Option D: Medicinal Chemistry

D.1 & D.2

D.1 Pharmaceutical Products and drug action

- Body systems involve thousands of reactions occurring simultaneously - ***metabolism*** - the sum of these processes
- Microorganisms vs. Body response
  - invaders vs. lines of defense
- Responses often manifest as symptoms of disease
  - Fever - fighting infection

D.1 Pharmaceutical products and drug action

Terminology

- **Drug -** a chemical that affects how the body works
  - includes good and bad results
  - often associated with illegal drugs
- **Medicine -** a substance that improves health
  - can be natural or synthetic
  - contain beneficial drugs
- **Therapeutic effect -** beneficial effect of a medicine

D.1 Pharmaceutical Products and drug action

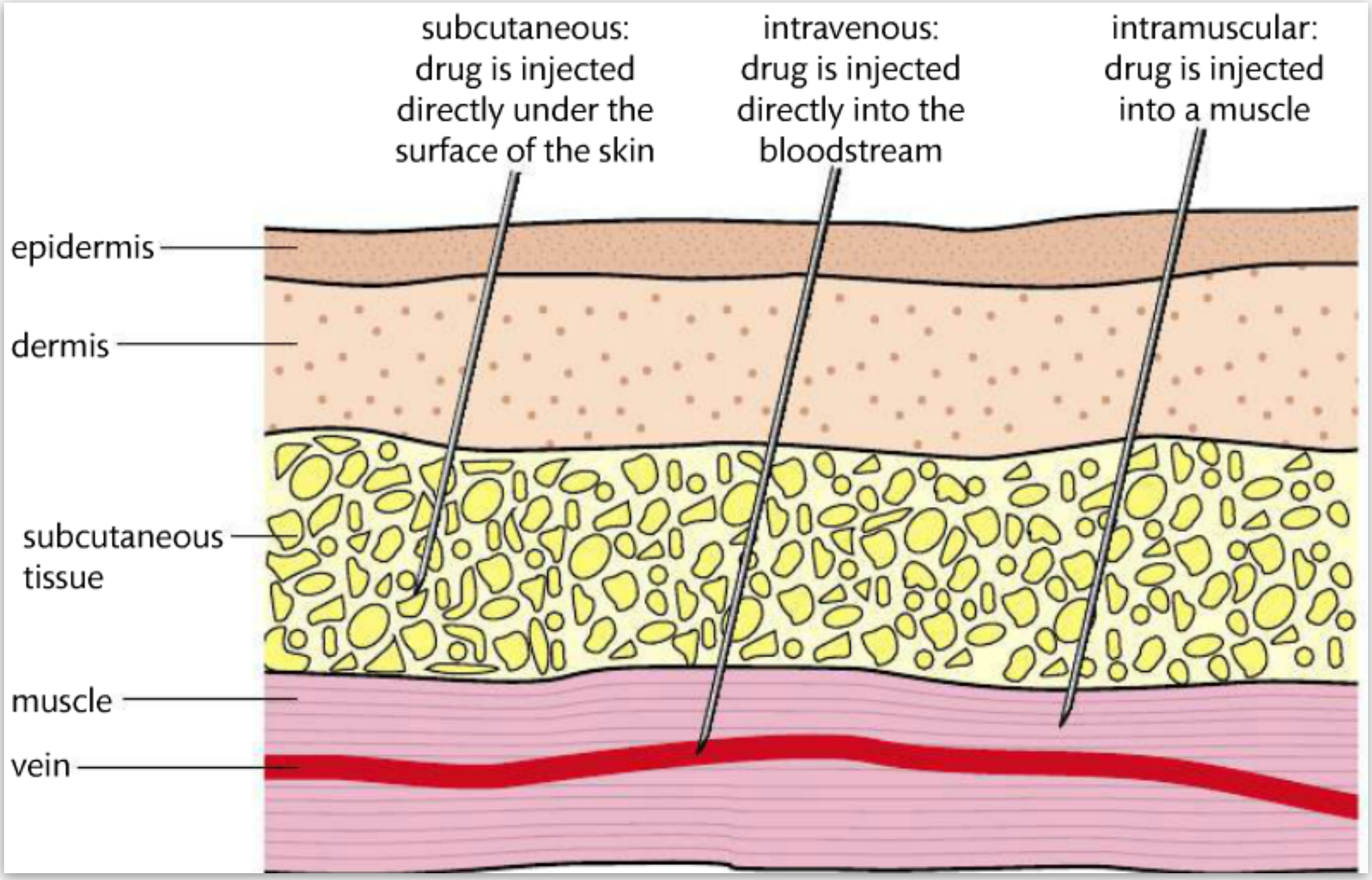
Drug Administration - Figure on pg. 862

- dependent on many things - drug, person, condition

Method of administering drug	Description	Example
oral	taken by mouth	tablets, capsules, pills, liquids
inhalation	vapour breathed in; smoking	medications for respiratory conditions such as asthma; some drugs of abuse such as nicotine and cocaine
skin patches	absorbed directly from the skin into the blood	some hormone treatments, e.g. estrogen, nicotine patches
suppositories	inserted into the rectum	treatment of digestive illnesses and haemorrhoids
eye or ear drops	liquids delivered directly to the opening	treatments of infections of the eye or ear
parenteral: by injection (see Figure 15.1)	intramuscular (into muscle)	many vaccines
	intravenous (into the blood, the fastest method of injection)	local anaesthetics
	subcutaneous (under the skin)	dental injections

D.1 Pharmaceutical Products and drug action

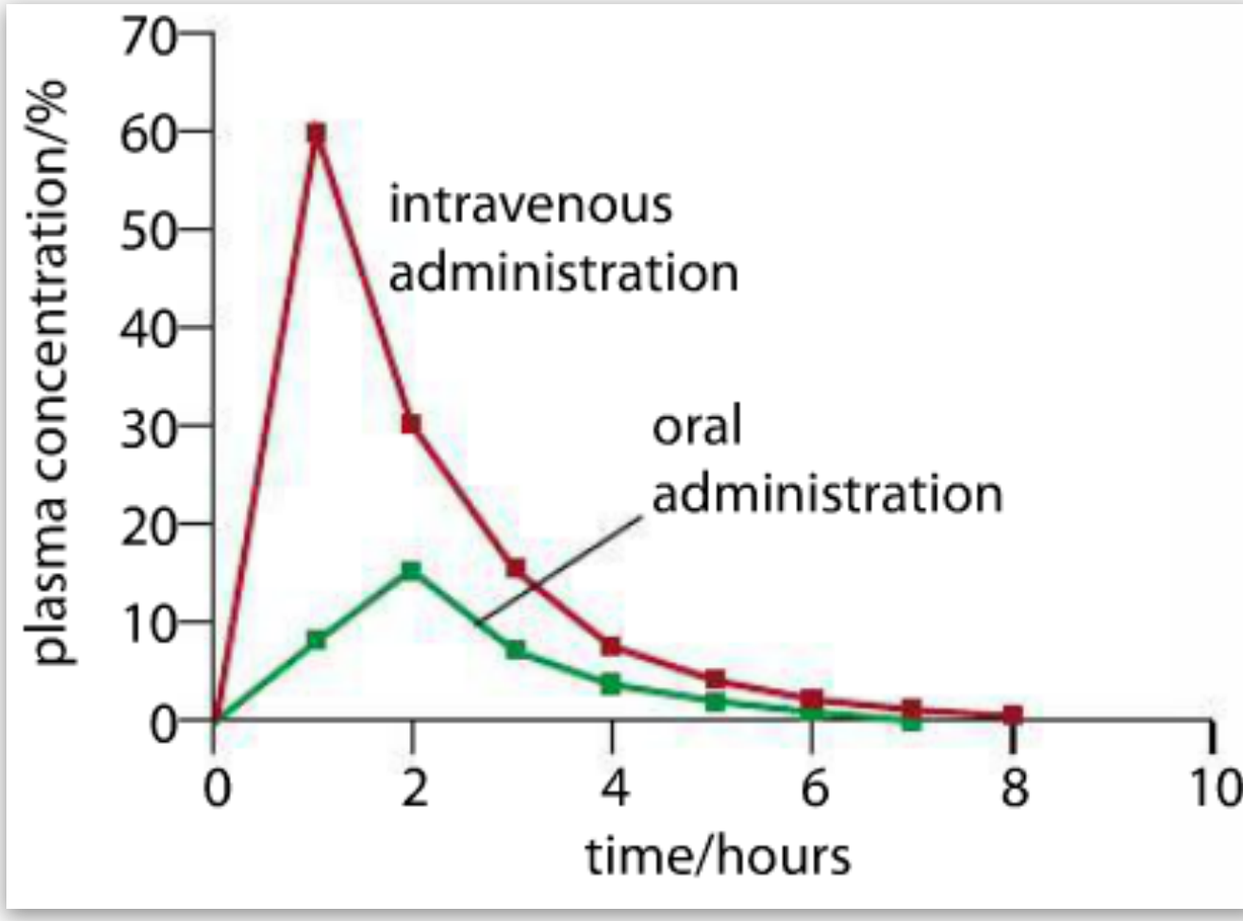
Drug Administration



D.1 Pharmaceutical Products and drug action

Bioavailability

- **Definition -** fraction of drug that reaches the blood supply
  - intravenous - 100% bioavailability
  - important when calculating **dosage**
    - how much drug to administer
- Orally administered drugs have relatively low bioavailability
  - **first-pass effect -** shown at right
- After swallowing, drugs get digested before entering bloodstream (enzymes)



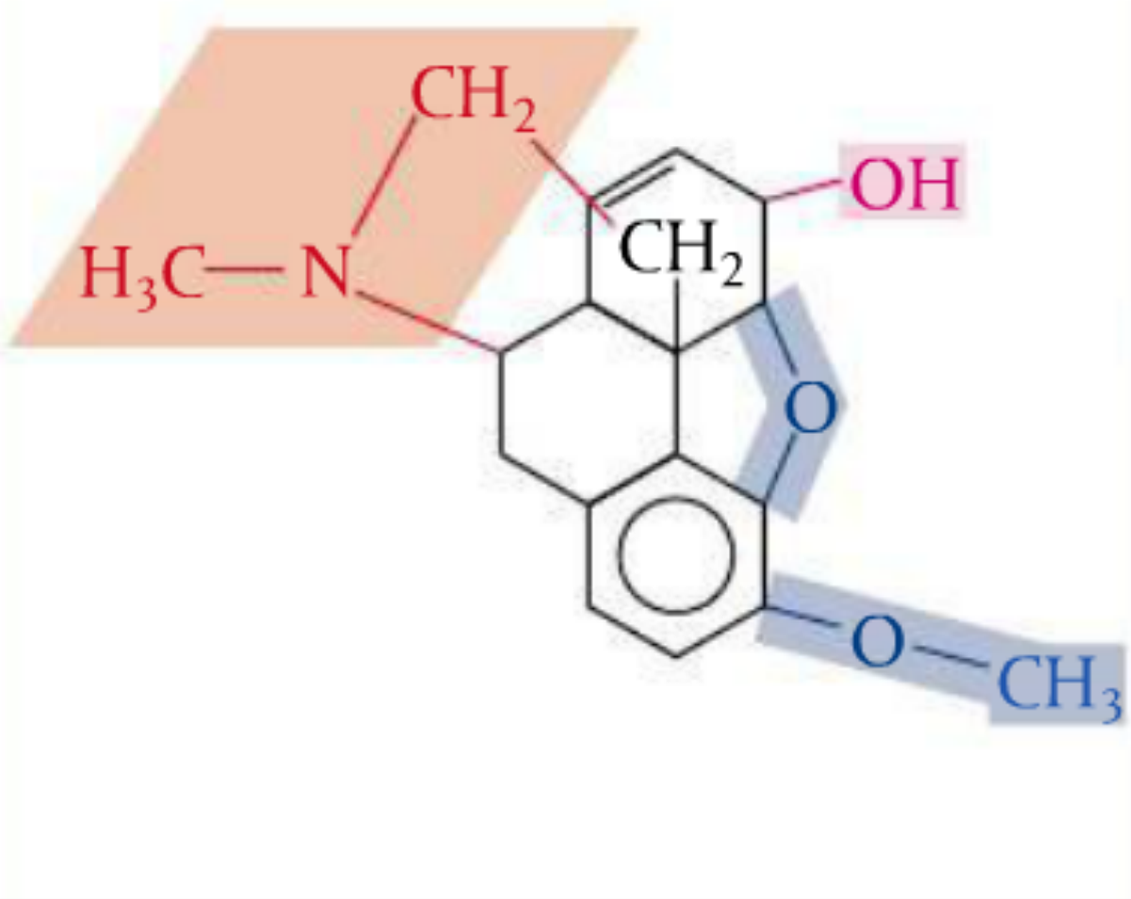
D.1 Pharmaceutical Products and drug action

