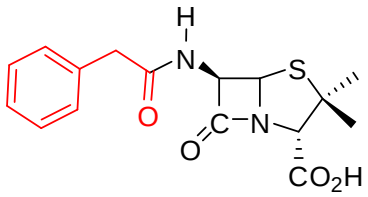
Continuation of Lecture 5. Liver metabolism

- **Avoiding liver enzyme metabolism** - also called first pass metabolism. elimination of drug after hydroxylation process
- Change the administration from "oral" to
  - Intravenous injection goes directly into the blood stream, different bioavailability
  - Intramuscular injection
  - Sublingual underneath the tongue
  - Inhalation
  - Rectal suppositories
- Need to adjust dosage

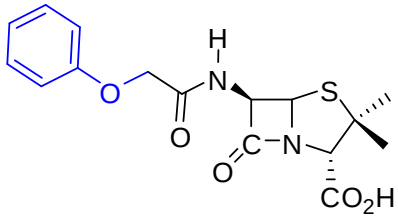
- Examples
  - Nitroglycerin — anti-anginal — serious heart problems underneath the tongue
  - Aspirin — analgesic — can be used rectally bolis - works much faster than oral
  - Propranolol — beta blocker

Other “metabolisms”

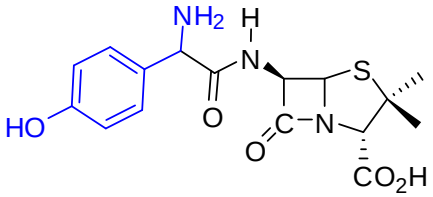
- Drugs (compounds) that are not acid stable do not survive stomach acidity.
  - Not useful as orally taken drugs, unless they can be formulated so that they pass through the stomach and then are absorbed in the intestines.
- Classic example: Penicillin antibiotics.



Pen G
ORALLY INACTIVE
INJECTION.



most common
Pen V
ORALLY ACITIVE



Amoxyxillin
ORALLY
ACITIVE

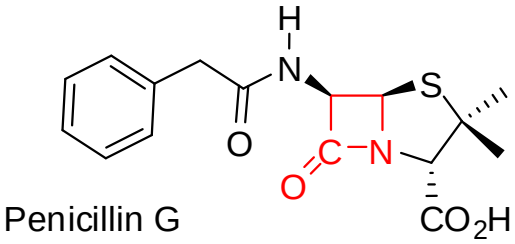
what's the difference? whyis one of them orally inactive and the other two aren't?
study the activity of these compounds, as a chemist you would recognize the 4 membered C ring, the important part of the pharmacology of these compounds. Relatively unstable, carbonyl grp, amide bond which tends to break. When the bond breaks, the activity is completely gone.
Pen G must be decomposed in stomach acid must more readily than the others.

Penicillins and acid stability

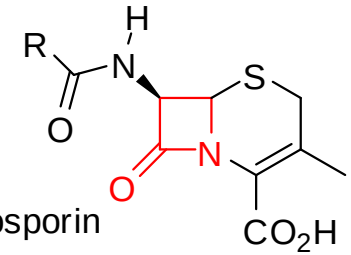
- All beta-lactam anti-biotics (penicillins and cephalosporins) are have some acid sensitivity

common anti biotics

-



Penicillin G



a cephalosporin

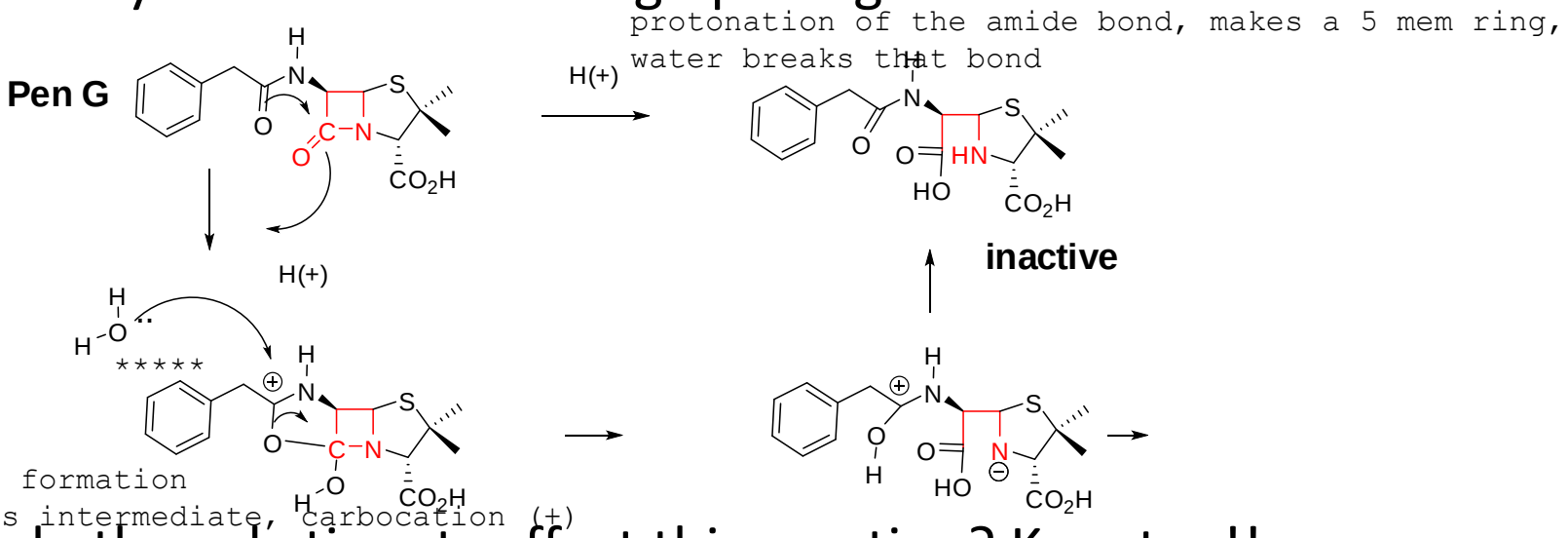
beta lactam ring
- required for anti-biotic acitiviy
-is incorporated into the bacterial cell wall
- creates a flaw in the cell wall, breaks the wall, cell dies
- prevents further growth of the cell wall

Higly strained four member ring
- REACTIVE TO BOTH ACIDIC AND BASIC CONDITIONS
The β-lactam ring is opened- Loss of anti-biotic activity

as a medicinal chemist, you investigate what happens when you treat these molecules with acid, etc...
what is the key? the key in breaking the beta lactyl ring, ...

