09/24/2015

Thursday, September 24, 2015 4:02 PM

Drug candidate discovery
Time line

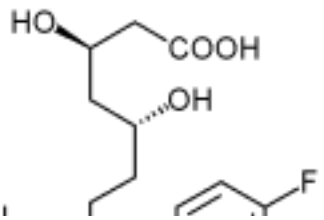
- Target identification
  - An enzyme, ion channel, protein, something that you want your drug to interact with (6 months-2years)
- High throughput screen (HTS) (3-4 months)
  - Identify active compound to "hit" (3 months) and more potent compound, hit=something that is active
- Hit to lead, identify lead compound including structural modification to improve activity (6-9 months)
- Lead optimization (LO) improve pharmacokinetics (absorption, bioavailabilty, distribution, etc) reduce toxicity (2 years)
- Candidate drug is established (CO) total time for target identification, screening for hit, optimizing hit can take to 3.5-5.5 years this is considered part of the preclinical research and development
  - Active-->hit-->lead

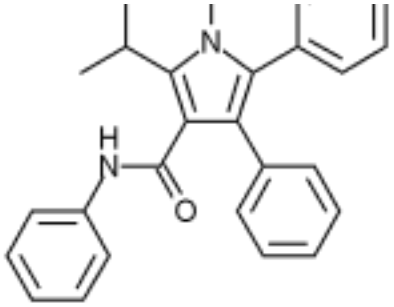
1. Target identification (biological mechanisms)

	Sales of drugs
• Enzyme inhibitor	38%
• Receptor antagonist (blocking receptor)	24%
• Receptor agonist (enhancing activity of receptor)	12%
• Ion channel modulator	8%
	~80%

What do these drugs look like?

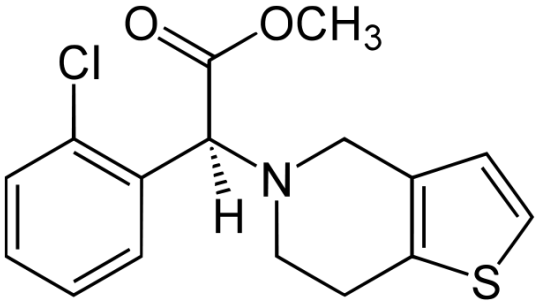
1) Enzyme inhibitors ex lipitor (lowers cholesterol, manufactured by Pfizer)





- Statin drug class

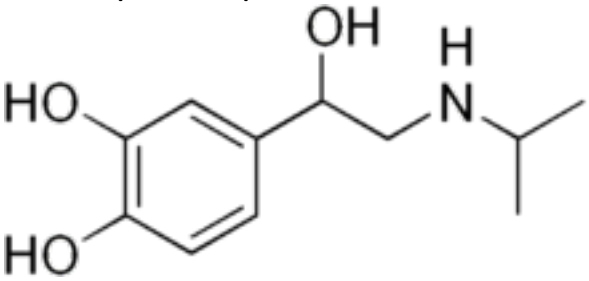
1) Receptor antagonist ex plavix (anti platlet drug, manufactured by Bristol Meyers Squibb)



- Inhibit $P2Y_{12}$ receptor on platlet cell membranes
- ADP class receptor
- Anti clotting

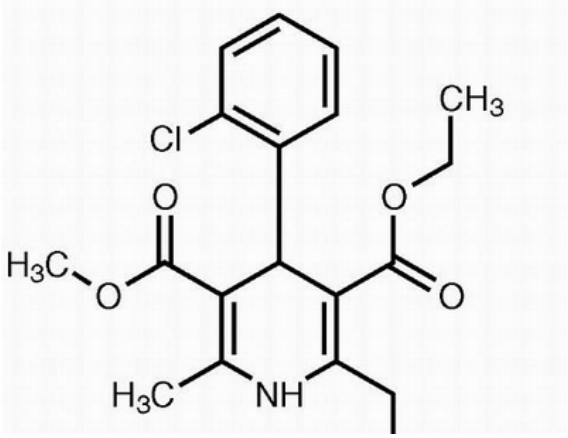
1) Receptor aogonist ex isoproternol (used to treat asthma, Valeant)