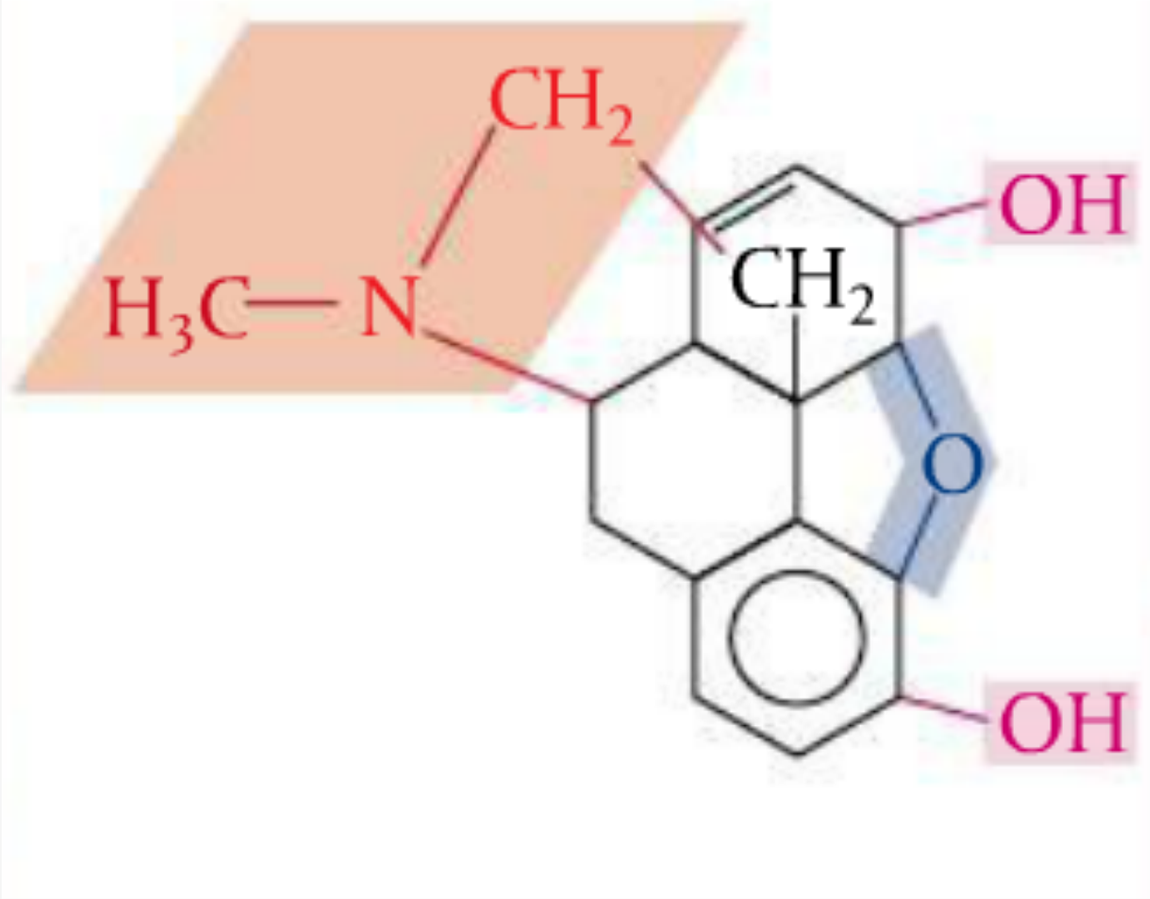
Bioavailability - cont'd

- Oral dosages are 4x higher than intravenous
  - Ex - Morphine (orally) - 30% bioavailability
  - More effective as intravenous
- Solubility
  - Need H_2O Solubility for blood transmission but lipid solubility for membrane transmission
  - Ex - Codeine is more lipid soluble (90% bioavailability - orally)
  - Compare structures on next slide

D.1 Pharmaceutical Products and drug action

Codeine vs. Morphine





D.1 Pharmaceutical Products and drug action

Physiological Effects

- **Therapeutic effect -** beneficial effect of a medicine
  - Intended Effect!
- **Side Effect -** not intended & vary greatly from one drug to another
  - some beneficial, some benign, some harmful
    - aspirin (pain relief) - helps against heart disease
    - allergy medicine - drowsiness
    - tylenol - damage to organs (at high doses over a long period)

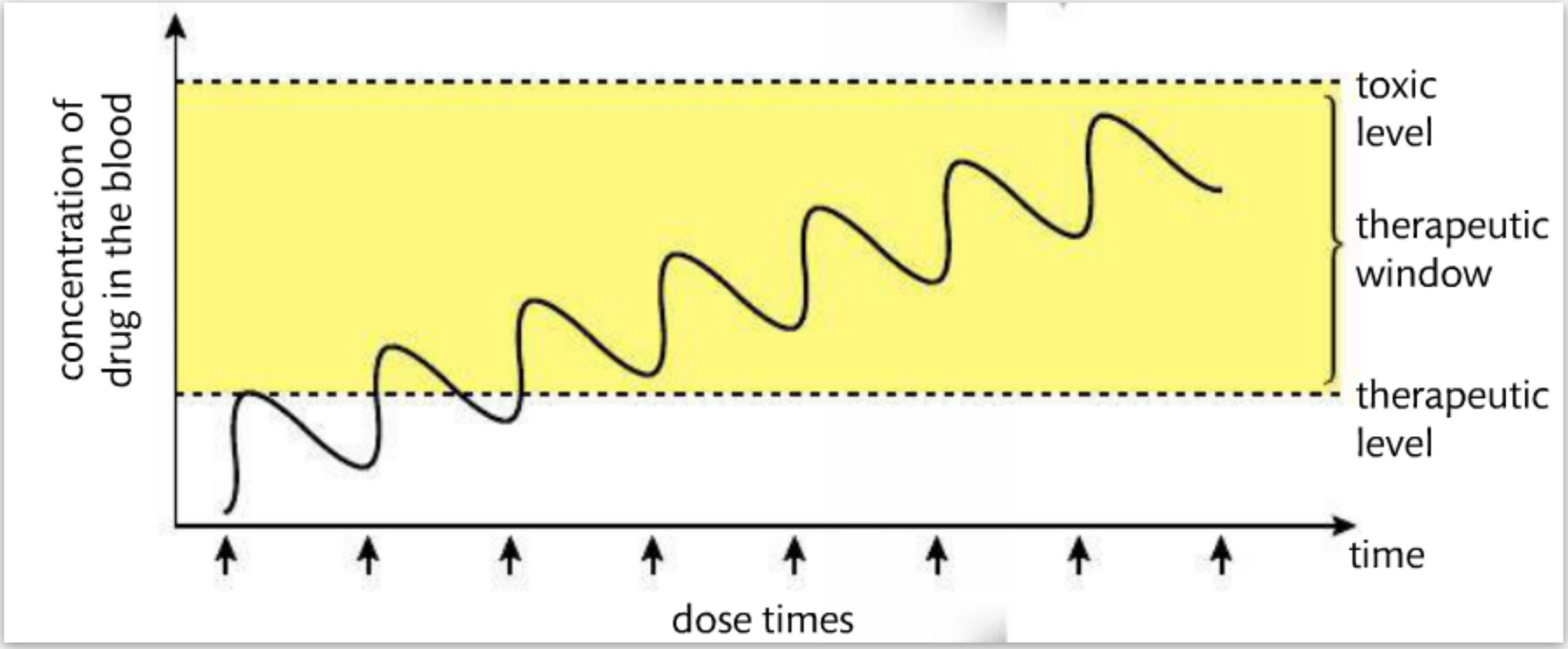
D.1 Pharmaceutical Products and drug action

Physiological Effects

- **Tolerance -** reduced response for a drug with the same dosage
  - higher doses for the same effect
    - increases risk for toxic side effects
- **Dependance/Addiction** - needs to take the drug in order to feel "normal" - suffers from withdrawal if not taken
  - symptoms of addiction can range from mild to severe
    - Headaches to death

D.1 Pharmaceutical Products and drug action

Dosage



- **Therapeutic Window -** above this range, unacceptable side effects may occur - below this range, it may not be effective

