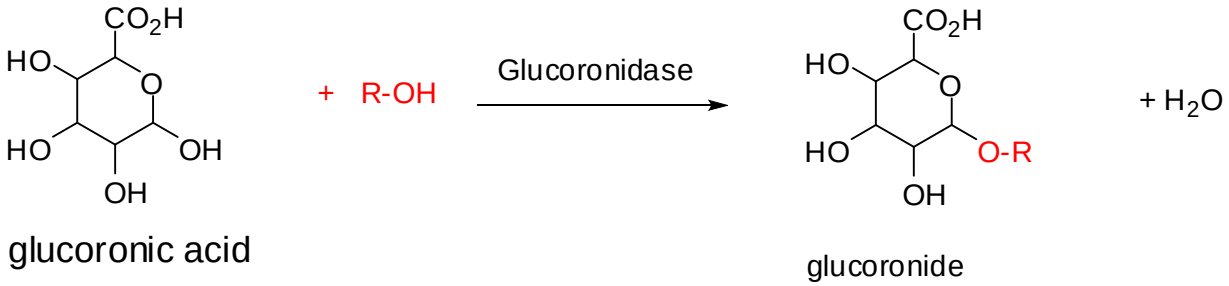
- Why?



Relativley stable carbon centered radical
Resonance with Oxygen lone pair

Excretion

- To make compounds more water soluble and ready for excretion via the kidney, alcohols and sulfonated or converted into glucoronides. **[Phase II metabolism]**



- These molecules have increased water solubility relative to the parent alcohols – readily excreted.