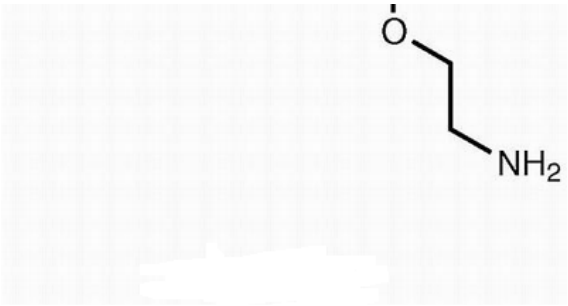
- Speeds up the heart rate, related to adrenaline



1) Ion channel modulator ex Norvase (used to treat hypertension, Pfizer)

- Blocks the Ca^{2+} channel



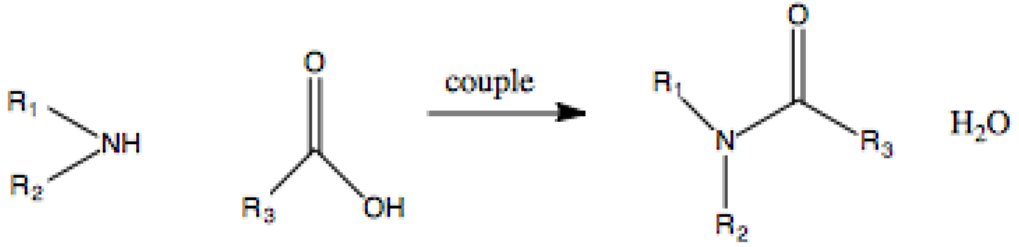


2. Bioassays

- After identifying your drug, you need to find a way to measure how the drug is interacting with your target
- Based on cells or isolated enzymes/proteins
- Need compounds to assess if they interact with target (can be time consuming, if you are measuring one compound at a time, drug companies have compound libraries which can be purchased)
- High Throughput Screening involves using a chemical library and testing to activity your target 100s-1000s of compounds
    - There are two types of libraries

1. Combinatorial libraries
    i. Generated using synthetic organic chemistry
    ii. Drawback=structure is limited

Ex. A typical "two component library"



Advantages: generate many different compounds quickly

Disadvantages: no real diversity in bonds, very difficult separations

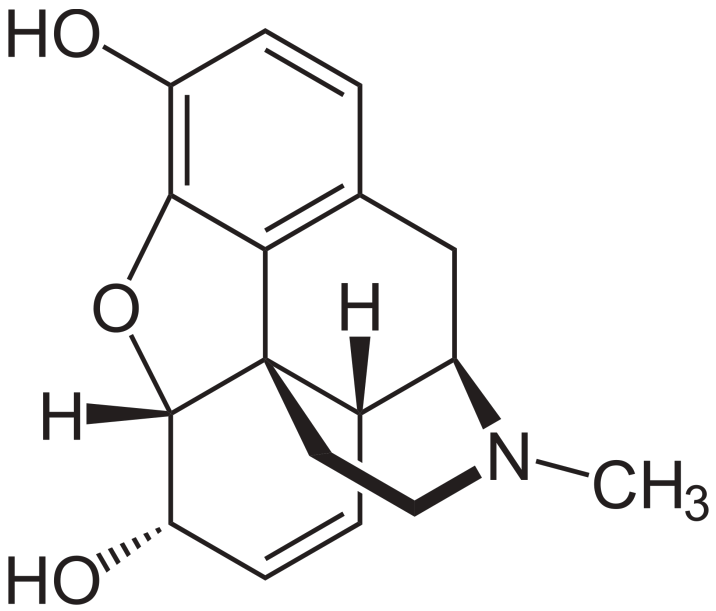
2. Natural product based libraries
    i. Use plant or bacteria extracts that contain many different compounds that you can use as your library