D.1 Pharmaceutical Products and drug action

Terminology

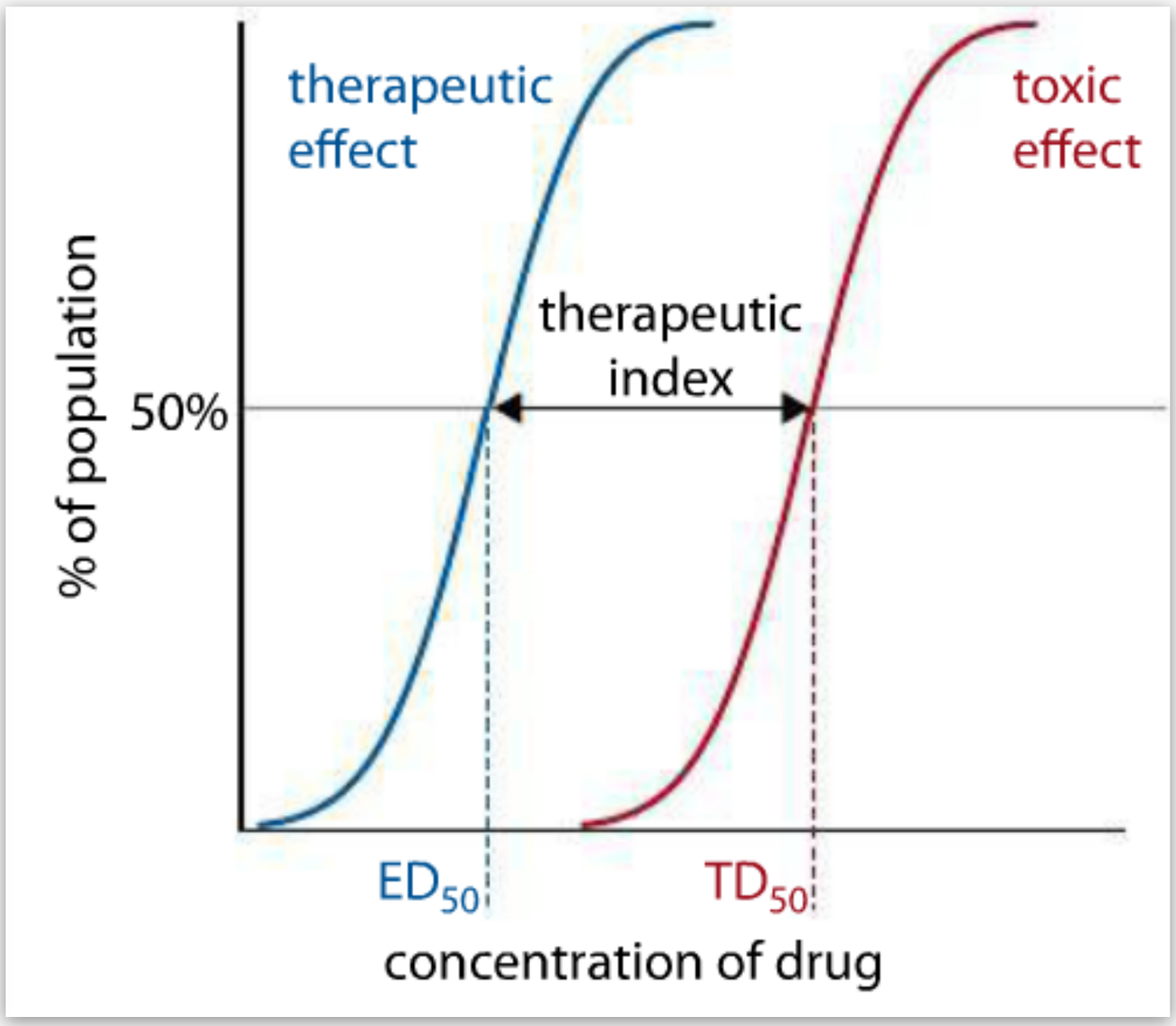
- **Therapeutic index (TI) -** ratio of dose that produces toxicity to the dose that produces a clinically effective response

- **minimum effect dose - ED_{50}** - dose that produces the therapeutic effect in 50% of population
- **lethal dose - LD_{50}** - dose that is lethal to 50% of population (animal)
- **toxic dose - TD_{50}** - dose that is toxic to 50% of population (human)

D.1 Pharmaceutical Products and drug action

Ratios:

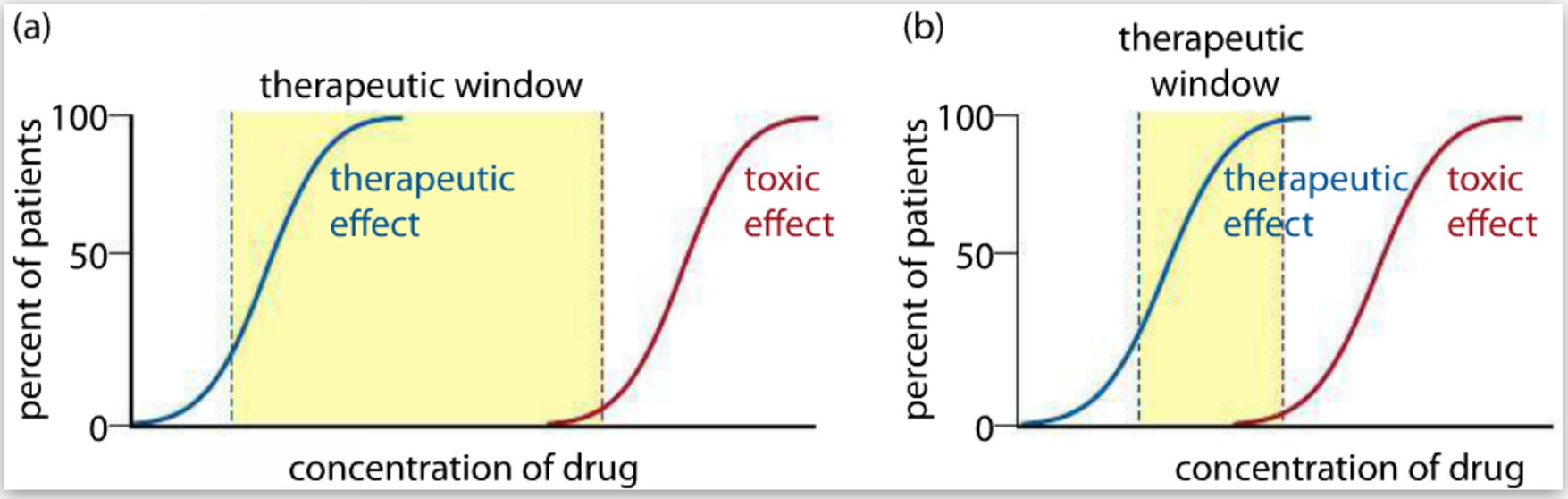
- in animals - TI = **LD_{50}/ED_{50}**
- in humans- TI = **TD_{50}/ED_{50}**



High TI is better because the range between therapeutic effect and toxic effect is large (high margin for error)

D.1 Pharmaceutical Products and drug action

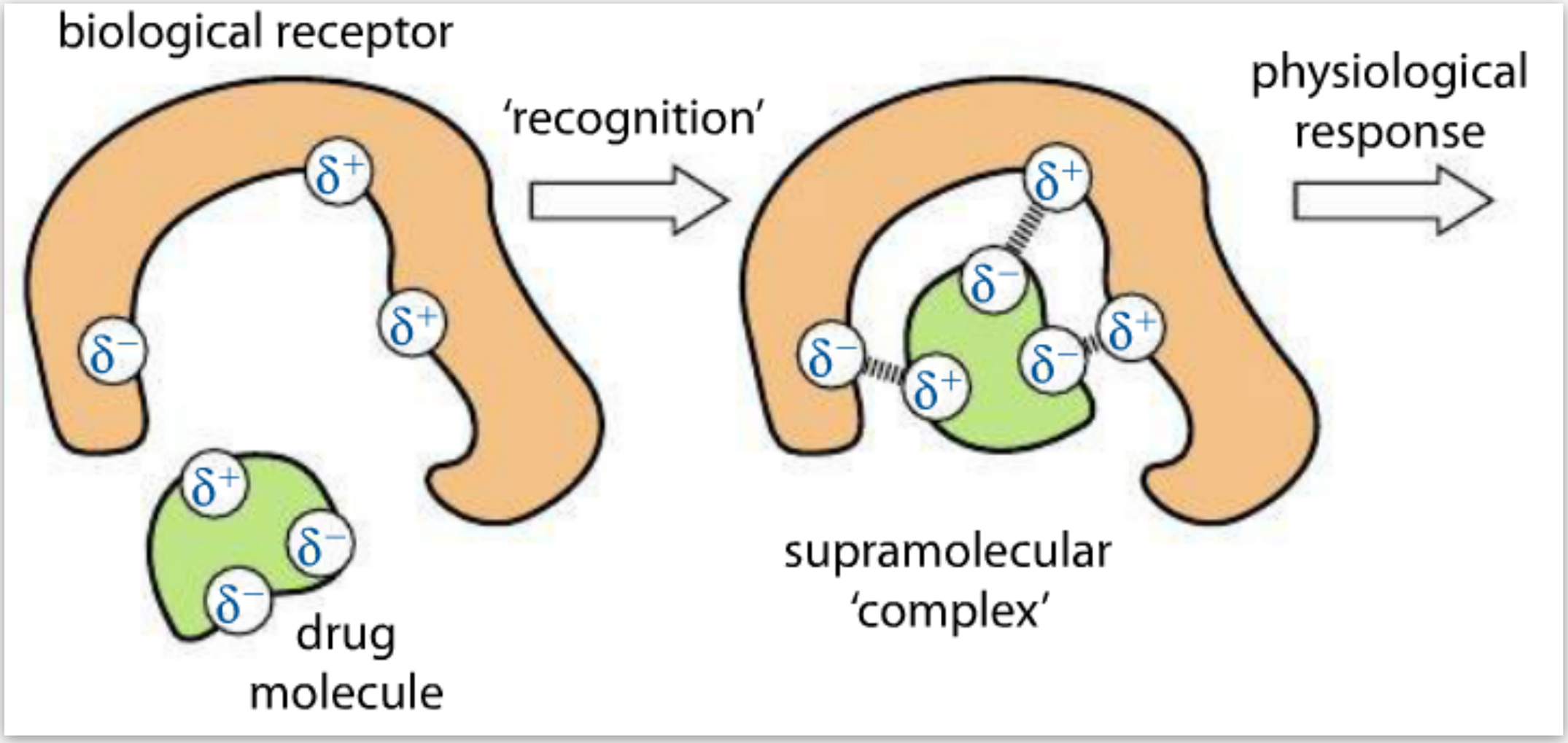
Drug	Therapeutic effect	Therapeutic index (TI)
penicillin	antibiotic	increasing value of therapeutic index
morphine	analgesic	
cocaine	stimulant	
ethanol	depressant	
warfarin	anticoagulant in blood	