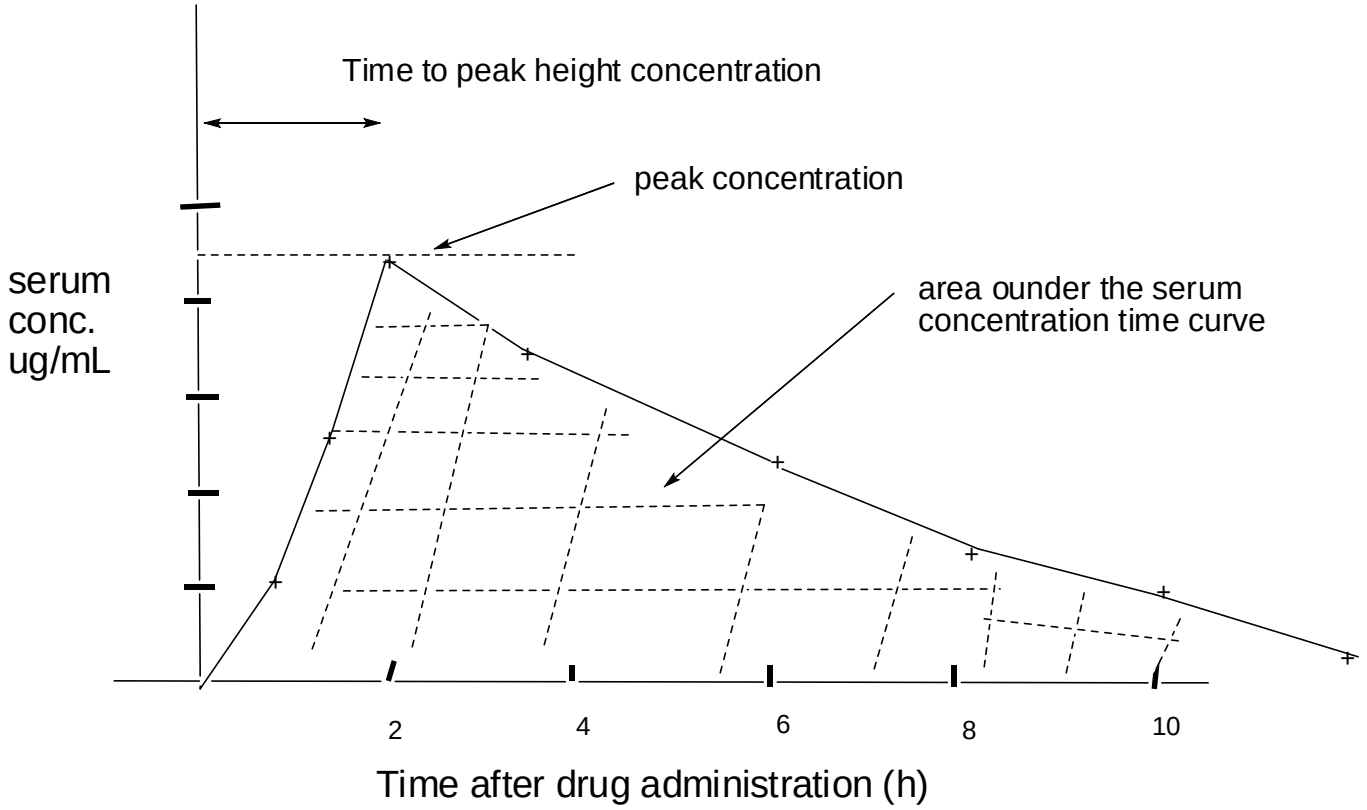
Bioavailability and bioequivalence

- Bioavailability-
  - The rate and extent to which an active drug ingredient is absorbed and becomes available at the site of action

- Bioequivalence-
  - Refers to a comparison of the bioavailability of the active ingredient from different formulation prepared by different manufacturers or even in different batches of the same drug product from the same manufacturer.

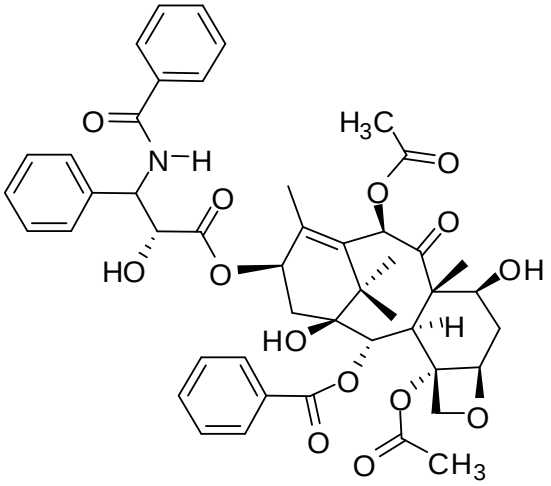
Bioavailability

- Is determined by studying the concentration of the drug and its metabolites over time in
  - Blood plasma –Urine-Distribution in different organs of the body



- Taxol

Orginally obtained from: Bark of pacific yew trees



Clinical Uses: Chemotherapy

ovarian,, breat. lung

Side effects:

Severe: Unusual bleeding and bruising
dizziness
severe exhaustion
skin rash

Common: nausea
vomitting
loss of appetite
change in taste
hair loss
tingling in hands and toes
change if colour of nails

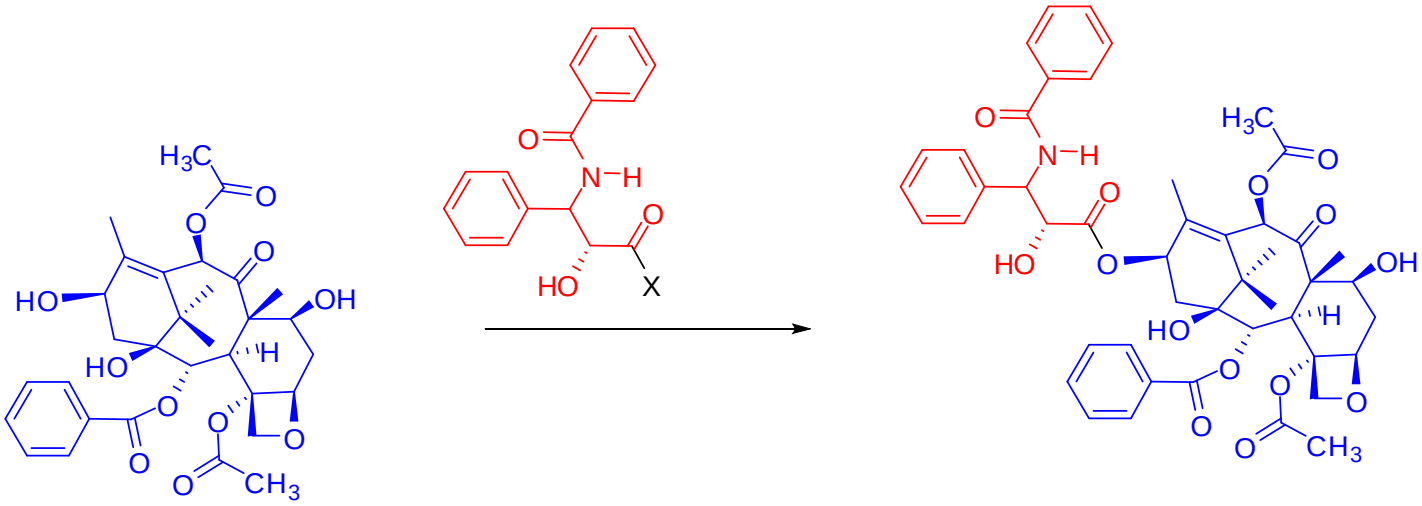
Currently produced by isolating arelated natural product called **baccetin III** isolated from an Eastern Canadain shrubb called *Taxus canadiensis* and then modifying this in the lab to give Taxol.
Baccettin III is now also produced by fermentation using cel lines from *Taxus canadiensis*

