

Drugs

Lecture Outline (Note: See textbook chapter 10)

- Definitions
- How Drugs Function
- Case Study: Aspirin
- Biochemical "problem"
- Traditional solution
- COX-2 inhibitors
- Morphine, Codeine, & Heroin
- Structural Relationships
- Insights into Drug Design

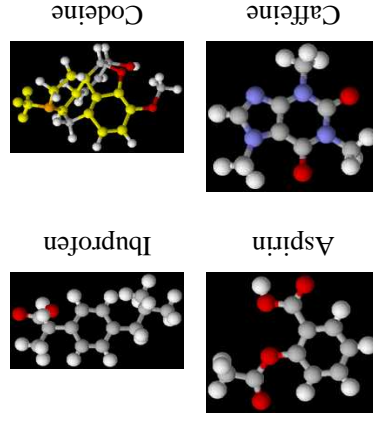
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Definition of a Drug

- Textbook (p. 394)
"Drugs are substances that prevent, moderate, or cure illnesses."
- A more general definition
A drug is any external substance that alters biochemical reactions in the body when taken - it changes some body function(s).

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Sample Drug Structures



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OldWives' Tales

Numerous 'Home remedies' have been known for a long time.

- Chicken Soup - **Actually appears to work !?**
- Fish is brain food - **Good source of protein and beneficial fats.**
- Carrots help vision - **Good source of Vitamin A.**
- Willow bark tea to relieve pain (Hippocrates, 4 B.C.) - **Natural source of 'aspirin'.**
- Don't swim right after eating - **Well, they can't all be right.**

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The Ideal Drug

- The perfect drug doesn't exist. However, there are certain characteristics that are desired in almost any drug.
- Achieves desired effect
 - Extent of change varies by dosage
 - Time of effect controllable
 - No undesirable side effects
 - Inexpensive

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Hormones

- Hormones are "simple" chemical released into bloodstream.
- All cells have a chance to "see" hormone
- Only appropriate cells have **receptors** for any particular hormone.

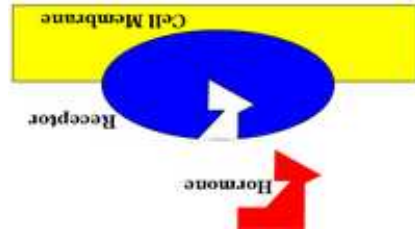
An imperfect analogy:

Lots of different cars (**different hormones**) drive on the streets in your neighborhood (**bloodstream**), but only your family's cars have the garage-door-opener (**specific hormone**) that opens your garage door (**specific type of cell**).

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Lock-and-Key Model

Receptors located on the surface of cells only bind a very limited number of substrates (often only one). The receptor is typically much more complicated (larger) than the substrate (hormone) that binds to it. (For an analogy, note that a lock is much more complicated than a key).



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Relief

Aspirin and other NSAID's (non-steroidal anti-inflammatory drugs) are taken to relieve pain and inflammation. Given above, two possibilities:

- Disable Prostaglandins - Since prostaglandins are causing the undesirable effects, stopping these should stop symptoms.
- Disable COX Enzymes - By disabling prostaglandin production at the source, smaller quantities of drug can be used, with same relief from symptoms.

NSAID's act as COX enzyme inhibitors. They bind to these enzymes and temporarily disable them.

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Prostaglandins

Several different types of prostaglandins, serving many roles. Two classes of COX enzymes are known.

- COX-1 prostaglandins
- Maintain kidney function
- Keep stomach lining intact
- COX-2 prostaglandins
- inflammation
- pain
- fever

Most NSAID's (including aspirin) stop both classes of COX enzymes.

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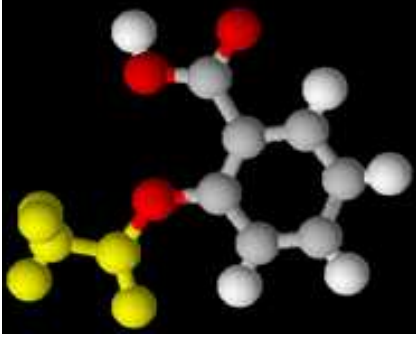
Case Study - Aspirin

(See also text pp 394-397 & 403-405)

