I. Licit vs. Illicit

Chemically no difference between drugs and medicines. Society associates “drug” with addiction, narcotics and crime.

- Not determined by chemical structure—governed by society and changes with time. *Examples:*

Drugs may be broadly classified as:

1. Those that cause a physiological response in the body.   
   - aspirin
   - anticancer drugs
   - morphine

2. Those that kill foreign invading organisms.   
   - antibiotics
   - antifungal agents

3. Recreational (subgroup of #1)

---

II. General

Tips for understanding organic chemistry:

1. Carbon ALWAYS forms 4 bonds.
2. Shortcut = bonds to C’s are shown as lines. Symbol for C and H bonded to C is not shown. There is a C at every corner or end of line without a symbol.
3. If <4 bonds to C are shown, the remainder are C-H bonds.

Example: Benzene \( \text{C}_6\text{H}_6 \)
II. General

Example: Find its formula.

II. General

More tips for understanding organic chemistry:
1. Functional groups are collections of atoms in arrangements that have predictable characteristics. Do not memorize groups, but know what is implied.
   Ex.

II. General

More tips for understanding organic chemistry:
2. Isomers- have the same formula but atoms connected differently.
   Remember: C= 4 bonds, H= 1 bond, O= 2 bonds
   Ex. C\(_2\)H\(_4\)O

III. What happens when you take a drug?

A. Aspirin
   • acetylsalicylic acid--from Salix, willow genus
   • B.C.-willow barked helped fever and pain
   • 1700’s -isolated active compound
   • 1800’s - modify structure to reduce irritation and bitterness…..done by Dr. Bayer

III. What happens when you take a drug?

Drugs are small molecules that bind at (“stick to”) protein functional sites

Drugs change protein function, by making the protein function better or by preventing its functioning

Aspirin analgesic anti-inflammatory agent
methysalicylate irritant, like aspirin differs only in 1 CH\(_3\) group
III. What happens when you take a drug?

How Does Aspirin Work?

• Most communication in body is not through nerves….but through hormones.

• Prostaglandins- hormones in almost every tissue and fluid that participate in many functions. (ex. transmission of pain, cause fever)

A reminder……

Enzyme inhibition = lock and key model

enzyme inhibitor product

COX-2 is a protein made in tissues that have been injured

• COX-2’s "job" is to produce swelling, due to prostaglandins, which results in a “pain signal”

• When trauma occurs, COX-2 causes signals that you experience as: “I feel a pain!”

- Aspirin is a small molecule that binds to COX-2, and won’t let it do its job (thus eliminating the pain signal)

- COX-2 is the "target" of aspirin

Problem! Your body contains another protein, called COX-1, that is very similar to COX-2

• COX-1’s "job" is to keep your stomach lining happy

• Aspirin cannot discriminate between COX-2 and COX-1. It “sticks” to both!

Aspirin sticking to COX-1 may cause an unpleasant SIDE EFFECT of an upset stomach or ulcers

Both proteins have an overall similar structure

COX-1: PLYTSIHLAQTYYFMQVHLSYPR–GMKNQGAYFPIL
COX-2: P–YILTSIHLAQTYYFMQVHLSYPR–GMKNQGAYFPIL

Why does aspirin stick to both COX-1 and COX-2?
III. What happens when you take a drug?

Other analgesics (Tylenol, Ibuprofen…):
- Have similar functions (Blocking prostaglandin synthesis)
- Ability to inhibit enzyme and other functions differentiate between analgesics = slight changes in the key that fits the lock.

Vioxx and Celebrex (the next generation of pain killers) were specifically developed by pharmaceutical companies to address the side effects associated with Aspirin, Motrin, and Tylenol.
- Vioxx and Celebrex still stick to COX-2, but they leave COX-1 alone, allowing it to keep doing its job keeping your stomach happy!