Taxol-production and formulation

- Production
  - Yew tree bark
    - Yield and cost:
  - Semi-synthesis via Baccatin III, obtained from needles of *Taxus canadiensis ,* an Eastern Canadian shrub
  - Fermentation process

Taxol: Semi-synthesis via Baccatin III

- Relationship between Taxol and Baccatin III



Baccatin III **Taxol**

- Opportunity for Taxol analogs -Taxotere

Taxol analogs -Taxotere

- Taxol vs Taxotere

  Efficacy

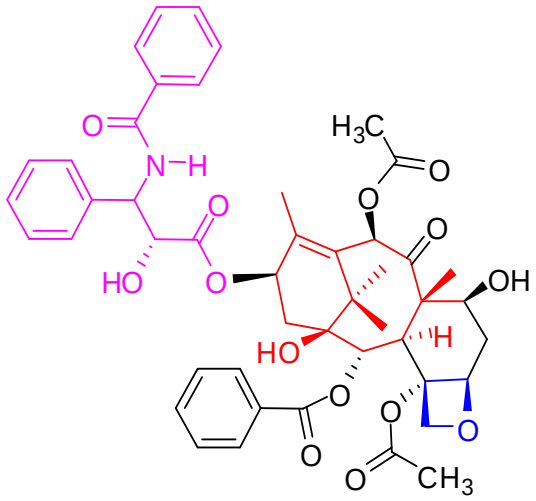
  Formulation

  Side effects

  Cost

Structure variety in natural products-ovarian cancer

- Taxol



Orginally obtained from: Bark of pacific yew trees

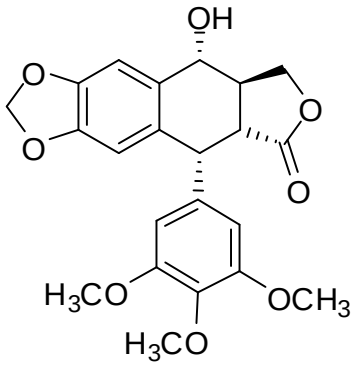
Clinical Uses: Chemotherapy

ovarian,, breat. lung

Discovered by screening for cytotoxic effects

- **********

- Podophyllotoxin
  - Small cell lung cancer

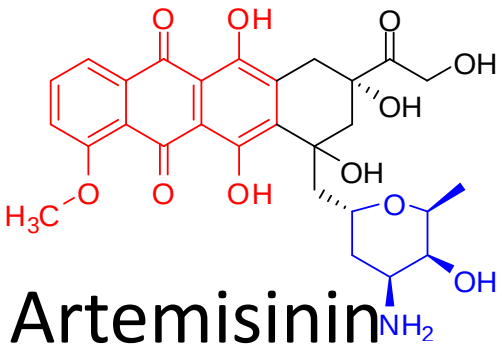


Isolated from the roots of the North American May Apple *[Podophyllum peltatum]*

Traditonal use natives: removal of warts

Structure variety in natural products

- Adriamycin



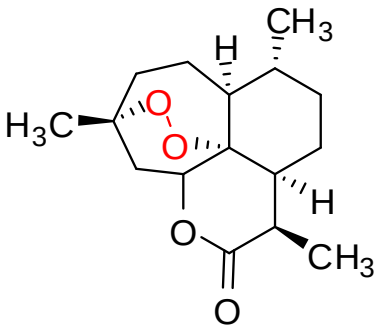
Discovered by screening for cytotoxixc activity

Clinical Uses, since the 1960s for a variety of cancers

including:

leukemia, , hidkins lymphoma, bladder, breast, stomach, lung...