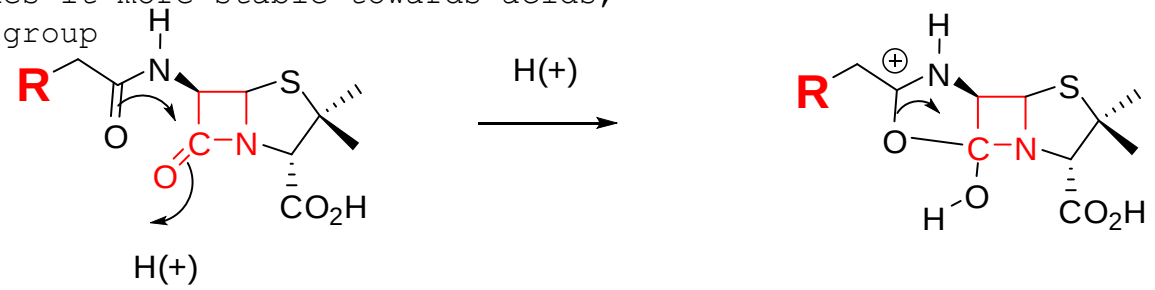
Explanation

- Acid catalyzed beta lactam ring opening



- How do the substiuents affect this reaction? Key step!!

******any substiuent added that favors formation of (+) charge makes it more stable towards acids, EWG - electron withdrawing group is used

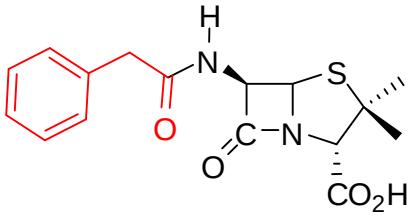


- Conclusion:
  - An electron withdrawing R group will disfavour formation of the intermediate and increase the acid stability of the lactam ring

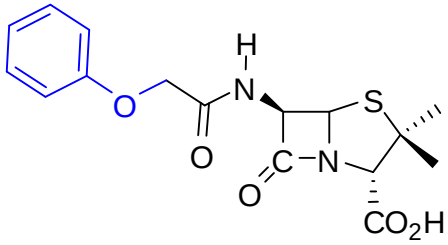
Prediction verified by observation

- .

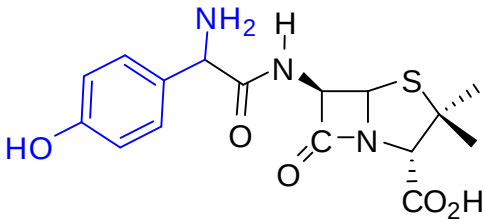
both of these are more stable to acids



Pen G
ORALLY INACTIVE
INJECTION.

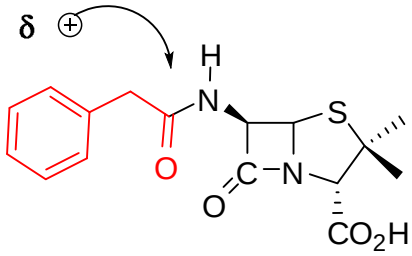


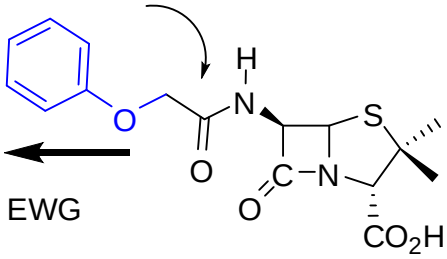
Pen V
ORALLY ACITIVE



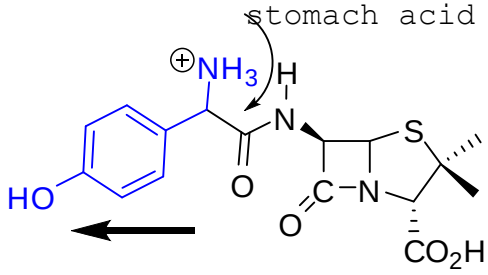
Amoxyxillin
ORALLY
ACITIVE

N becomes protonated by stomach acid





EWG



EWG

carbonyl group, how do the substiuents effect the stability?

EWG destabilize the δ ⊕
making it less likely to get involved.

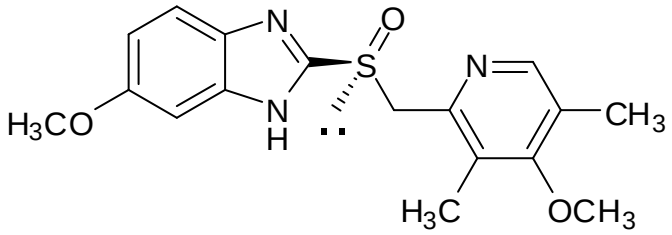
Omeprazole -> Nexium for treatment of acid reflux

Astra-Zeneca product. Totally synthetic

- Amongst the top selling drugs world wide.
  - 14.4 B$ between 2001 and 2005

prevents excess stomach acidity.

- A proton pump pro-drug that is activated by acid



Uses:
-Treatment of acid reflux (heartburn)
- dudenal ulcers in cpmbination with amoxycillin

- A major cause of ulcers is a bacteria- H. pylori;
- In the combination, amoxycillin kills the bacteria and omeprazole controls the stomach acidity allowing the stomach lesions to heal.

prevents hospitalization.