Advantages: highly diverse set of structures, likely bioavailable in the human body

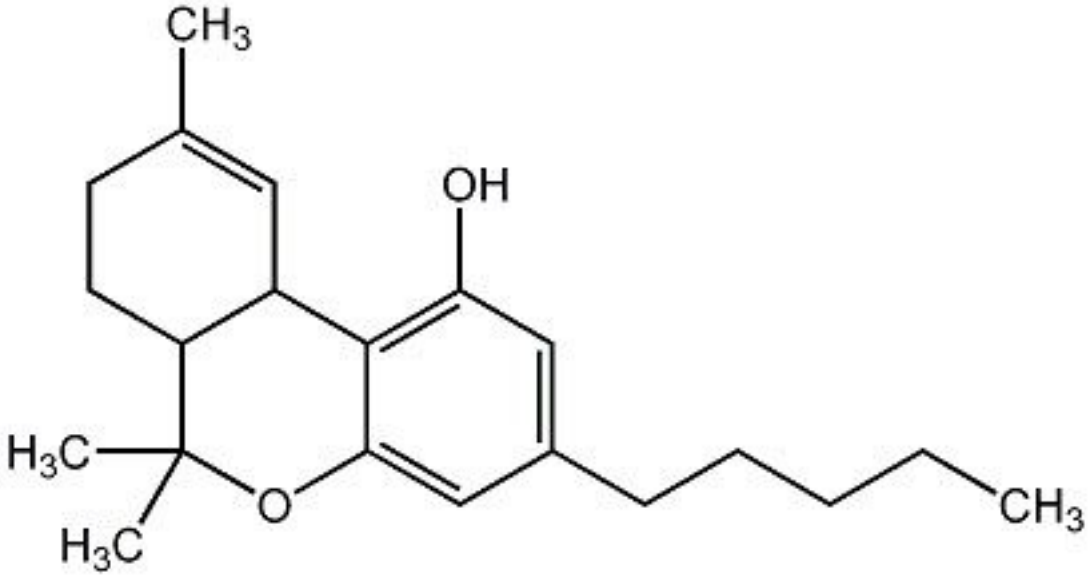
Disadvantages: complex mixture and often difficult to isolate and identify active component

Ex. Plant sources

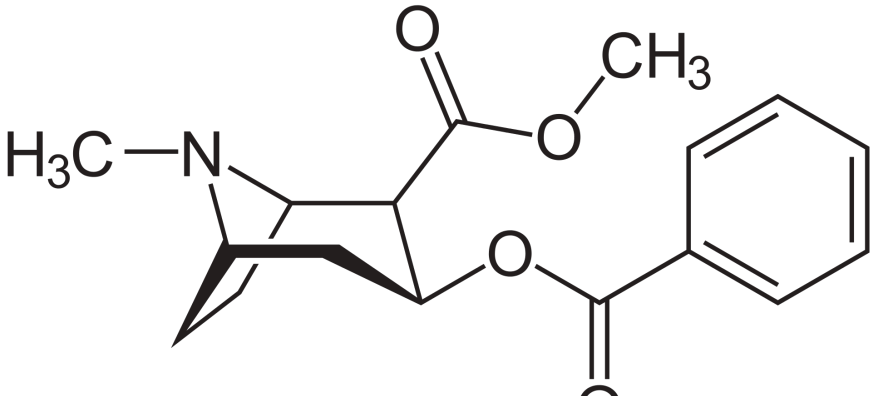
A) Morphine which is isolated from the opium poppy (1803) it is an opioid receptor agonist