- Artemisinin



Artimisinin -discovered in a screening program of tradional Chinese Medicines by Chinese Army Doctors

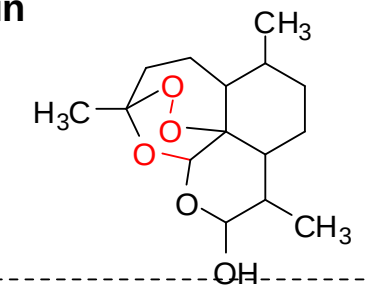
Currently, the most effective medicine for the treatment of malaria

Typically: Artimisinin Combination Therapy {ACT} to slow the development of resistance

Now being investigated as a potential anti-cancer compound based on studying the mechanism of action. Key: the peroxide bond

Structure variety in natural products- Antimalarials

Artemisinin

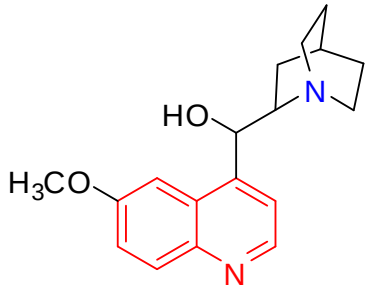


Based on Chinese Traditional Medicine

Best, most potent anti-malarial

Obtained from a shrub native to China: Artemesia annua

Quinine

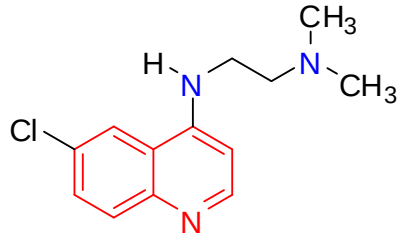


Based on traditional knowledge (Peru)

Isolated from the Chincona tree bark

First known potent antimalarial

Choroquine

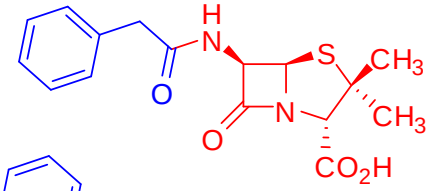


Synthetic
Excellent antimalarial
some resisant parasite

Structure variety in natural products

- **The Penicillins 1928->1942->**

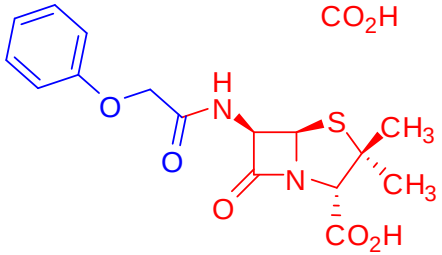
Penicillin V



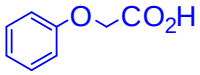
Original naturally produced penicillin from the penicillium mold
Gram positive activity

Poor oral activity

Penicillin G

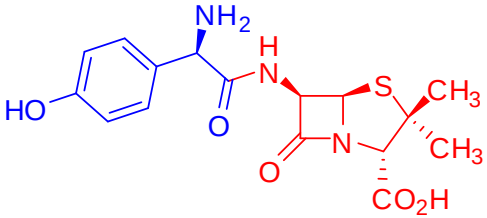


Also produced via fermenation by adding



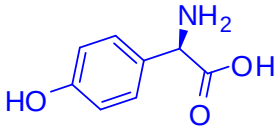
Gram positive activity
Good oral activity

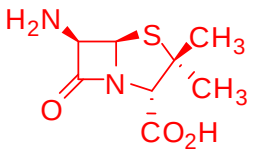
Amoxycillin



Broader spectrum activity; includes Gram Positive and some Gram negative bacterial

Orally active
Produced semi-synthetically

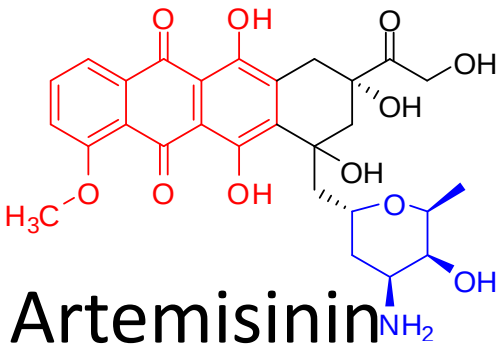




6-amino-penicillanic acid

Structure variety in natural products

- Adriamycin



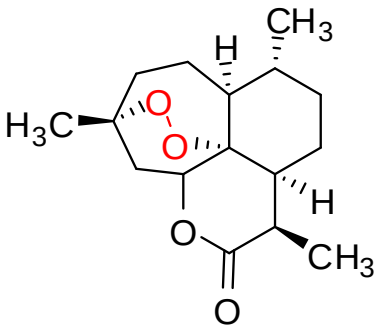
Discovered by screening for cytotoxixc activity