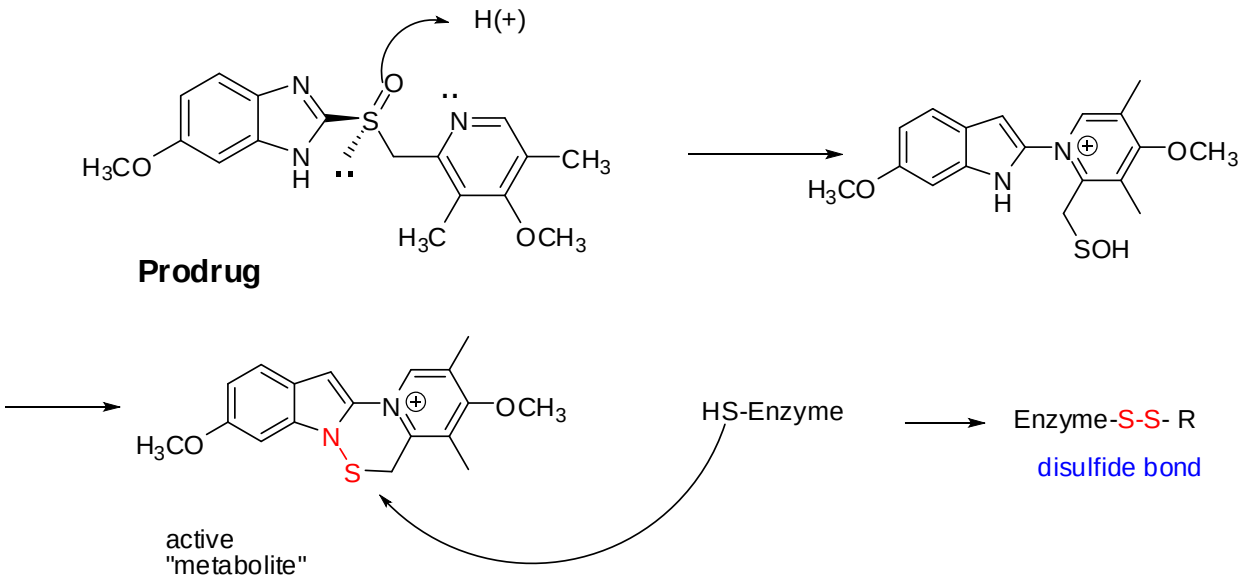
- Ulcers , major cause- long term use of NSAISs

NSAIDs

using omeprazole allows your stomach to recover.

has to be activated or metabolized. very susceptible to acids, doesn't survive the stomach, ensure it survives the stomach by coating it, and then once it's in the intestine it can be absorbed, and then it can be activated in the bloodstream

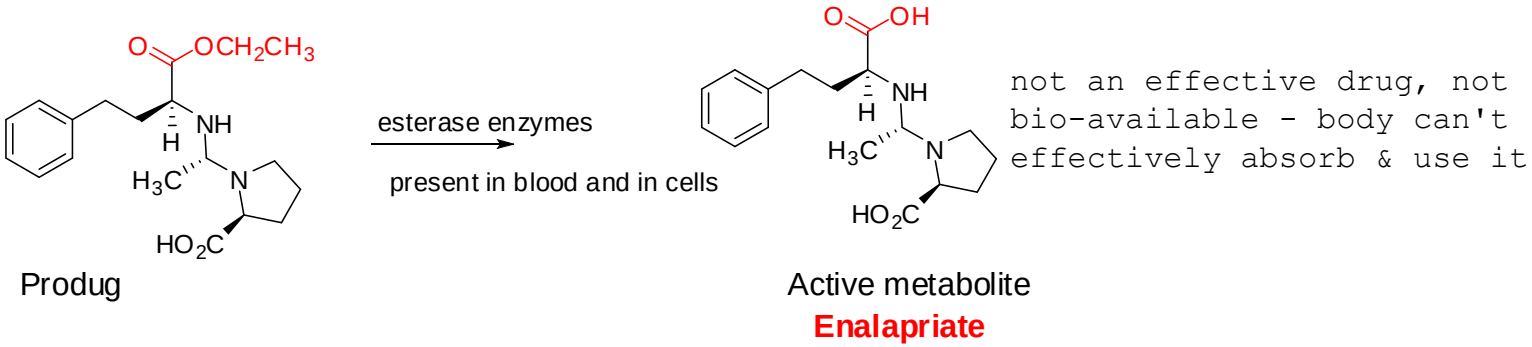
From Pro-drug to the active principle



- Nexium/omeprazole is not stable in the stomach. It is necessary to protect it by formulation. Coating the drug to protect it until it is in the intestine.

ACE inhibitors

- Angiotensin Converting Enzyme inhibitors
  - Used to treat hypertension.
- ACE raises blood pressure –ACE inhibitors prevent this
- Enalapril (Vasotec) amongst the most effective ACE inhibitors



Produg

Active metabolite
Enalapriate

- Enalaprilate is the effective drug. Not orally bio-available –too polar and not absorbed. Effective via injection!
- Converting the di-acid into the monoacid – ethyl ester reduced polarity. The compound is absorbed into the blood stream and then converted into the active drug.

making it lipid soluble

allowing it to become orally available.