penicillin vs. warfarin

D.1 Pharmaceutical Products and drug action

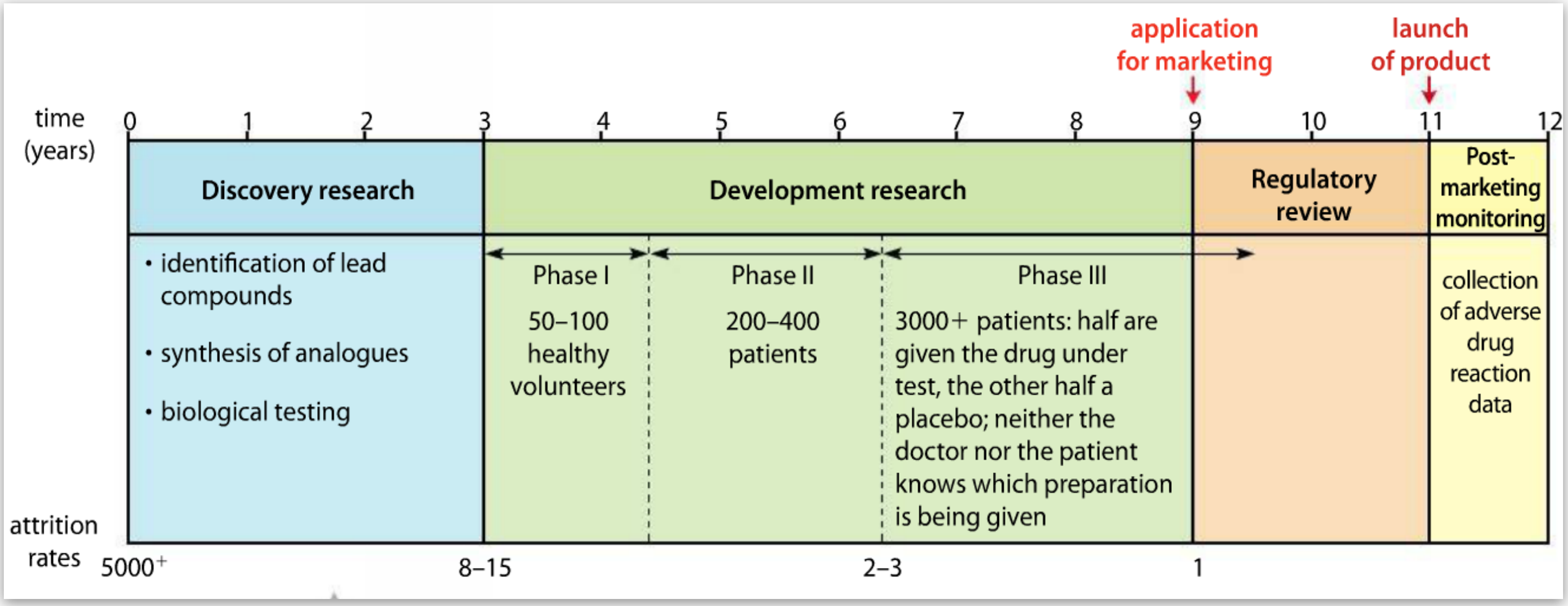
Drug Action - Interactions w/ Receptors



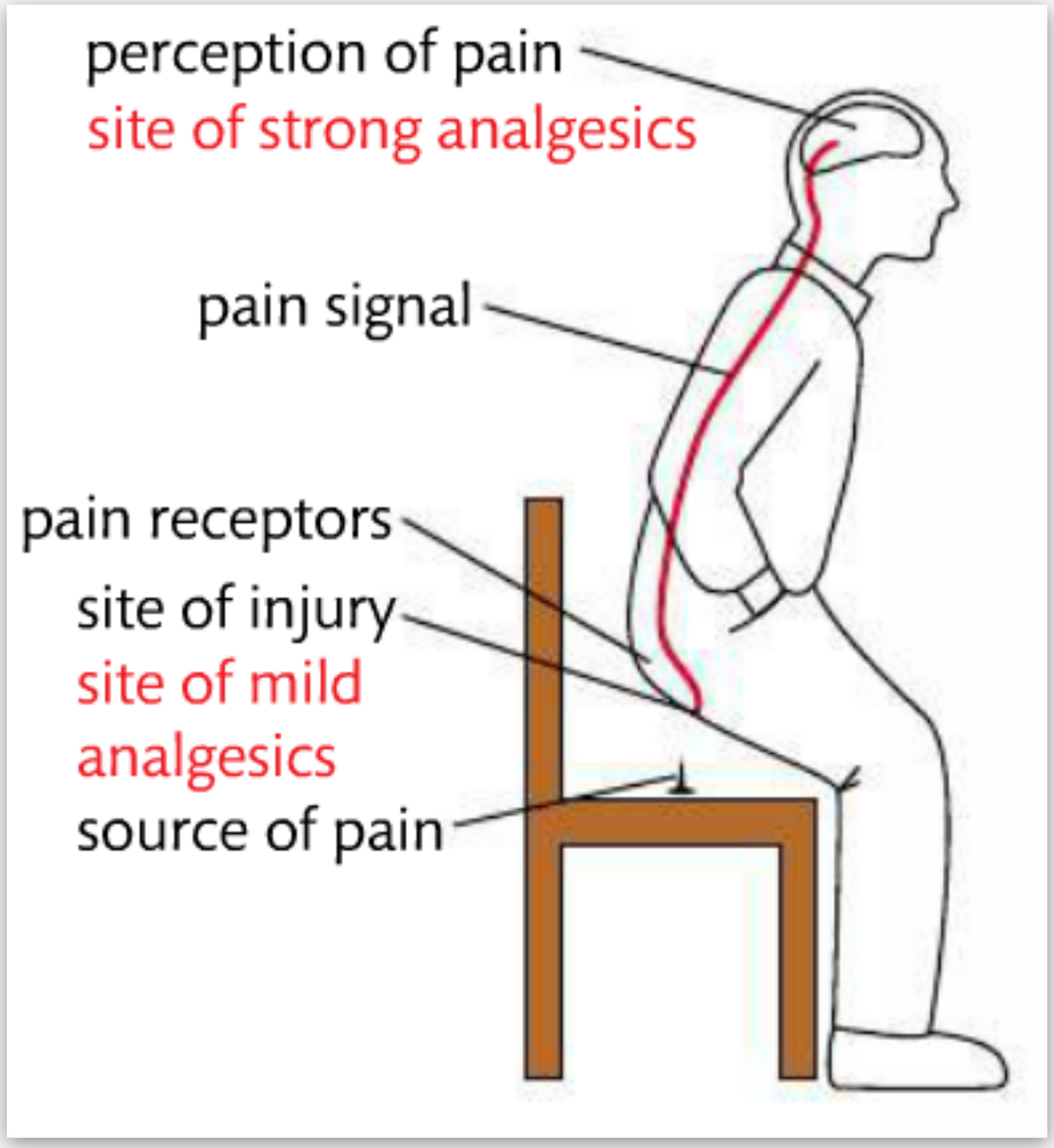
- the better the drug, the better the chemical "fit"
- drug/receptor understanding leads to drug design

D.1 Pharmaceutical Products and drug action

Development Stages for a new Medicine



D.2 Aspirin

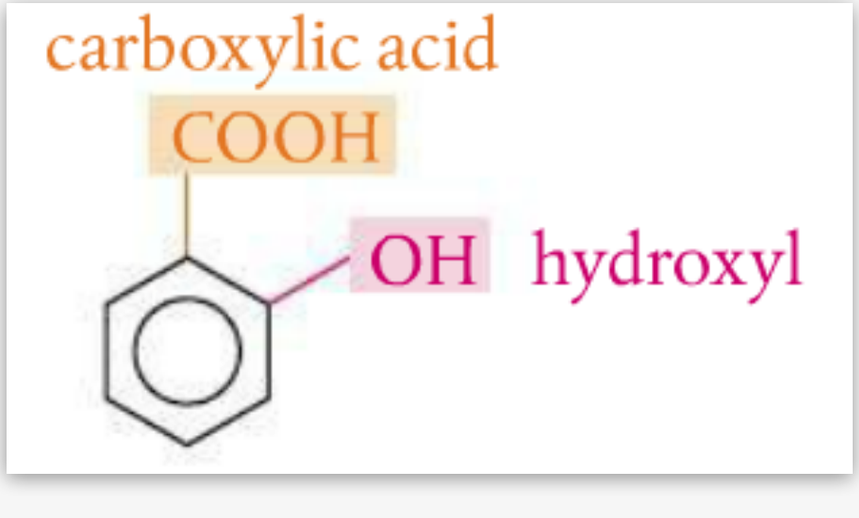


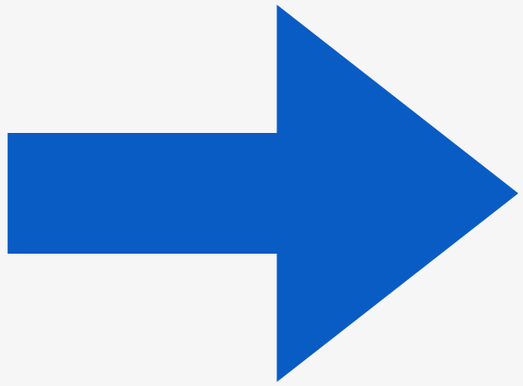
- effective painkillers block the pain signal to the brain
- non-steroidal anti-inflammatory drug (NSAIDs)
- mild analgesic
  - prevents stimulation of nerves @ site of pain
  - inhibits release of prostaglandins - inflammatory response - therefore reduces swelling and pain
- non-narcotic - doesn't interfere with brain function

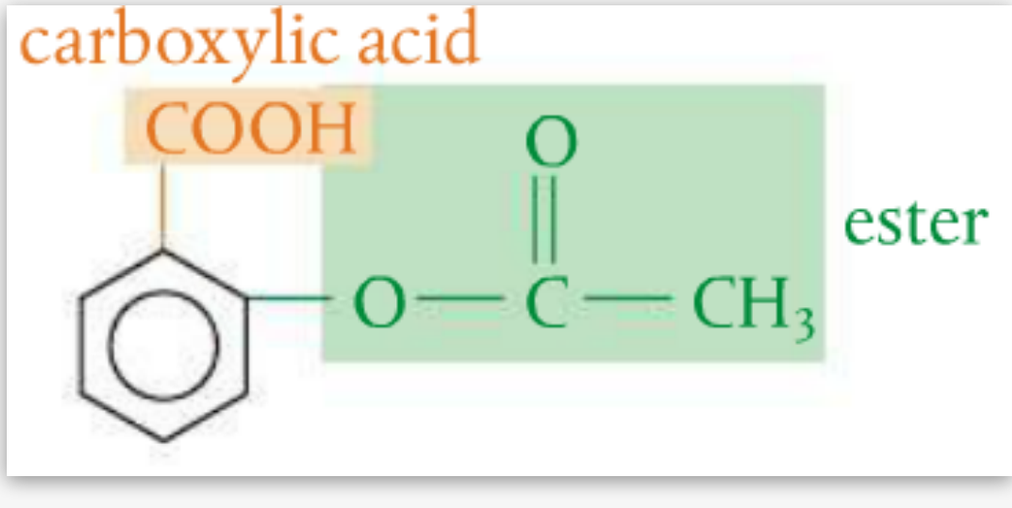
D.2 Aspirin

Development

Table 37 - data booklet







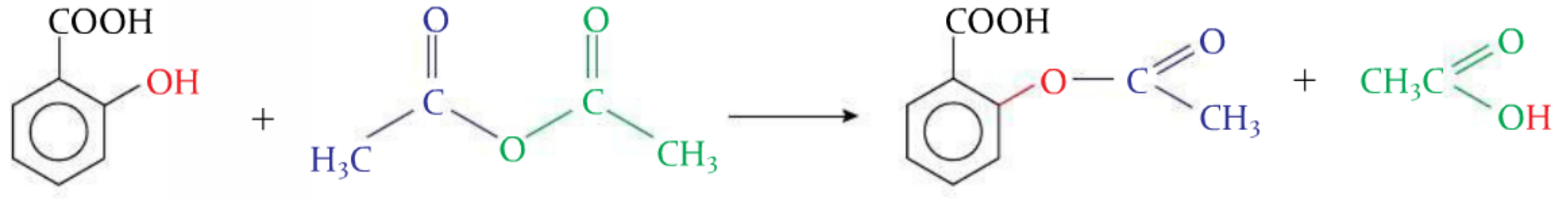
- 400 BC
- chewing willow bark
- Salicylic Acid
- *Vomitsville*, but you stopped hurting

- 1890 - Bayer
- ester derivative
- acetylsalicylic acid (aspirin)
- also an antipyretic (fever reducer)