IV. Chirality

Stereoisomers: molecules with the same formula and connectivity but a different spatial arrangement

Enantiomer: A specific type of stereoisomer. Non-superimposable mirror images.
- Molecular handedness
- The two mirror images are different enantiomers. The molecule that can exist as 2 enantiomers is referred to as chiral.

Example: CFCIH(CH₃)
IV. Chirality

DNA, sugars, amino acids are all chiral molecules and can exist as either enantiomer.

The Problem:
It is easier to make (in a lab) a racemate of the two enantiomers than 1 pure enantiomer.

If only one of the enantiomer gives desired effect, what happens to the other?

IV. Chirality: A Case Study
Thalidomide
- 1958 - introduced as a sedative for normal sleep. Also prevents nausea in pregnancy. Non-prescription.
- FDA was unsure of safety tests and did not allow its sale in the US
- 1959 - 12 cases of phocomelia (seal babies)
- 1960 - 83 cases
- 1961 - 302 cases!

IV. Chirality: A Case Study
Thalidomide
- Found link between thalidomide in 1st trimester of pregnancy and the disease.
- Thalidomide is chiral and was made and administered as a racemate.
- One enantiomer is a safe sedative, the other is a teratogen.
IV. Chirality: A Case Study

Thalidomide
- Now being considered as a lead drug for the treatment for AIDS. Would you support its use?

IV. Chirality
- FDA now requires all chiral drugs now used to be administered as one pure enantiomer.
- Hard to make only one enantiomer in lab.
- Hard to make a racemic mixture and purify.
- Conclusion: Pharmaceutical companies tend to avoid new chiral drugs. Eliminates some keys.

V. 3 Approaches to Drug Development

C. Knowledge and Planning
  i. Slightly alter structure of known drug.
     Based on lock and key model
     ex. FK-506, taxol

VI. Steroids
- A class of compounds (range from the Pill to cholesterol)
- 4 carbon rings fused together
- double bonds in rings and atoms hanging off of rings determine function.
- Most are hormones

Steroids perform many functions in the body:

<table>
<thead>
<tr>
<th>Function</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regulation of secondary sexual characteristics</td>
<td>Estradiol (an estrogen); testosterone (an androgen)</td>
</tr>
<tr>
<td>Reproduction and control of the reproductive cycle</td>
<td>Progesterone and the gestagens</td>
</tr>
<tr>
<td>Regulation of metabolism</td>
<td>Cortisol; cortisone derivatives</td>
</tr>
<tr>
<td>Digestion of fat</td>
<td>Cholic acid; bile salts</td>
</tr>
<tr>
<td>Cell membrane component</td>
<td>Cholesterol</td>
</tr>
</tbody>
</table>

A. Cholesterol
- Needed for cell membrane rigidity
- Made in body
- All other steroids are made from cholesterol
VI. Steroids—Three Examples

B. Fertility Steroids

In pregnant women, fertilized egg sends steroid hormone (progesterone) to block release of this hormone. Progesterone also tells uterus to get ready.

To increase or decrease fertility, change levels of this progesterone outside of pregnancy.

B. RU-486: the “morning after pill”

• Binds where progesterone (released by fertilized egg) would
• Does not cause any action (simply prevents action initiated by progesterone)
  – antagonist, fits lock but won’t open it.
• Uterus is not prepared and fertilized egg does not implant (RU-486)
• Fetus expelled (misoprostol)

B. RU-486: the “morning after pill”

• May be replaced by “off-label” use of methotrexate (blocks folic acid and cell growth) and misoprostol.
• FDA had already approved methotrexate for cancer and arthritis.
• FDA had already approved misoprostol to protect stomach lining.
VI. Steroids

C. Anabolic Steroids

• Developed to help seriously ill people gain muscle mass
• Based on testosterone’s promotion of muscle growth (known)

VII. Getting a New Drug to Market

• First, discover which protein(s) in the body causes the disease (the DRUG TARGET)
• Next, find or design a chemical (DRUG) that will modulate with the drug target to stop the disease
• Finally, determine if the drug is effective and if there are unwanted SIDE EFFECTS caused by the drug

Interesting fact: All of the current drugs act on less than 500 known “drug targets” within the body. It is estimated that there are thousands of drug targets still waiting to be discovered.
VII. Getting a New Drug to Market

- Generic drugs - chemically the same as brand name but cheaper-only marketed after patent expires.....not paying for research.