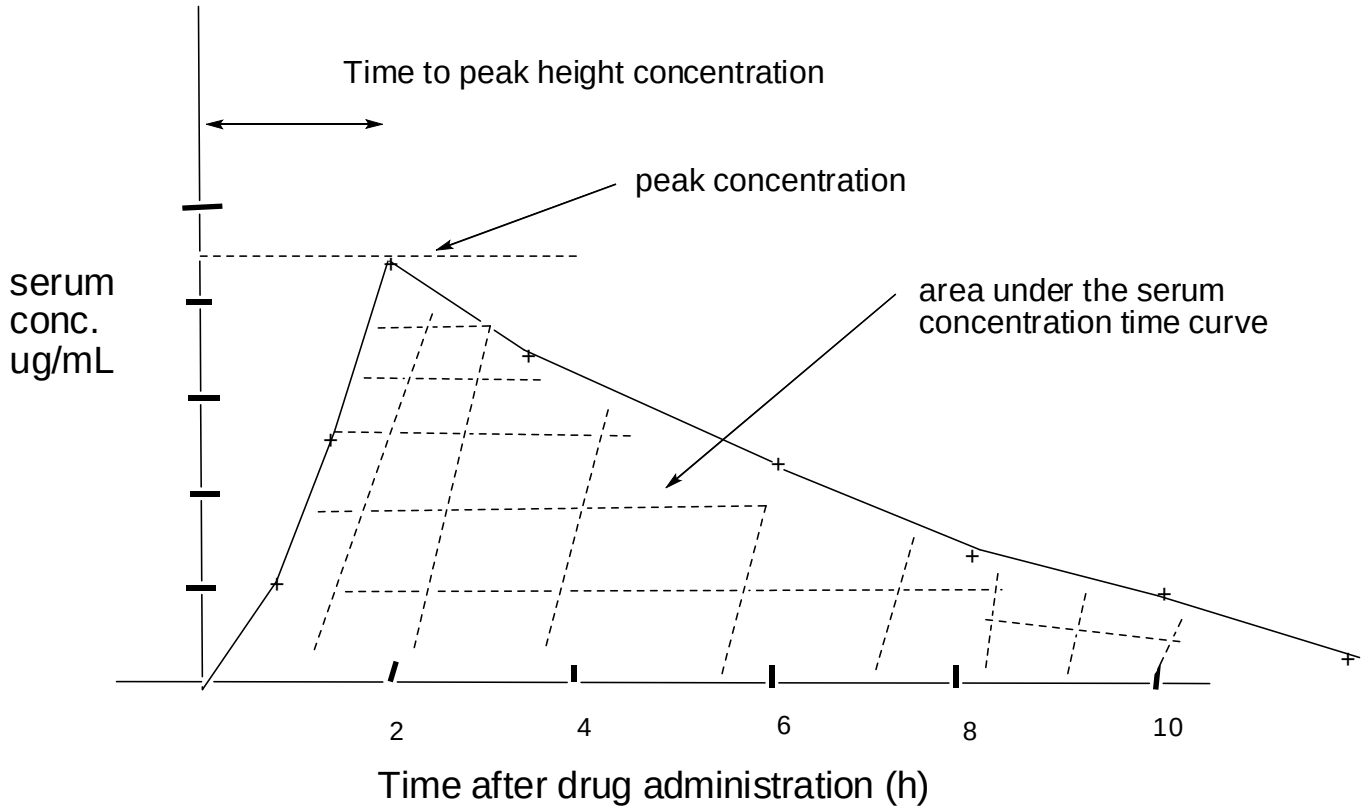
Definitions

- 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



Lecture 6
Plant derived Natural Product Drugs

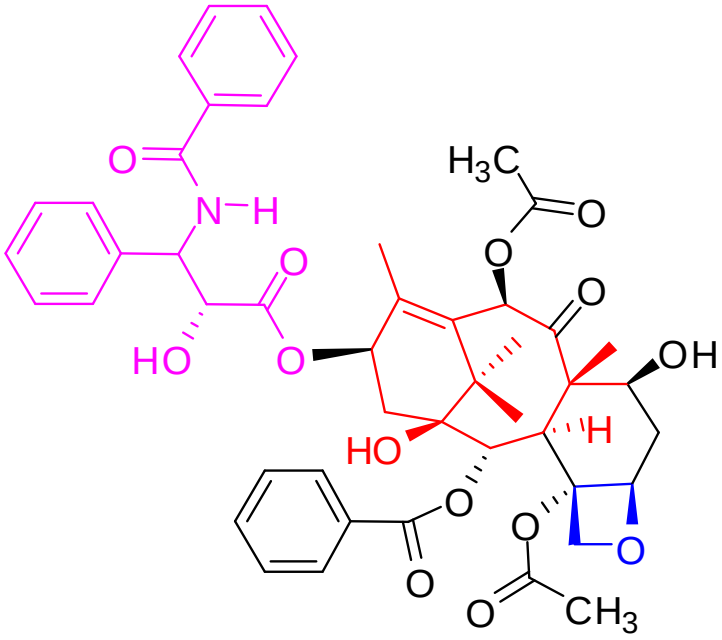
Plant derived Natural Product Drugs

- Aspirin [ASA] from the use of willow bark to treat fevers and inflammations
- **Quinine** *from the chinchona tree bark to treat malaria
- **Artemisinin** * from *Artemisa annua* to treat malaria
- Morphine and codeine from poppies to treat pain
- Meformin from French Lilac to treat Type II diabetes
- Digoxin from foxglove to regulate heartbeat
- Reserpine from an Indian shrub to treat hypertension
- Vincristine and vinblastine from Madagascar periwinkle to treat childhood leukemia
- Etosposide from the North American May apple to treat lung and kidney cancers
- **Taxol** * from Pacific yew tree for various cancers
- SinSusto from a Costa Rican vine to treat anxiety –TD

Taxol- anti-cancer "poster child"

synthesized by chemists 2-3 times, in a difficult way, took years and years

- Isolated (1967) from the bark of the Pacific yew tree
- Identified as cyto-toxic in a cancer screen potential for cancer
- (1969) 1200 kg of bark resulted in 28 g of crude and eventually 10 g of pure compound.



Taxol

- Between 1969 and 1988 many cancer experiments (small clinical trials) were carried
- Most encouraging result from the US National Cancer Institute: **A 30% response rate in refractory ovarian cancer!** for even the most resistant strains
- Crisis situation: Supply:
  - very difficult to get the material
  - To get sufficient amount for serious clinical trials – needed to harvest ~360,000 trees – a rare species. not widespread
- national cancer institute
- NCI – invited Bristol Myers Co. to take over, solve the supply problem, and complete clinical trials
  - big pharm company
  - NCI gave them all their data, they needed a company with a large amoutn of resources

Taxol-

- Bristol Myers Company
  - solved the supply problem,
  - carried out additional clinical trials
  - within 2 years fined an Investigational New Drug (IND) application because it was an important drug, only 2 years.
- Approved in 1992. Bristol was also given the rights to the name Taxol ®
- Annual sales in 2000 1.6 B $
- **Application – Lung, ovarian, breast, head and neck cancers.**

"success story"

Taxol. How the supply problem was solved.