D.2 Aspirin

Synthesis

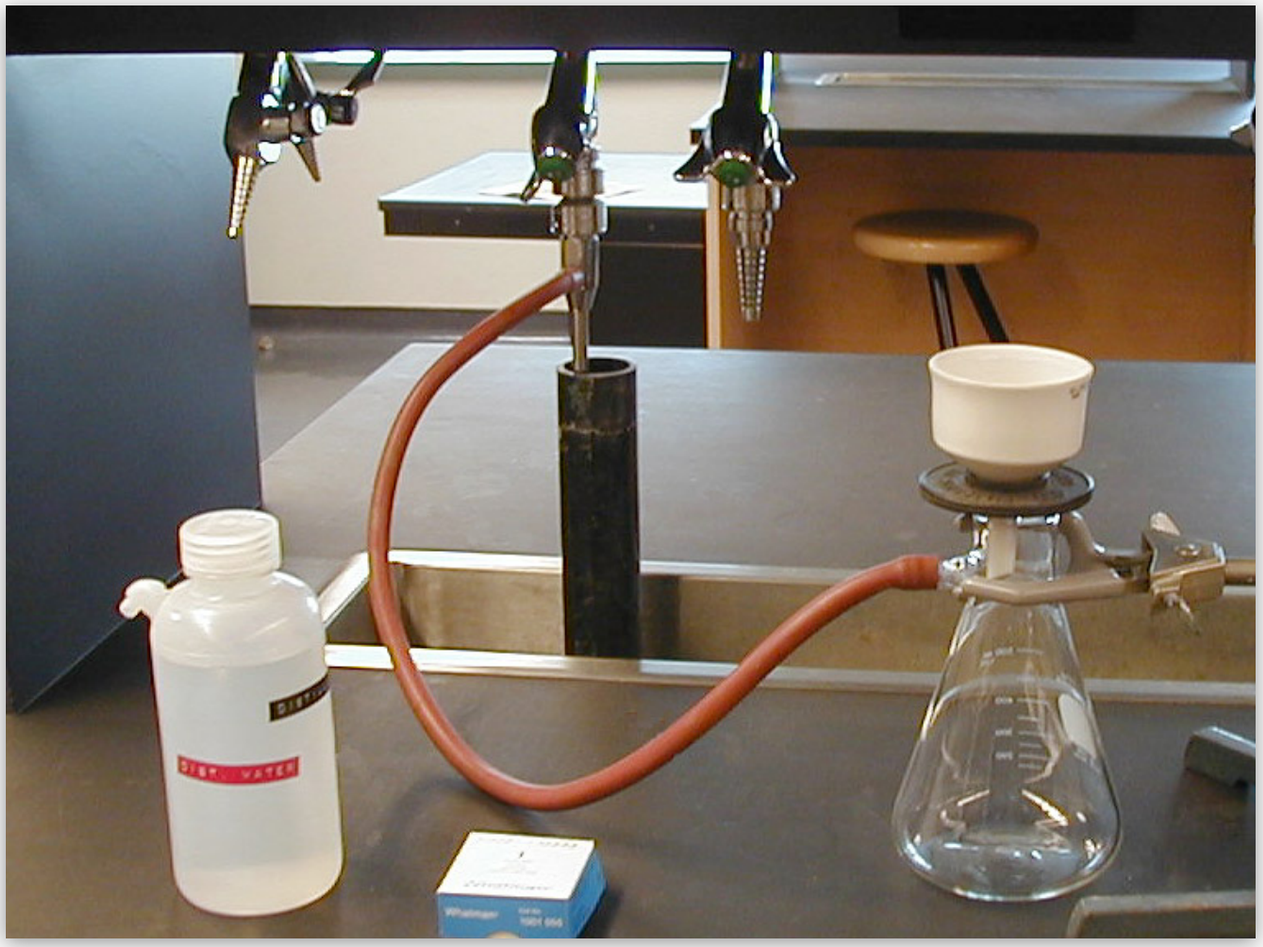
- Through Esterification (Condensation) Reaction
- salicylic acid + ethanoic anhydride --> aspirin + ethanoic acid
- Conc. Sulfuric or phosphoric acid is added to reactants and warmed gently
- then isolated and purified from the mixture of products



D.2 Aspirin

Purification

- Cool product to form crystals, then washed with chilled water and suction filtered
  - aspirin has a low solubility in water, removes any soluble acids
- Recrystallization - dissolve filtrate in minimum volume of HOT ethanol
- Cool mixture slowly, collect the crystals that form through filtration



D.2 Aspirin

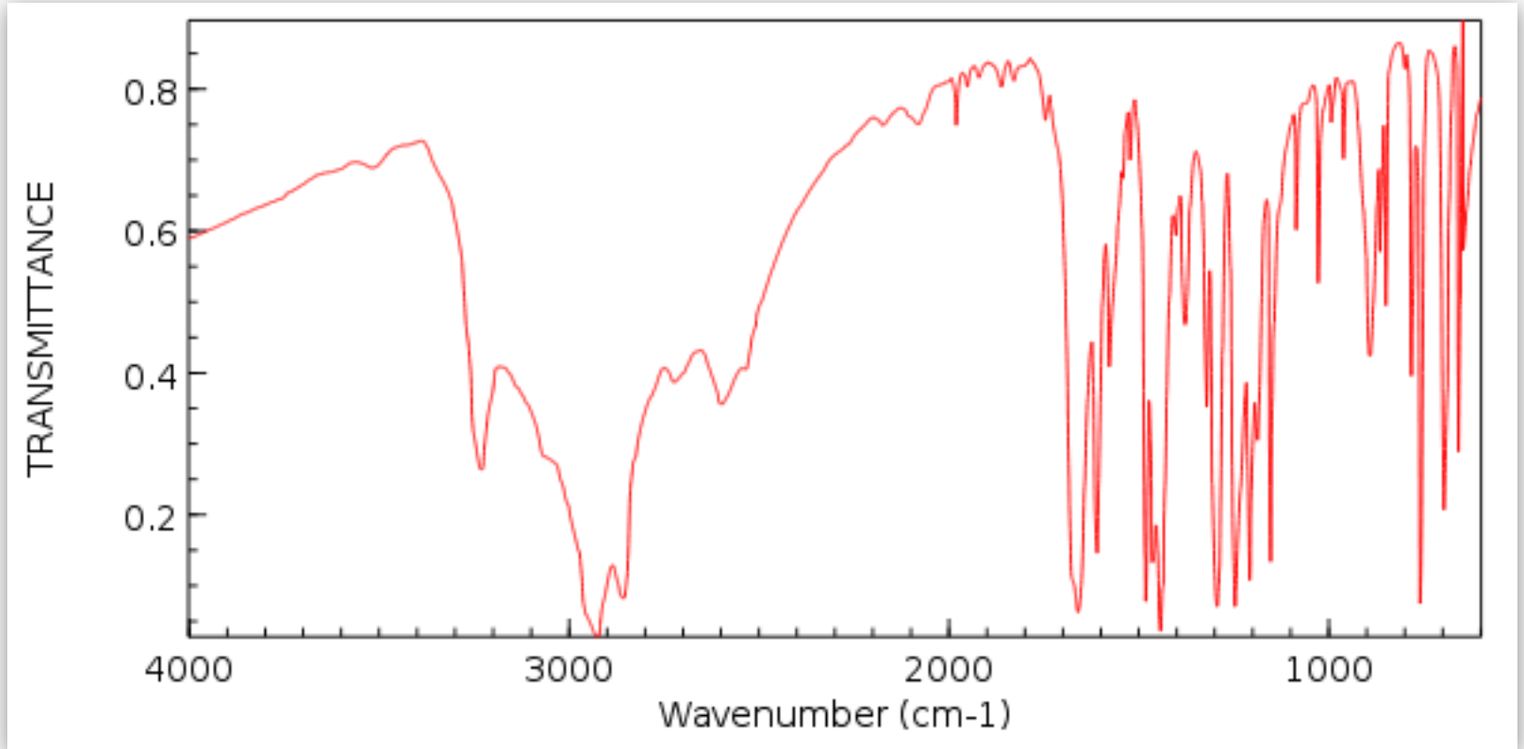
Physical Analysis (test for purity)

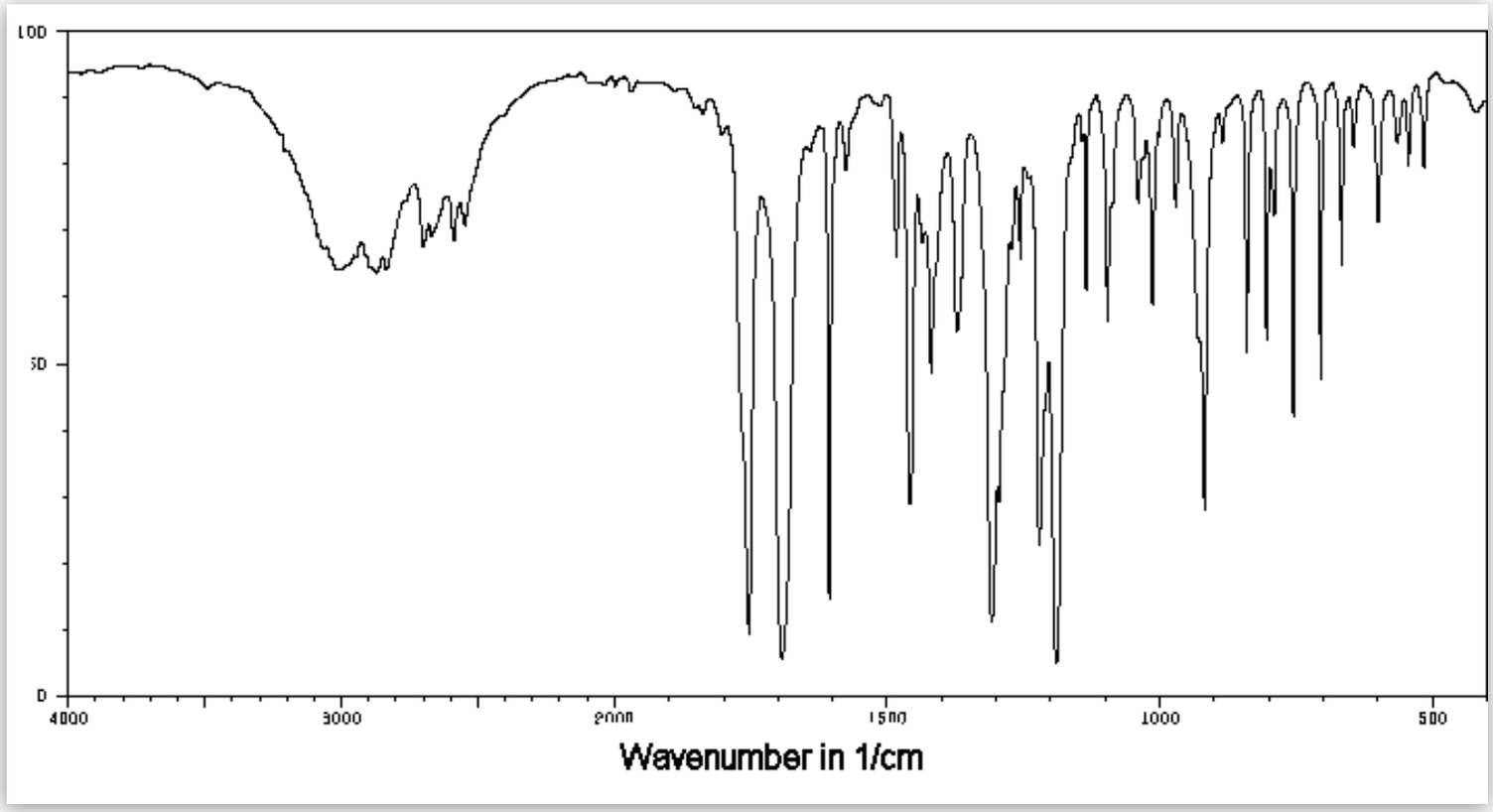
- Melting Point Determination
  - aspirin: 138-140˚C
  - salicylic acid: 159˚C
    - a mixture would have a lower MP than S.A. and would be less defined (broad)
- Yield - from stoichiometry (1:1 ratio)