Clinical Uses, since the 1960s for a variety of cancers

including:

leukemia, , hidkins lymphoma, bladder, breast, stomach, lung...

- Artemisinin



Artimisinin -discovered in a screening program of tradional Chinese Medicines by Chinese Army Doctors

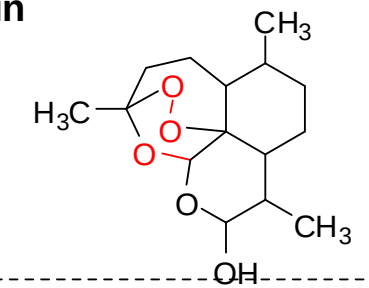
Currently, the most effective medicine for the treatment of malaria

Typically: Artimisinin Combination Therapy {ACT} to slow the development of resistance

Now being investigated as a potential anti-cancer compound based on studying the mechanism of action. Key: the peroxide bond

Structure variety in natural products- Antimalarials

Artemisinin

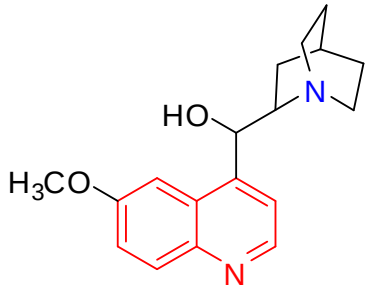


Based on Chinese Traditional Medicine

Best, most potent anti-malarial

Obtained from a shrub native to China: Artemesia annua

Quinine

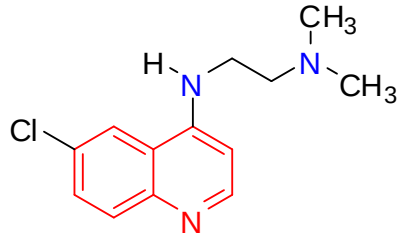


Based on traditional knowledge (Peru)

Isolated from the Chincona tree bark

First known potent antimalarial

Choroquine

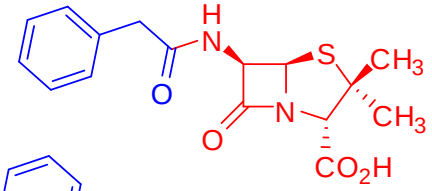


Synthetic
Excellent antimalarial
some resisant parasite

Structure variety in natural products

- **The Penicillins 1928->1942->**

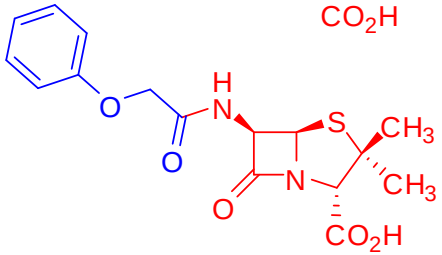
Penicillin V



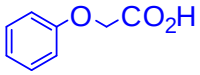
Original naturally produced penicillin from the penicillium mold
Gram positive activity

Poor oral activity

Penicillin G

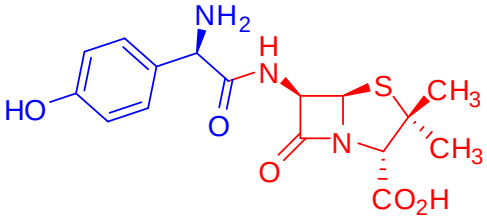


Also produced via fermenation by adding



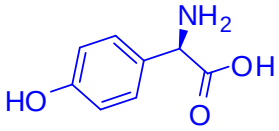
Gram positive activity
Good oral activity

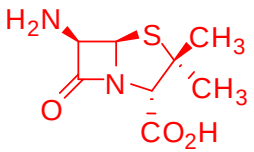
Amoxycillin



Broader spectrum activity; includes Gram Positive and some Gram negative bacterial