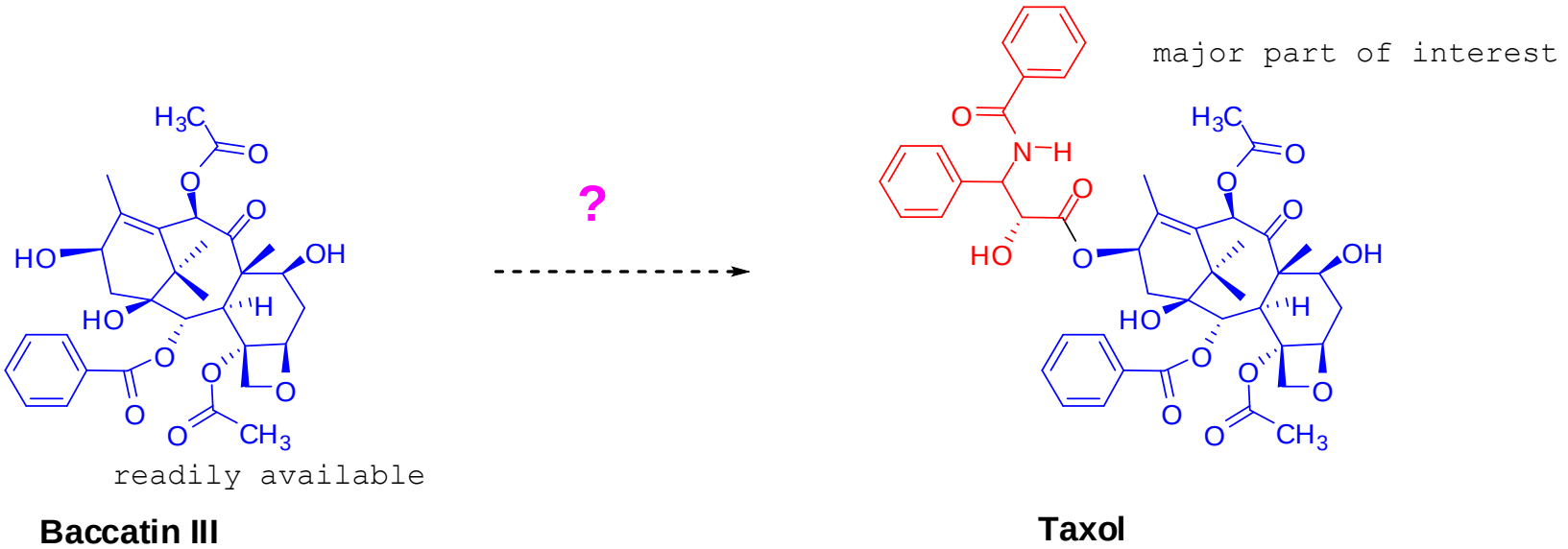
- **Find another source?**
- **Total chemical synthesis**? NOT viable!!! Far to many steps. 75 chemical steps, yield is 0.0002%
- **Realistic possibility:** Another natural, less destructive source.
  - Needles of various yew trees or related species
  - *Taxus canadiensus* needles and European ornamental yew shrubs removing needles, maybe they will regrow, & regrow new branches, instead of cutting trees down - more renewable supply (slow growing tree)
    - Contained small amounts of Taxol and much larger amounts of a related compound called baccetin III

needles contained a small amt of taxol, better than the bark of yew tree, contained a significant amount of compound called baccetin III, what is the relationship?

Taxus canadiensus (Ontario)

Growing ends are harvested

Relationship between Taxol®and baccatin III



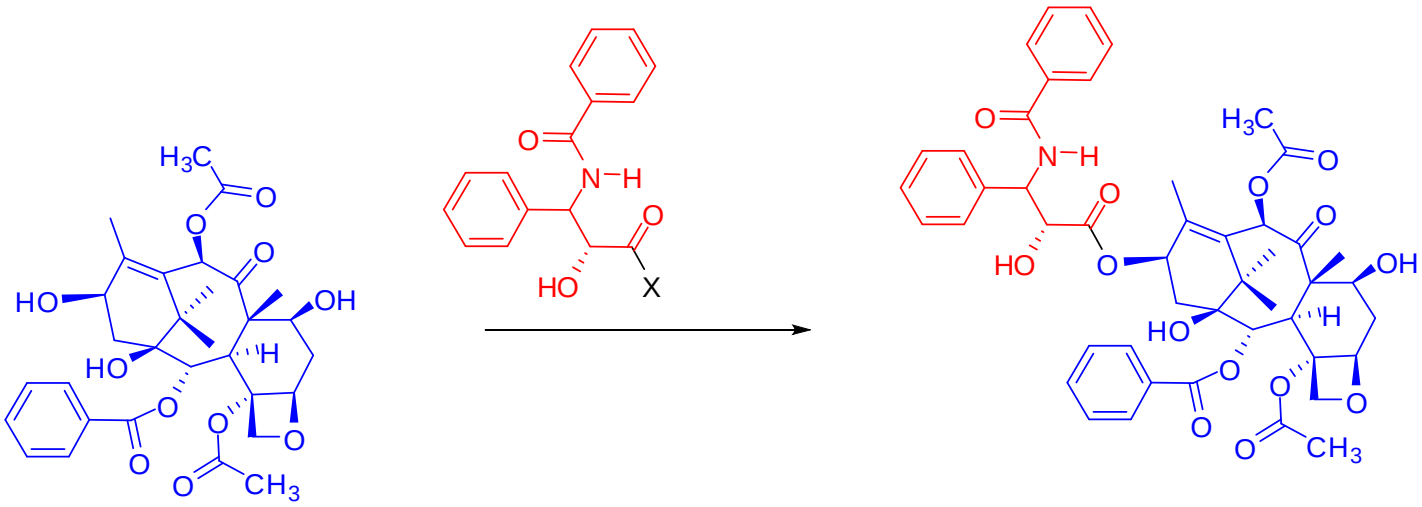
- Challenge: Convert the much more readily available baccetin III into the needed Taxol
- Opportunity: Use Baccetin III as a platform to create new (more effective) anologs : ->Taxotere!

different side chain.

add different substituents, this is typically what medicinal chemists do - take a lead structure & attempt to improve it.

Taxol: Semi-synthesis via Baccatin III

- Relationship between Taxol and Baccatin III

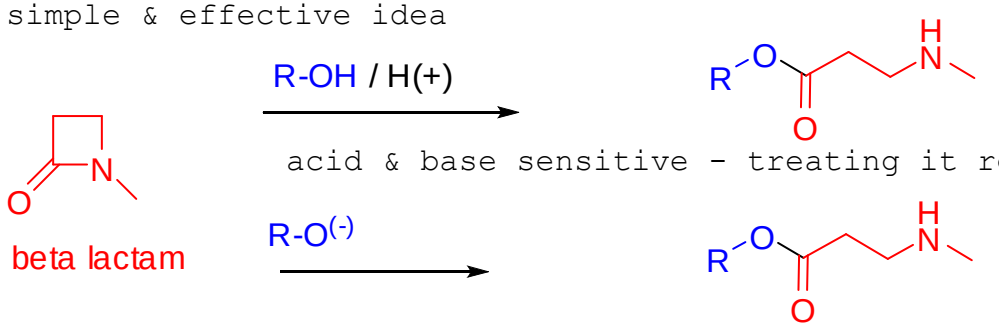


- In principle a simple acylation reaction:
- Alcohol + activated acid derivative -> ester
- In real life: Frustratingly difficult.