D.2 Aspirin

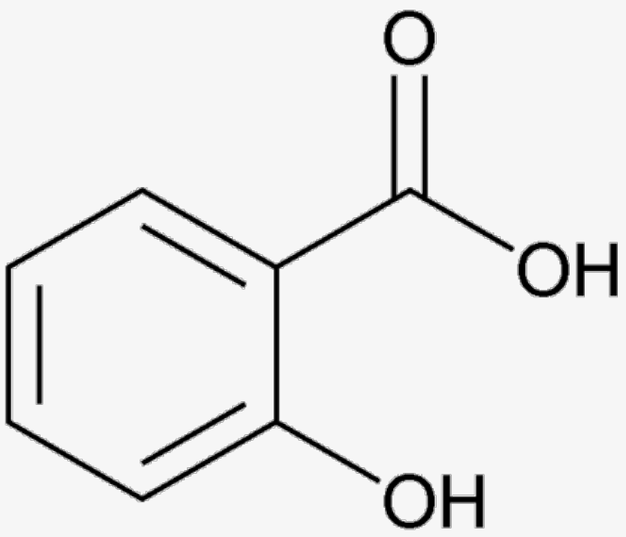
IR Spectra Analysis

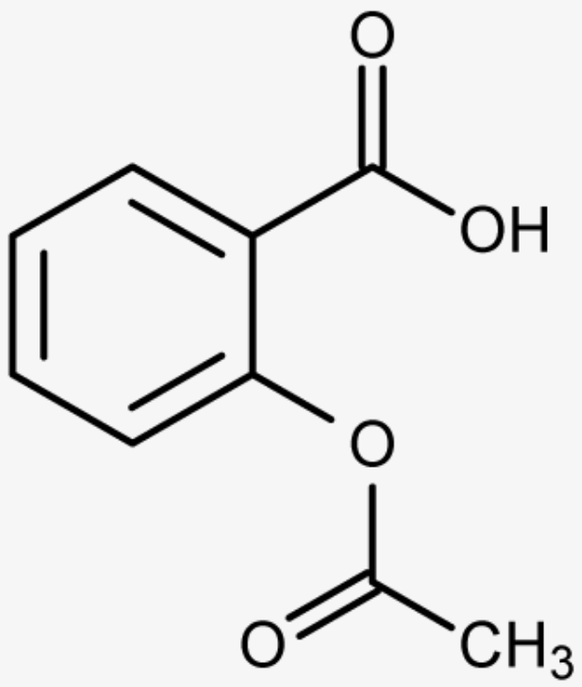
- Do you see any major similarities?
- Major Differences?
- Difficult to tell apart?

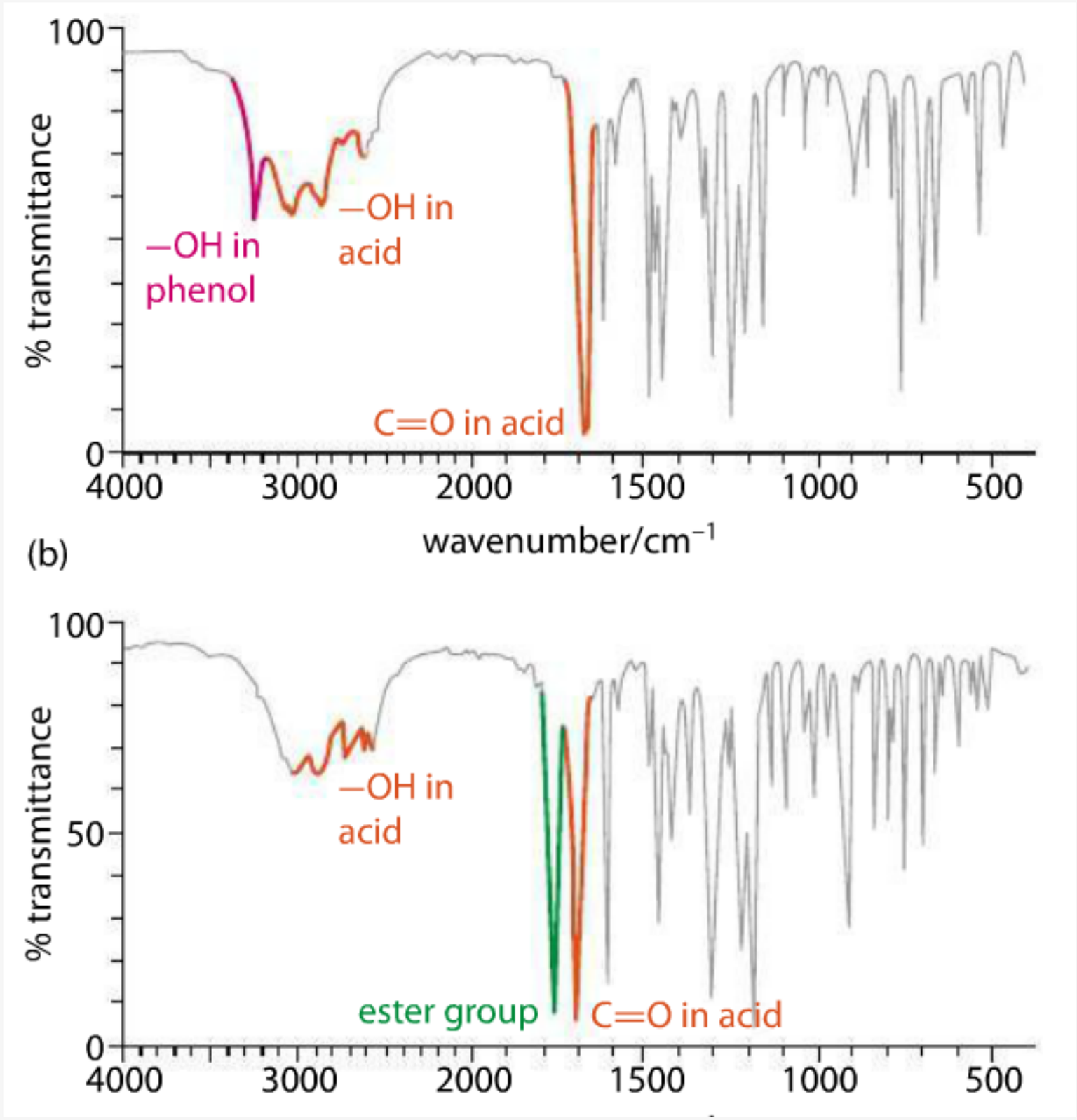




D.2 Aspirin


O
OH
OH


O
OH
O
O
CH3


100
% transmittance
0
—OH in phenol
—OH in acid
C=O in acid
4000
3000
2000
1500
1000
500
wavenumber/cm−1
(b)
100
50
0
% transmittance
—OH in acid
ester group
C=O in acid
4000
3000
2000
1500
1000
500

D.2 Aspirin

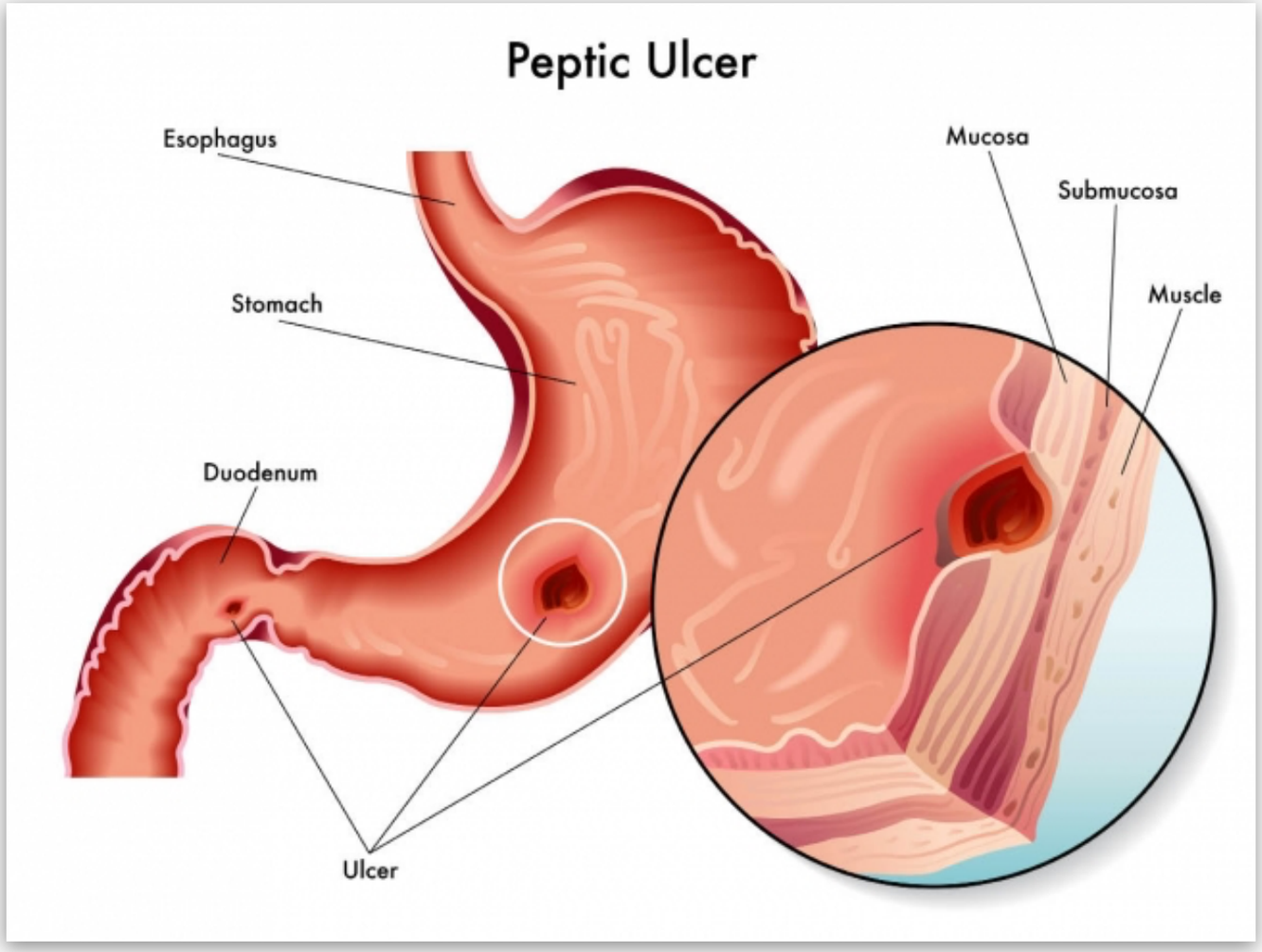
Physiological Effects

- Blocks prostaglandins (analgesic effect)
- Reduces fever and inflammation
- Anticoagulant - reduces clotting of blood
  - useful treatment for heart attacks and strokes
  - used as prophylactic (small daily dose)
- Negatives - irritation/ulceration of stomach and duodenum (leads to bleeding)