- Our bodies contain cyclooxygenase (COX) enzymes.
- COX enzymes catalyze production of relatively large quantities prostaglandins.
- Prostaglandins are responsible for:
 - Producing fever and swelling
 - Increasing sensitivity to pain
 - Inhibit blood vessel dilation
 - Regulate production of acid and mucus in stomach
 - Assist kidney function

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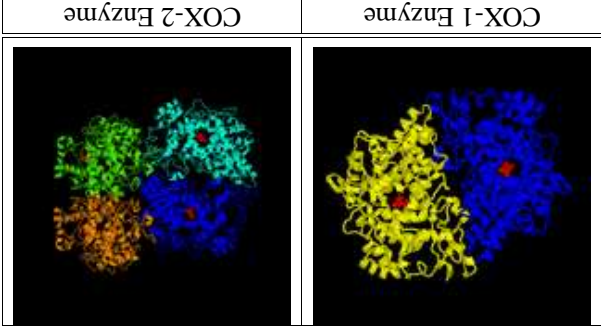
Aspirin



The red atoms are the acetyl group, which is not present in willow bark.

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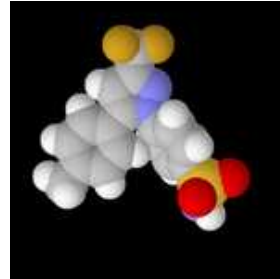
COX Enzymes



Red atoms are a non-selective inhibitor.

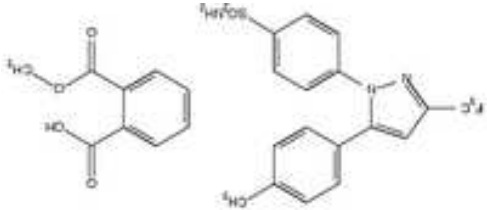
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COX-2 Inhibitor



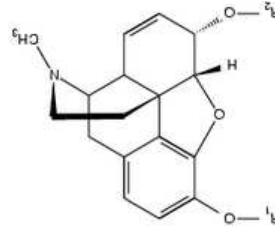
Celebrex (Celecoxib) structure shown above. Only binds to COX-2 Enzymes

Celebrex



Celebrex (left) is more complicated than aspirin (right). The larger size and rigid shape make this compound unable to get into the binding site of the COX-1 enzyme.

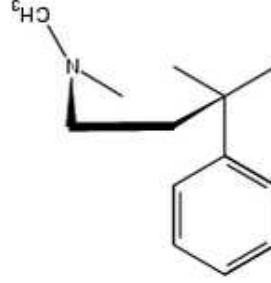
Morphine and Friends



	R ₁	R ₂
Morphine	H	H
Codeine	CH ₃	H
Heroin	CH ₃ C(O)-	CH ₃ C(O)-

Morphine Rule

The following substructure MUST be present:

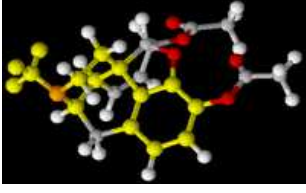


(See Figure 10.12 - textbook page 407)

Morphine Rule - Heroin



Morphine



Heroin

Morphine, codeine, and heroin have very similar structures. As might be expected, they also have very similar properties.

- Mechanism
 - All are believed to change the pain receptors in the brain. The pain signal is not turned off, but its affect is not "normal".

Thalidomide

Thalidomide is an example of a drug whose mirror image is a different compound. (Right- and Left-handed forms exist).

- Demerol: Effective pain-reliever.
- Methadone: Used to treat Heroin addiction.

Using morphine rule:
Goal: Design a drug with pain-relieving qualities, but without the addiction and other side effects.

Related Compounds

Morphine



Codeine

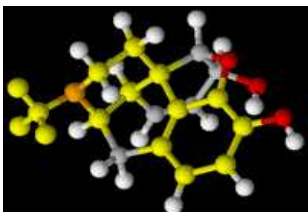


Morphine Rule - Codeine

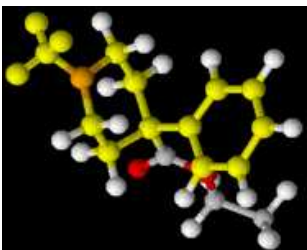
- Rarely starts from scratch.
- Relies on structure/function relationships.
- Once promising candidate found, derivatives made to seek "best" of the bunch.
- Comparison leads to understanding of necessary and unnecessary structural features.

Drug Design

Morphine



Demerol



Morphine Rule - Demerol