Solution: Prof. Robert Holton -Florida State University

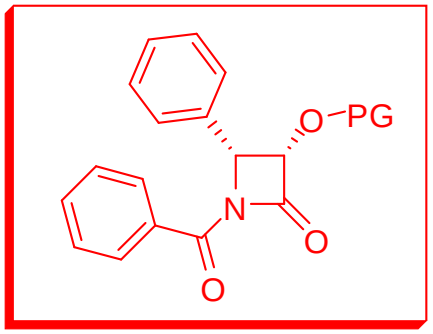
- Recalled beta lactam chemistry

simple & effective idea



acid & base sensitive - treating it results in an ester

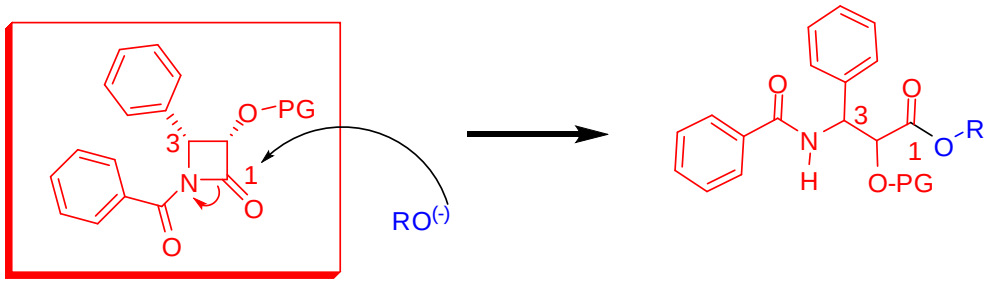
- Applied this to the Taxol problem
  - Needed first a specific beta lactam
  - Correct relative absolute
  - Correct absolute Stereochemistry



treated under the right conditions, made an effective synthesis 80-90% taxol

Success!

- –



Success!

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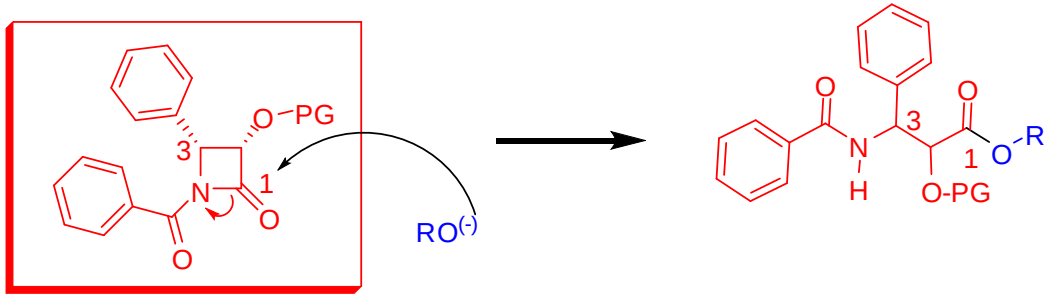
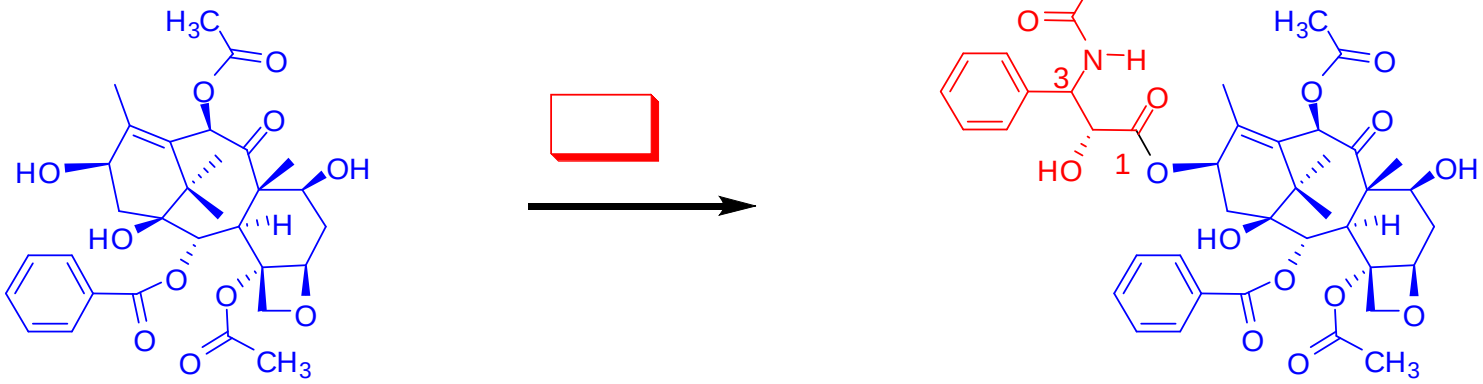




Baccatin III

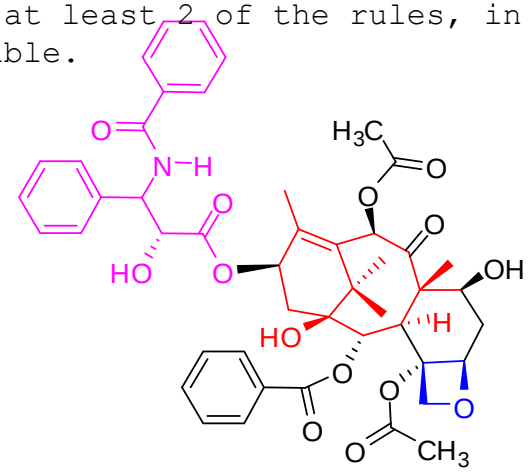
Taxol

Holton's imagination idea is rewarded

- The Holton chemistry combined with the new sourcing of baccatin III solved the Taxol supply problem.
- Florida State University patented this chemistry and licensed it to Bristol Myers.
- As of December 2005
  - Taxol had generated $351-million for Holton and FSU. in royalties
  - That's three times more than the University of Florida earned from Gatorade. [they invented it]

Taxol formualtion

- Taxol –highly effective –not drug like according to the Lipinski rules violates at least 2 of the rules, in the reality it isn't easily bioavailable.



Molecular Weight = 853

Log P= <5

H-bond donors = 4

H-bond accpetors: 10 (15!)