D.2 Aspirin

Physiological Effects - Negatives

- Irritation/ulceration of stomach and duodenum (leads to bleeding)
- Large # of people are allergic (especially if you have asthma)
- Been known to cause Reye's syndrome in children under 12



D.2 Aspirin

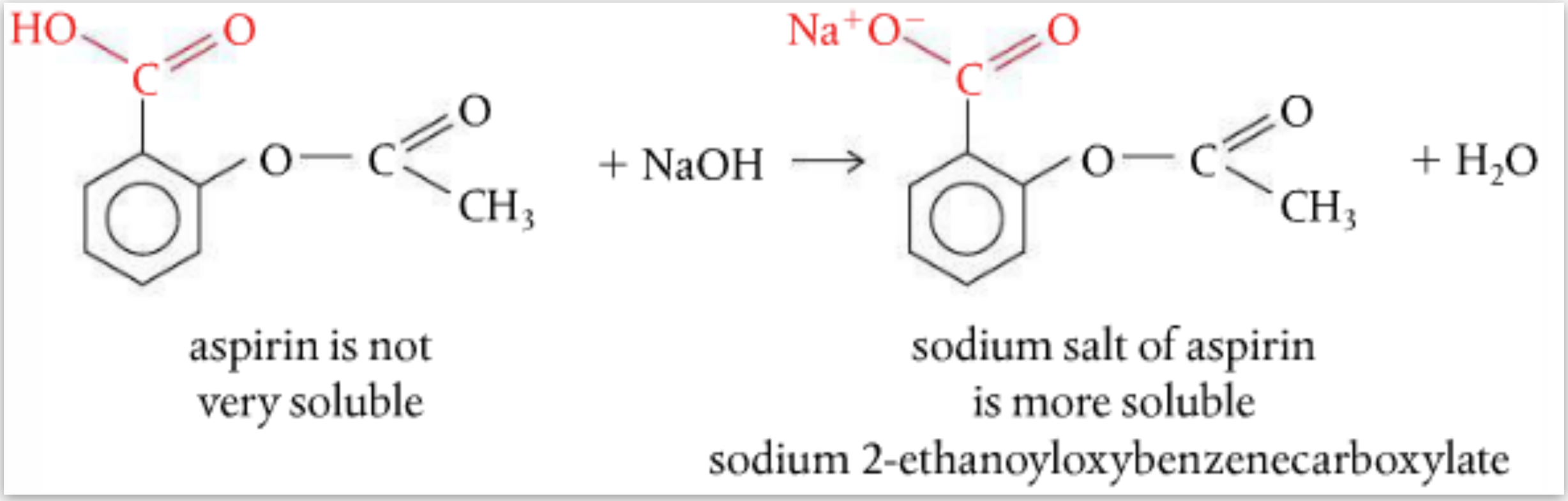
Physiological Effects

- **Synergy** - making the physiological effects greater by mixing with other drugs (alcohol)
  - increased risk of bleeding and ulcers

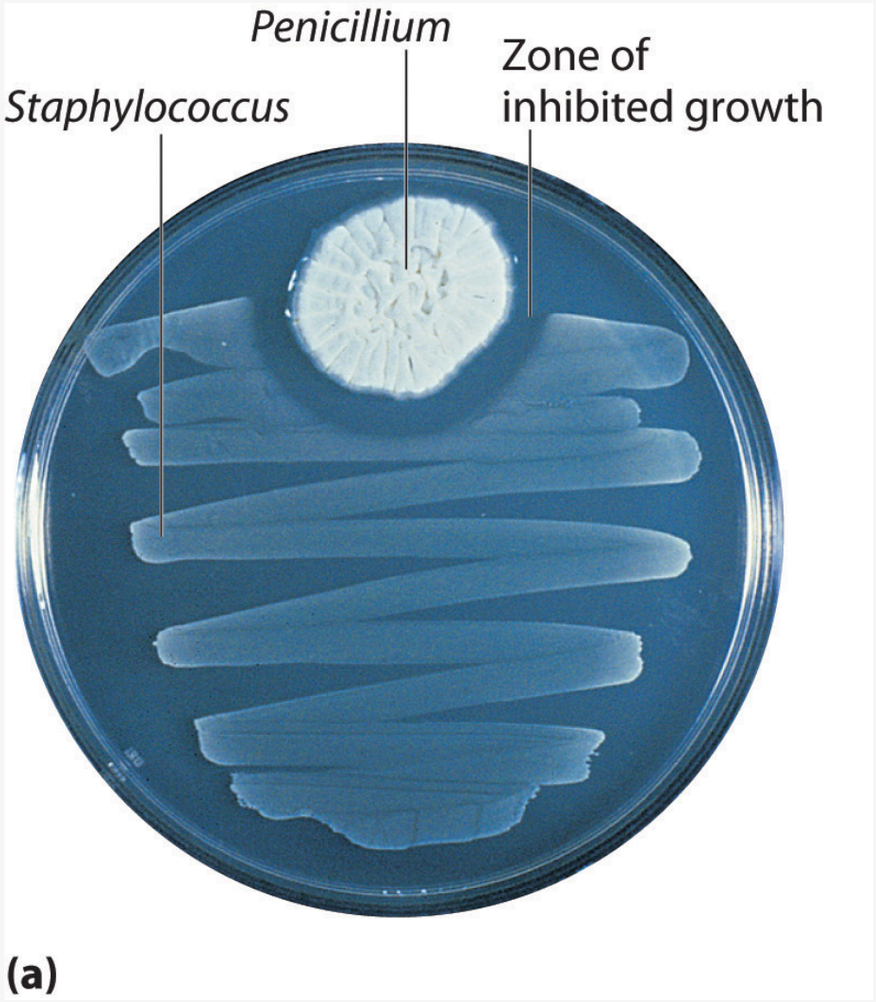
D.2 Aspirin

Modification for absorption + distribution

- Aspirin - low solubility in water, can increase bioavailability through chemical modification



D.2 Penicillin



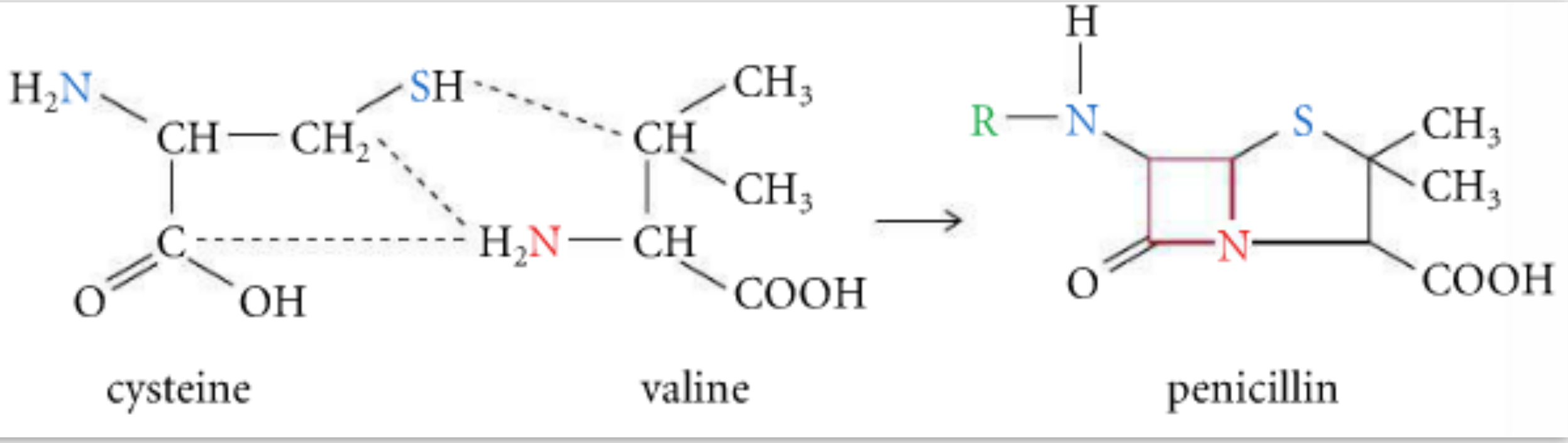
(a)

- gave birth to drugs known as antibiotics
- created by microorganisms, which have action against other microorganisms
- Fleming wasn't a chemist, published his findings, but did not isolate and identify the active ingredient

D.2 Penicillin

Action of Penicillin

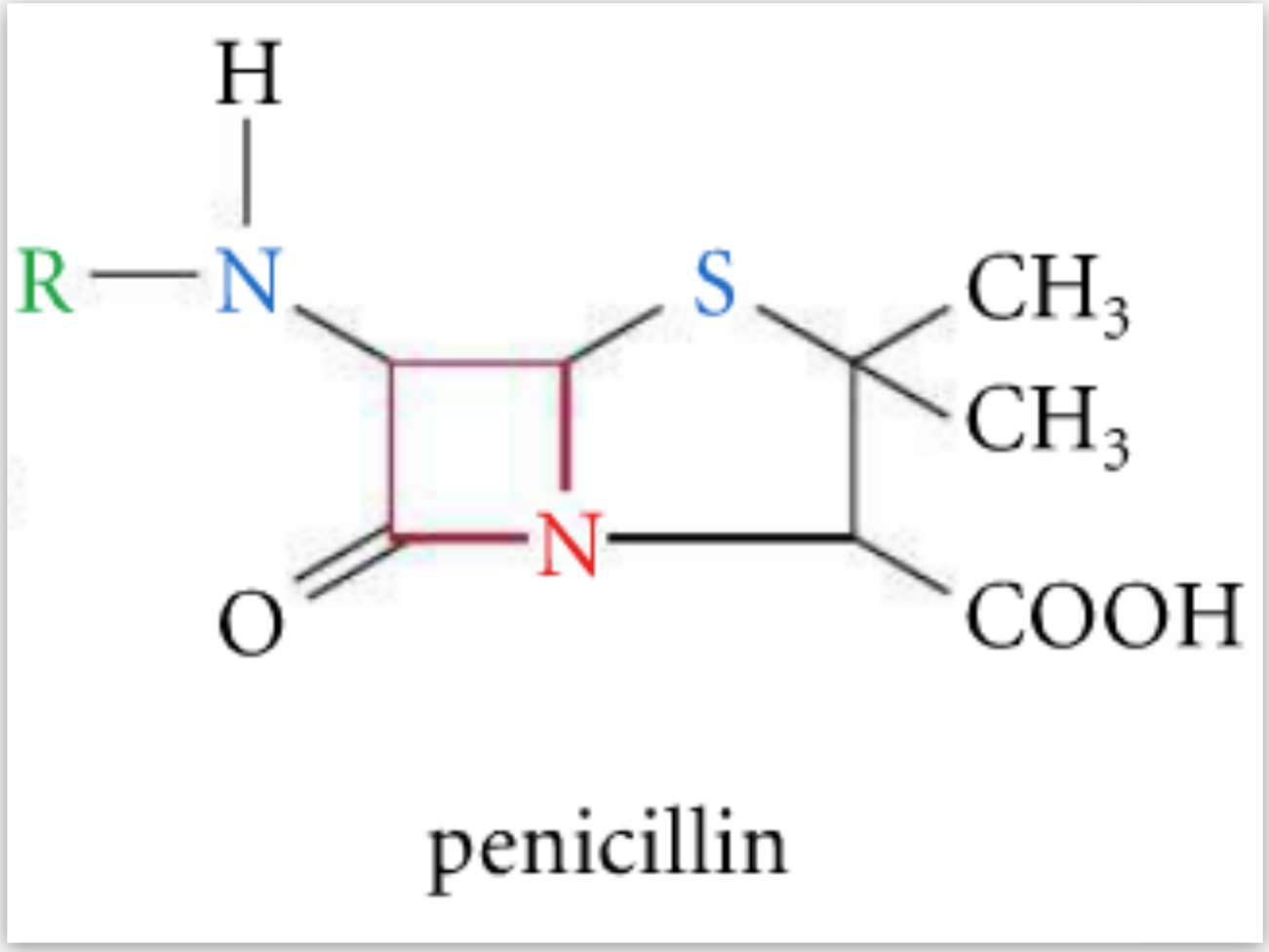
- Isolation occurred using X-Ray Crystallography (Penicillin G was major constituent of the mold) (Hodgkin, 1945)
- Penicillin - the dipeptide formed from 2 amino acids (cysteine and valine)
- Contains a 5-membered ring w/a sulfur atom - thiazolidine - attached to a four membered ring containing a cyclic amide group (**beta-lactam**)