VIII. Case Study #1-Viagra

A. How it works

- Active component of dynamite
- Funding for Nobel Prizes
- Vasodilator
- WWI explosive packers show low blood pressure
- Nobel refused to used compound for treatment

A. Background

- Research shows nitroglycerin converted to NO in the body. (Molecule of the year 1992, Nobel prize 1998).
- Nitric oxide is naturally occurring vasorelaxant

- cGMP is the true vasodilator
- This reaction is catalyzed by the enzyme soluble guanylate cyclase.
- Nitric oxide activates this enzyme.

A. What does Viagra do?

- cGMP, the true vasodilator, is degraded in a reaction catalyzed by a second enzyme phosphodiesterase (PDE).
- Chemists at Pfizer made >1,400 compounds looking for an inhibitor for PDE to increase cGMP levels to treat high blood pressure.
- Lead compound, sildenafil was in Phase II clinical trials but lacked promise. Gave volunteers "max-out" dosage. Side effects arose....

- Male Erectile Dysfunction (MED)
- Affects 10% all men, 52% of all men 40-70 years old.
VIII. Case Study #1-Viagra

A. What does Viagra do?

- Sildenafil is now sold under the trade name Viagra.
- 88% MED patients respond to Viagra.
- Who shouldn’t take Viagra?
- Will Viagra “help” men without ED?

Case Study#2: Scientific Approach

- Consecutive game streak of 2,130 games (broken by Cal Ripken, Jr. in 1995)

ALS

- Progressive disease where motor neurons degenerate or die.
- Brain can’t communicate and control muscles. Later stages have complete paralysis although the mind is fully functioning.
- 300,000 people in the U.S. have ALS

Nitrotyrosine Facts

- Tyrosine is a naturally occurring amino acid.
- Tyrosine is converted in vitro to nitrotyrosine by two methods:

Nitrotyrosine & ALS

- Nitrotyrosine could be made by rx with peroxynitrite in vivo.
- Peroxynitrite can be generated from the reaction of nitric oxide and superoxide

Nitrotyrosine & ALS

- Superoxide is destroyed by a different enzyme called superoxide dismutase (SOD).
  \[ 2 \text{O}_2^- + \text{SOD} \rightarrow \text{O}_2^{2-} + \text{O}_2 \]
- ALS patients have genetically modified/hindered form of SOD---thus more superoxide around.
- This supports the theory that more peroxynitrite could exist and result in more nitrotyrosine formation in ALS patients.
Nitrotyrosine & ALS

- Controversy: Nitric oxide and superoxide are both very reactive. Some scientists say they would have to be generated in close proximity simultaneously to react with each other. Since they are generated by two different enzymes odds are slim.

Case Study #3: The Scientific Approach

Anthrax:
- Means “coal” in Greek (from color skin turns if infected).
- Recorded in ancient Egyptian documents, the Old Testament and by Virgil.
- Caused by infection by *Bacillus anthracis* through respiration, ingestion or skin exposure.
- Fatal if caused by inhalation. Great threat as a bioterrorism weapon.

Anthrax

*Bacillus anthracis* makes three proteins:
- 1. Protective Antigen (PA)
- 2. Edema Factor (ED)
- 3. Lethal Factor (LF)

Approaches to Shutting Down Anthrax

1. Find the 3D shape of LF (the “lock”).
2. Find a molecule that has a complementary 3D shape that will prevent LF from working.