# of Atoms = 113

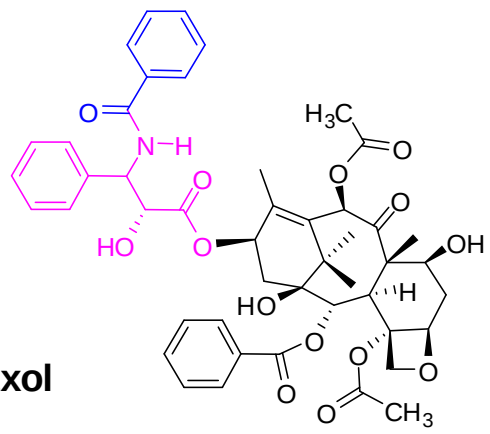
Is this a good drug candidate?

- Poor bioavailability
  - Extremely insoluble in virtually all solvents
  - Eventually formulated with a combination of ethanol and Cremophor: prepared by reacting 35 moles of ethylene oxide with each mole of castor oil. **Not a single compound**
  - **Administered via iv.**
  - **SIDE EFFECTS : a combination of Taxol and cremophor!**

castor oil comes from the glands of beavers, weird combination with ethylene oxide

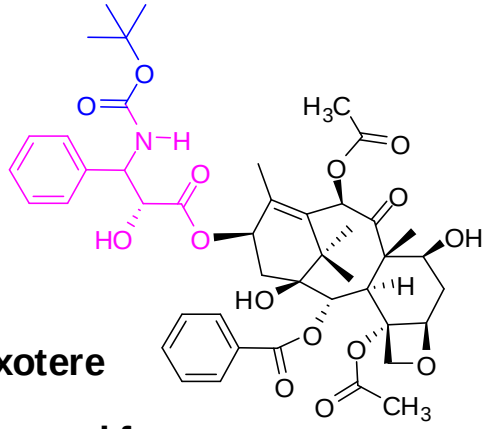
part of many many cancer cmpds

Taxotere – a Taxol analog



Taxol

make it more bioavailable



Taxotere

prepared from baccetin III

much much more bioavailable - by a factor of 5

Taxotere –much easier to formulate

- Can be administered orally compared to Taxol
- Taxotere is highly bioavailable either intravenous of via oral administration
- Clinical trials suggest somewhat better results compared to Taxol
- No side effects due to formulation. Still typical side effects of all “toxic” anti-cancer compounds

taxotere usually works a little bit better than taxol and has fewer side effects. becoming the dominant drug in this area.

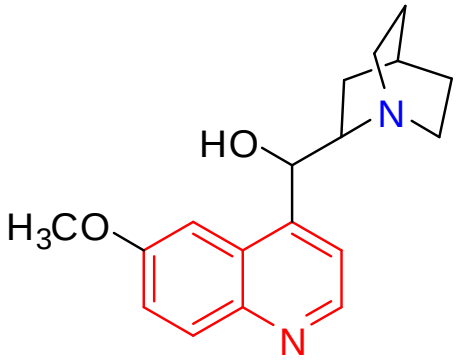
Malaria

- A major health problem in poor tropical countries still causing > million deaths world wide /year – mostly young children with not acquired immunity and old people.
- Simplest, most effective solutions
  - Reduce mosquito population via insecticides
    - DDT!!
  - Prevent transfer of the parasite from mosquito to humans via bed netting
- Gates Foundation- potential vacccines

would be a more effective control method.

Malaria

- Anti-malarial drugs
- Jesuit Priest/ healers in Peru- extracts from the chincona tree bark
- Active ingredient isolated and identified in the 1800's by chemists as quinine.



called an alkaloid
considered the standard

Based on traditional knowledge (Peru)

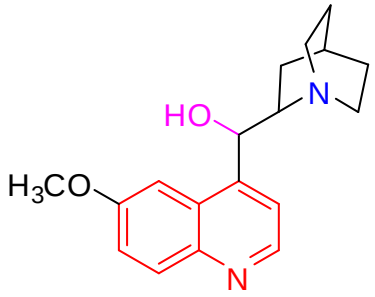
Isolated from the Chincona tree bark

First known potent antimalarial

as a chemist, were interested in perhaps the N and hydroxyl grp, and the two benzene, purine rings

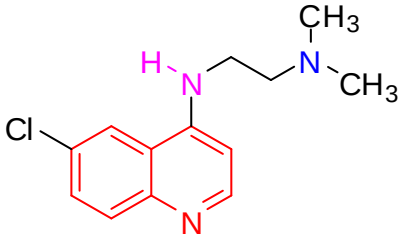
Malaria

- Attempts at synthetic analogs by German and American medicinal chemists due to lack of access to natural quinine in WWI and WWII and thereafter.
- Best compounds: chloroquine and mefloquine
  - Based on simplified quinine analogs



Quinine

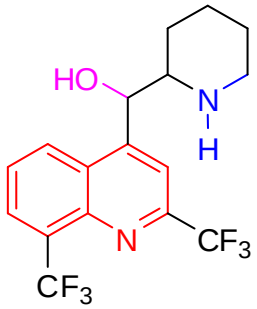
Based on traditional knowledge (Peru)
First known potent antimalarial



Choroquine

Synthetic
Excellent antimalarial
some resisant parasite

development of some resistance



Mefloquine [Lariam]

Developed by the US army ~ 1970

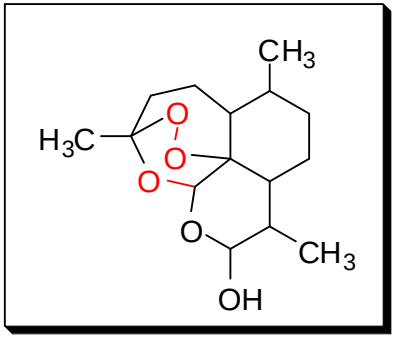
Excellent malaria preventative
occasionally severe neuropsychiatric side effects

Anti-Malarial based on Traditional Chinese Medicine

- China mandated a search for an anti-malarial in the 1970s based on TCM
- Searched and bio-assayed all TCMs reported to have fever reducing properties

would not be expected to be effective because it's structure is so different

- Discovered the compound "artimisinin" from Artimesia annua – a amazing and surprisingly stable structure.
  - Three oxygen atoms in a 6-membered ring
  - A peroxide structure,
    - Relatively few stable peroxides are known
    - Peroxide structure is crucial to its mechanism of action.



has no N

Involves free radicals due to O-O bond cleavage

in the presence of iron

free radicals then kill the parasite

golden standard, prevents malaria, and treats serious cases, almost no side effects

Current Malaria treatments

- World Health Organization:

considered that arthemisinin and derivatives of therof to prevent rapid development of artemisinin resistant parasite. this is the last good chance of having a really good anti malarial drug - you must use this carefully.

recommending careful use and artemisinin combination therapy [ACT]
so that there's another drug, they work together, and prevent the build up of resistance.

because of this unique structure, the WHO prompts the chemists to make another synthetic analogue that has all the important features such as a peroxide bond, and then other alternatives that may be even better acting than the natural material.

a compound that has been dested , has a pentagon ring with 3 oxygens in it.
required considerable trial and error to get this structure.