D.2 Penicillin

Beta-lactam

- part of the molecule responsible for anti-bacterial properties
- constrained 90° bond angles (from 109.5° and 120°) break easily and cause the biological activity of the molecule



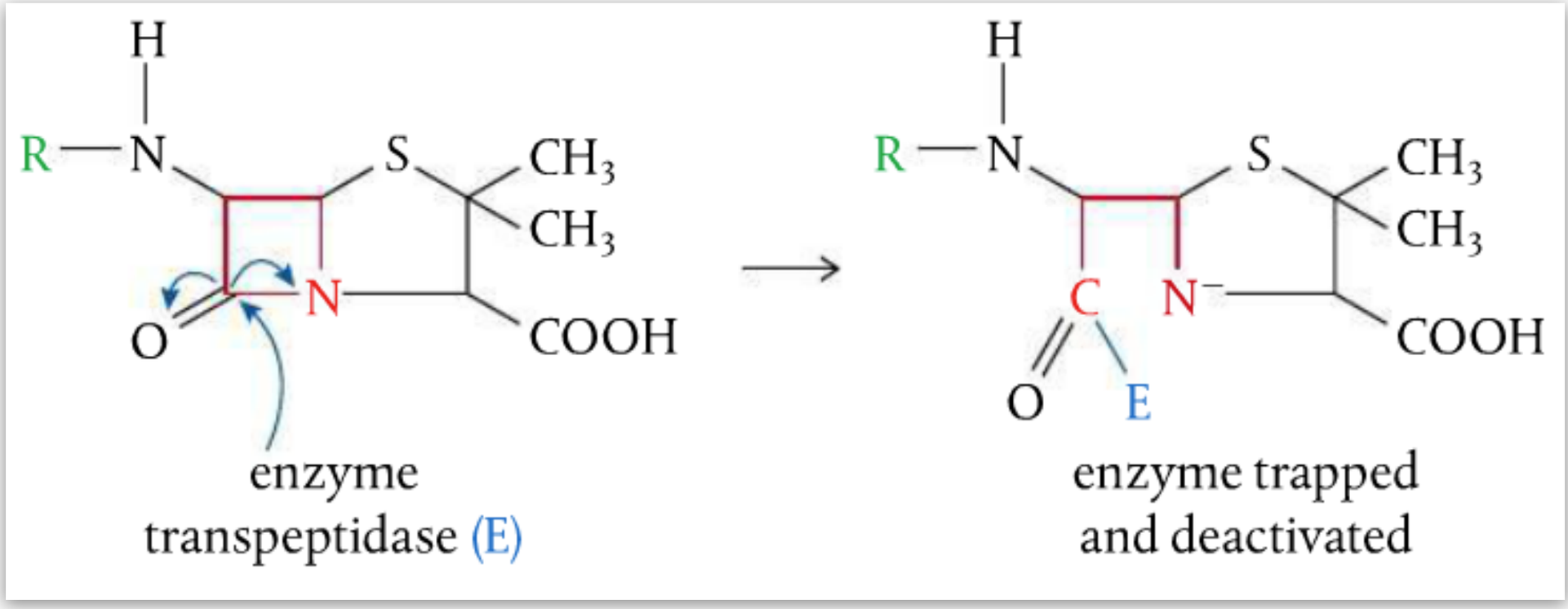
penicillin

general penicillin structure on table 37

D.2 Penicillin

Action of Penicillin - cont'd

- beta-lactam - disrupts formation of cell walls in bacteria by inhibiting transpeptidase - a key enzyme



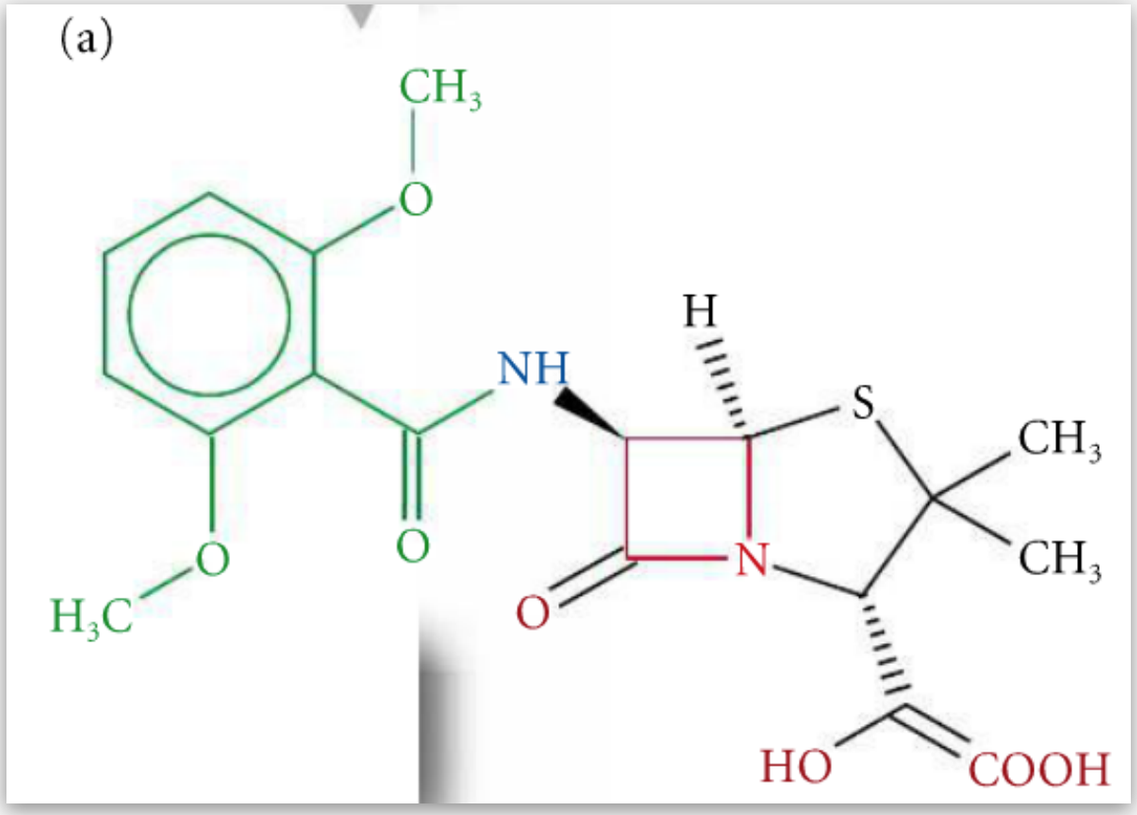
- disadvantage to Penicillin G - broken down by stomach acid - must be injected directly into blood

D.2 Penicillin

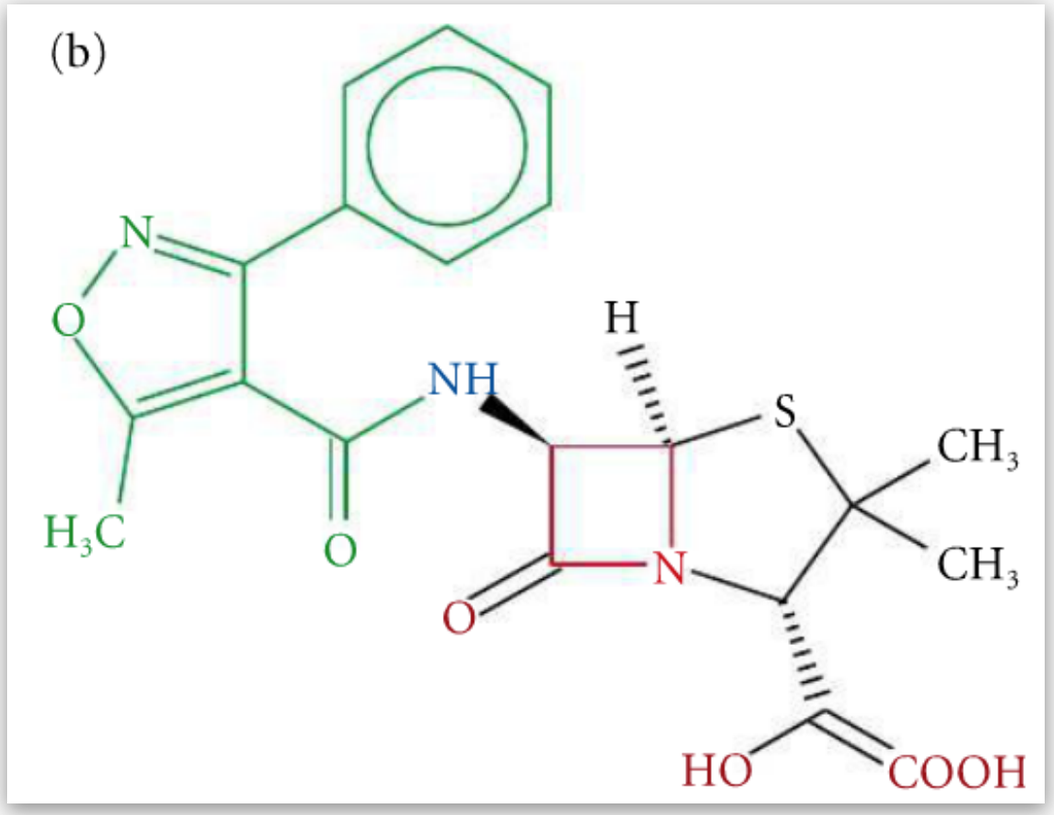
Antibiotic Resistance - bacteria fight back!

- penicillin resistant bacteria produce **penicillinase** or **beta-lactamase** which can open the beta-lactam ring and rendering the drug inactive

methicillin



oxacillin



D.2 Penicillin

Antibiotic Resistance - cont'd

- penicillin is legislated to be prescription only & doctors are encouraged to not overprescribe
- "patient compliance" - taking the full course of medicine to ensure the disease does not spread