Approaches to Shutting Down Anthrax

1. Find the 3D shape of the PA heptamer.
2. Find a molecule that has a complementary 3D shape that will block the entry of EF and LF.
IX. Drugs Involved in Neurotransmission

- Nerve impulses are carried along a nerve fiber by electrical impulse carried by the movement of ions.

- How do impulses cross the synapse?
  - One nerve releases neurotransmitters that bind to receptors on next cell. Receptors then start impulse in that cell.

- To stop current impulse and allow a 2nd one to come, neurotransmitter (acetylcholine) must be removed.

- Inhibiting this enzyme prevents neurotransmission.
  - Nerve gases (WWII) mimic the shape of acetylcholine. Bind to enzyme and don’t let go.

WWII Gases

- Sarin (Agent GB)-most potent nerve gas
- Soman (Agent GD)
- Tabun (Agent GA)

  All very easy to make

- Parathion
- Malathion
- Carbaryl

  All bind tightly to enzyme, but not as tightly. Use?
Chemical Weapons Convention

- Chemical agents were used in the Iran-Iraq War and the Gulf War.
- Most countries (not Iraq or Libya) signed an agreement to destroy all existing gaseous weapons by 2004.
- Problems?

Chemical Weapons Convention

- How to destroy arsenal? Hydrolysis or incineration.

Drugs of Abuse

<table>
<thead>
<tr>
<th>Table 10.1 Drug Schedules</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CLASS</td>
<td>Description</td>
</tr>
<tr>
<td>SCHEDULE I</td>
<td>Drug has no current accepted medical use, Drug has a high potential for abuse</td>
</tr>
<tr>
<td>SCHEDULE II</td>
<td>Drug has current accepted medical use, Drug has high potential for abuse</td>
</tr>
<tr>
<td>SCHEDULE III</td>
<td>Drug has current accepted medical use, Drug has intermediate potential for abuse</td>
</tr>
<tr>
<td>SCHEDULE IV</td>
<td>Drug has current accepted medical use, Drug has low potential for abuse</td>
</tr>
<tr>
<td>SCHEDULE V</td>
<td>Drug has no accepted medical use, Drug has low potential for abuse, Drug has a high potential for abuse</td>
</tr>
</tbody>
</table>

X. Marijuana

- A preparation of leaves and flowering top from Cannabis sativa
- Used for thousands of years
- Grows almost anywhere (differ in size and content)
- Active component (main) is THC (tetrahydrocannabinol)
- Mostly C and H
- Low bp
- Fat soluble

X. Marijuana

- THC is fat soluble
- Metabolites are stored in fat and liver and slowly released in urine (can be detected up to 10 days)

XI. Alkaloid Drugs

Alkaloids: bitter, basic N-containing compounds from plants

A. Caffeine
- Alkaloid in coffee beans and tea leaves
  (100-150 mg/cup)
XI. Alkaloid Drugs

B. Nicotine
- Alkaloid in tobacco
- Very toxic! 50 mg is fatal

D. Opium
- Dried poppy sap - a mix of alkaloids (25% weight)
- ~4000 BC man discovers use of opium poppy for pleasure and pain.
- Named for Roman god of dreams
- Potent analgesic/cough suppressant
- 25% of opium by weight is morphine
- 1803 Sertturner isolates morphine.
- 1925 Sir Robert Robinson gets structure of morphine.
- 1929 NRC-NAS charged with stopping growth of opium abuse.

Codeine is also found in opium
- Not as addictive but a better cough suppressant
XI. Alkaloid Drugs

D. Opium
• codeine is also found in opium
• not as addictive but a better cough suppressant

• Opium alkaloids are the most powerful constipating agents known to man.

Morphine
- 1940 Discover the analgesic activity of meperidine
  - Synthetic (not in poppy)
  - Loss of 3 chiral centers
  - Synthetic cake walk

Fentanyl
- Binding site like morphine
- Analgesia, euphoria, respiratory depression
- Dependence
- 50-80 x as effective as morphine.