Orally active
Produced semi-synthetically



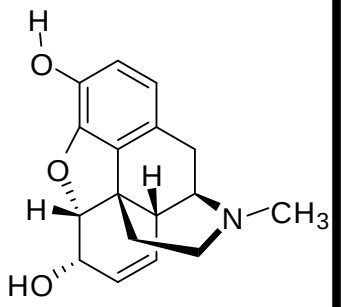


6-amino-penicillanic acid

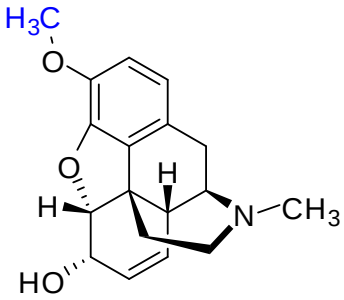
Structure variety in natural products

- Morphine –Alkaloids- natural or semi-synthetic

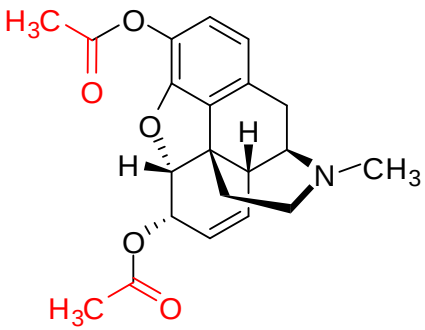
Morphine



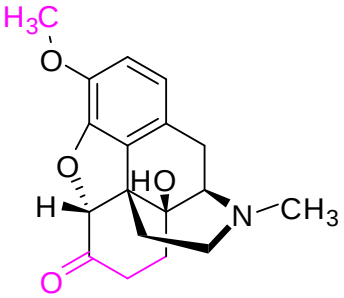
Codeine



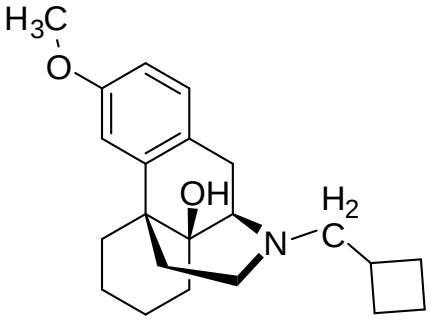
Heroin



Oxycodone



- Butorphanol
  - Synthetic

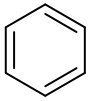


CNS active alkaloids

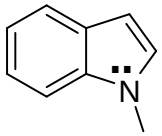
Common structure requirement for CNS active compounds:

Basic nitrogen atom joined to an aromatic ring via a satruated two carbon units

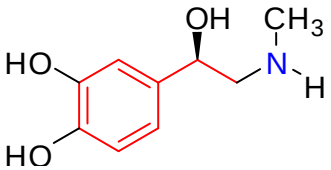
Aromatic rings are planar rings with all sp2 hybridized atoms with 6, 10, 14π electrons