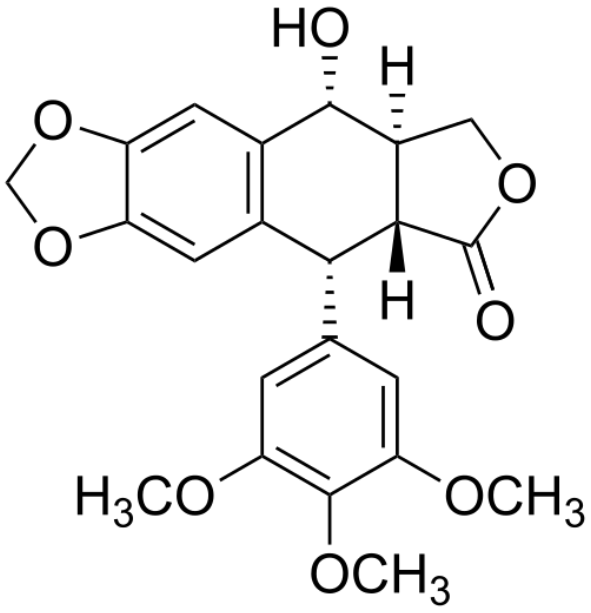
B) Tetrahydrocanniabinal (THC) from the cannabis plant (1964), it is an agonist for cannabinoid receptor which is involved in appetite, pain sensation, mood, and memory



C) Cocaine isolated from the cocaplant in 1860, inhibits the nerve reuptake of the neurotransmitters in the brain, mood enhancer

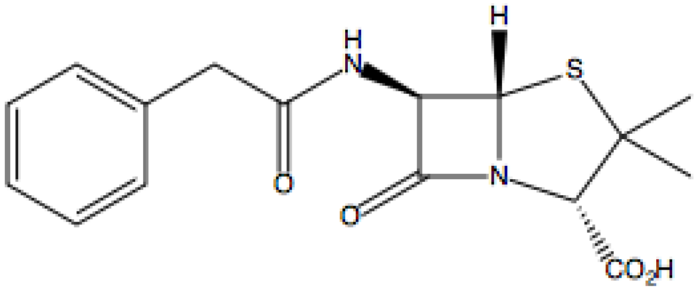


D) Podophylotoxin is an anti cancer agent and is found in the mayapple root plant, enzyme involved in mitosis inhibitor

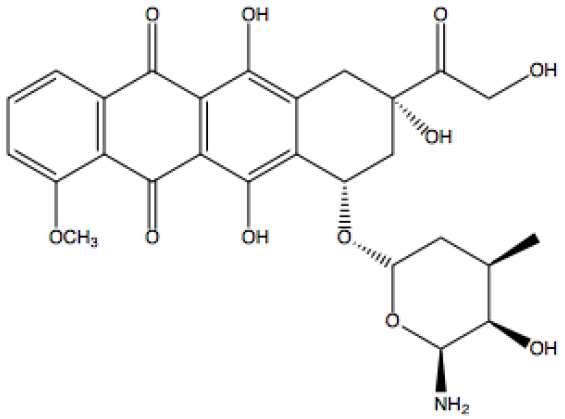


Microorganisms

A) Penicillin Ca (antibiotic)



B) Adriamycin (anticancer)



C) Erythromycin (antibiotic)

HTS-is an industrialized process which brings together validated tractable targets, and chemical diversity to rapidly identify noel lead compounds for early phase drug discovery

Ethnopharmacology

- Study of the use of plant derived materials in the traditional societies to maintain and improve health
- It is important because 80% of the world uses plant to treat health issues ie tea
- One main application is to identify a compound in these treatments
- Ex is quinine found in chincona, tree in Peru, 17th century used to treat shivering found in Malaria ultimately malaraia became resistant which led to chloroquine
- Chloroquine found in WWII (1943-1945) parasite eventually became resistant to this which led to Mefloquine
- Mefloquine was developed during the vietnam war (1970)
- The most modern potent anti malaria drug is artemisinin example of ethnopharmacology found in Chinese traditional medicine