Fentanyl is completely synthetic.
Search for analogues/derivatives to reduce dependency.
ALL PREPARED BY SYNTHETIC ORGANIC CHEMISTRY.

O'Brien, Lisa; Kemp, Sheelagh; Dupuis, Lee; Taddio, Anna.
Pharmacologic management of painful oncology procedures in pediatrics.

XI. Alkaloid Drugs

E. Heroine
• Chemists wants to keep analgesic properties of morphine but lessen addiction

  morphine ——— heroine + acetic acid (vinegar)

• As for THC (pot), why would the brain have a specific receptor for opiates?
• Search for brain chemical that fit these receptors
XI. Alkaloid Drugs

F. Cocaine

- from coca bush
- local anesthetic and stimulant
- leads to feelings of euphoria and feelings of power at high levels
- Blocks re-uptake of dopamine.

Sigmund Freud:
- 1st proponent for cocaine
- Used to anesthetize eyes for surgery
- Had a friend use it to kick morphine
- Controversy over addictiveness
- Liver enzymes destroy in ~1 hr

XI. Alkaloid Drugs

Chemistry of cocaine:

Street cocaine is what chemists call cocaine hydrochloride, a salt.

The blood brain barrier
- A tight knit layer of endothelial cells coating 400 miles of capillaries in the CNS.
- Can only cross if:
  - Matching membrane-bound protein transporter
  - Slipping through non-polar cell membranes. (Nicotine, alcohol, cocaine, heroin...)

Salts are water soluble but have high boiling points.
BP is so high it decomposes if you try to smoke it.
How to administer cocaine?
XI. Alkaloid Drugs

To help cocaine across the blood brain barrier- remove its charge:

To remove the H⁺, add a base to react with it.

XI. Alkaloid Drugs

Free-basing cocaine:
Get street cocaine (an acidic salt)
Dissolve in water that contains a base

XI. Alkaloid Drugs

Cocaine summary:
• Crack and cocaine differ only in an acidic proton, removed by a base.
• Crack (what chemists call cocaine) is nonpolar, has a low pb, and crosses the BBB faster.

XI. Alkaloid Drugs

Drugs related to cocaine (similar structure):

G. Hallucinogens

distortions of reality
and deep meditation
XI. Alkaloid Drugs

LSD (lysergic acid diethylamide)
- Does not occur in nature
- Swiss chemist Albert Hoffmann prepared it while studying rye fungus metabolites.
- Accidentally ingested, experienced “restlessness, dizziness, fantasy-filled delirium including a kaleidoscopic play of colors…”
- Ate 0.000250 g to be sure it was the LSD (3 hits worth)
- Gave LSD to professionals to test.
- Only tiny amount needed for effect (0.1-0.2 mg/dose)

XI. Alkaloid Drugs

Bufotalin (also bufotenine):
lick toad directly or collect secretion and smoke it.
(called stones)

Other “natural” hallucinogens:
- morning glories- ancient Aztecs talked to gods
- datura- contains scopolamine
- nutmeg
- peyote

H. β-Phenyl Ethyl Amines

- Mescaline
- Norepinephrine - a neurotransmitter
- Epinephrine - adrenal
XI. Alkaloid Drugs

H. Phenethyl amines.

Oxycontin

Scientists determined many psychoactive drugs have similar features. Strip down structure to make synthesis easier.

XI. Alkaloid Drugs

I. Amphetamines:
• Structure is based on adrenaline
• 1932-used in inhaler to clear stuffy nose

• amphetamine abuse is epidemic level in some counties
• easy to make—many labs
• synthesis uses LAH (produces H₂)

XI. Alkaloid Drugs

J. Ecstasy MDMA
• Closely related to methamphetamine.
• Depletes serotonin levels due to release
• Impairs visual and verbal memory
• 4-6 hr effect (to rebuild serotonin)

X. Herbal Remedies

• Loose regulation by FDA
• May be beneficial or hazardous
• Risk-benefit analysis
• Natural ≠ safe!!!