benzene ring is a 6π eletron aromatic ring

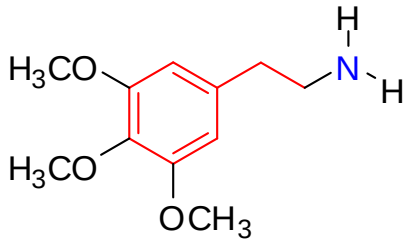


indole ring is a 10π eletron aromatic ring

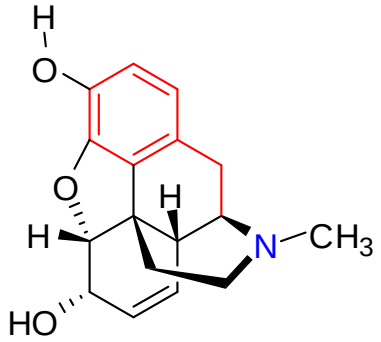


Adrenaline = epinephrine

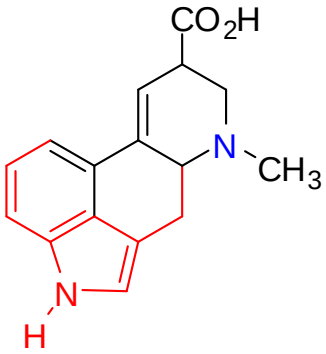
Natural CNS Active compounds



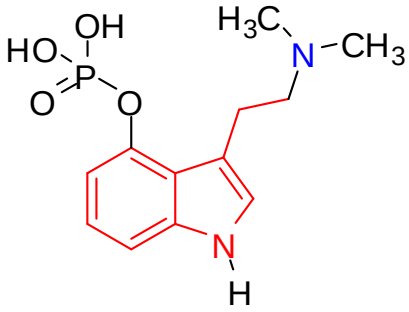
mescaline
peyote cactus



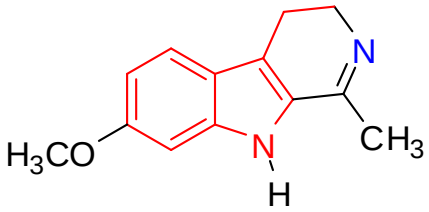
Morphine



Lysergic acid
Ergot fungus
growing on rye



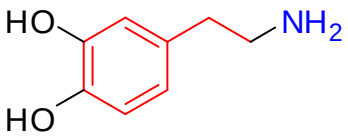
Psilocybin
[sacred mushroom



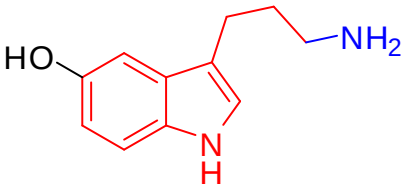
Harmaline
Halucinogenic drink
Amazon: Ayahusca

Neurotransmitters and “street drugs”

- Dopamine , serotonin and amphetamines

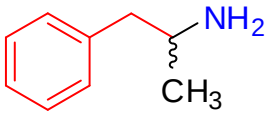


Dopamine
neurotransmitter

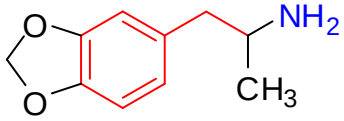


Serotin
neurotransmitter

contributes to feeling well



amphetamine
stimulant



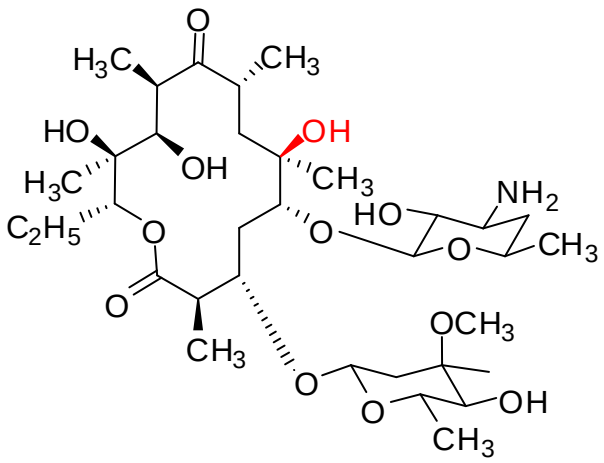
MDMA (3,4-Methylenedioxy-N-methylamphetamine)

Ecstasy,

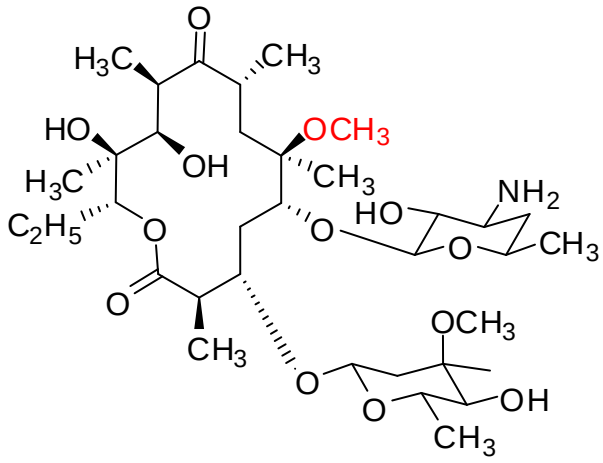
Structure variety in natural products

- Macrolide antibiotics from micro-organisms
  - Erithromycin and Clarithromycin

Erithromycin



Clarithromycin



The Nexium Story

- Discovery of Omeprazole
  - Mixture of enantiomers
- Success of Omeprazole
  - Patent Expiry
    - Preparation and repatenting of a single isomer
    - Creation of Nexium as a single enantiomer
    - Clinical trials
      - Omeprazole vs Nexium
    - Ethical issues vs monetary gain