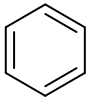
compound can be made dirt cheap - inexpensive for those in need who have malaria
- generally poor.

CNS active alkaloids

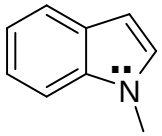
Common structure requirement for CNS active compounds:

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

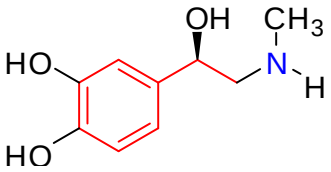
Aromatic rings are planar rings with all sp2 hybridized atoms with 6, 10, 14π electrons



benzene ring is a 6π eletron aromatic ring



indole ring is a 10π eletron aromatic ring

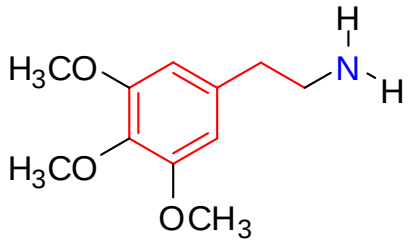


Adrenaline = epinephrine

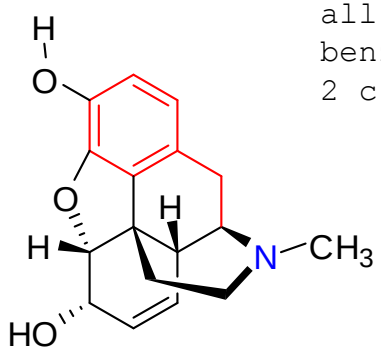
aromatic ring, 2 compounds, then a N.
the platform that a lot of these compounds work on.

Natural CNS Active compounds

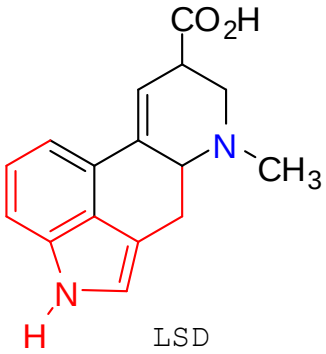
all of these follow the benzene ring,
2 c - then a Nitrogen



mescaline
peyote cactus

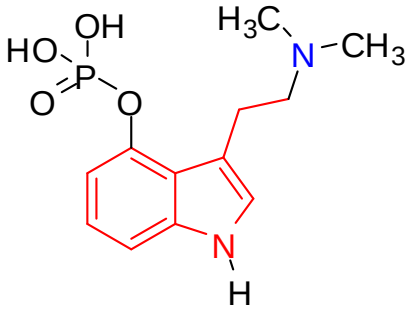


Morphine

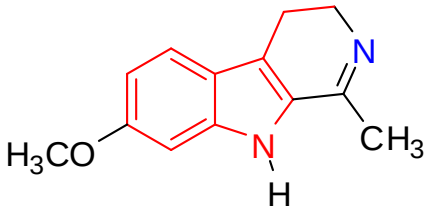


LSD

Lysergic acid
Ergot fungus
growing on rye



Psilocybin
[sacred mushroom

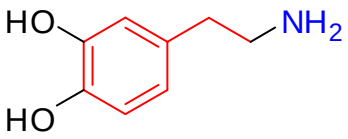


Harmaline
Halucinogenic drink
Amazon: Ayahusca

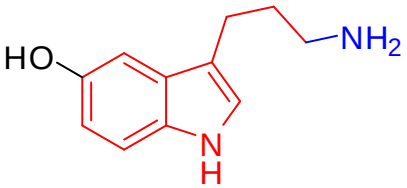
DMT

Neurotransmitters and “street drugs”

- Dopamine , serotonin and amphetamines

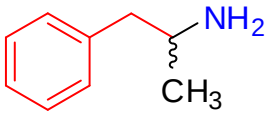


Dopamine
neurotransmitter

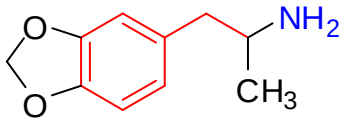


Serotin
neurotransmitter

contributes to feeling well



amphetamine
stimulant



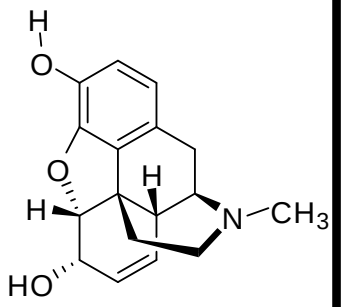
MDMA (3,4-Methylenedioxy-N-methylamphetamine)

Ecstasy,

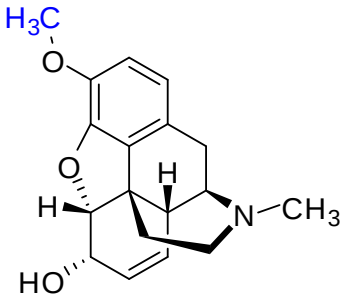
Structure variety in natural products

- Morphine –Alkaloids- natural or semi-synthetic

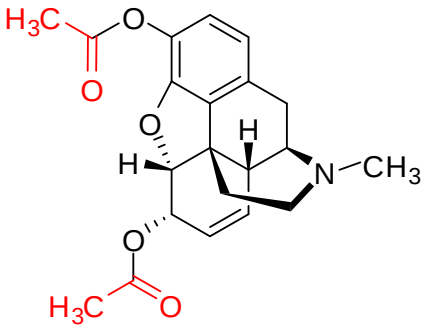
Morphine



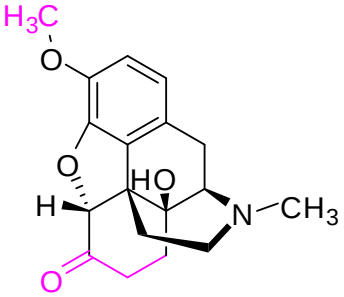
Codeine



Heroin



Oxycodone



- Butorphanol
  - Synthetic