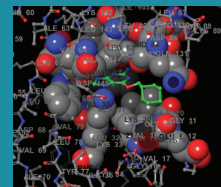


MOLECULAR SIMULATIONS

LIGAND AND RECEPTOR CONFORMATION



Example of Molecular Docking Simulation

Receptor Conformations

- When one is performing molecular docking, oftentimes, the receptor is treated as a rigid structure for computational practicality; in reality proteins are dynamic structures
- When one chooses a protein model, one is choosing a single conformation of a dynamic protein (it is as if one is taking a single "snapshot" of a protein)
- Thus one may need to try multiple different protein models to get an accurate idea of the interactions of a protein

Ligand Conformations

- However, slight variations of how the ligand is placed can vastly improve the docking scores of a ligand
- These are called poses; one ligand docking to a single binding site may have several different poses it could interact with the protein, all affecting the strength of a binding attraction

COMPUTATIONAL DATA

-How do we know how well a drug interacts with a receptor? Common methods include:

What are some good tools we can use to measure binding of a ligand to a protein?

-Binding revolves around thermodynamic favorability, and as a result the methods revolve around this

- Free Energy Perturbations
- Docking Score/Binding Energy Predictor
- Entropy Predictors
- Molecular Dynamics Simulations
- Monte Carlo Simulation

DRUG REPOSITIONING

-The unique thing about drugs is that they oftentimes are able to interact with multiple different areas of the body and be used for multiple different purposes

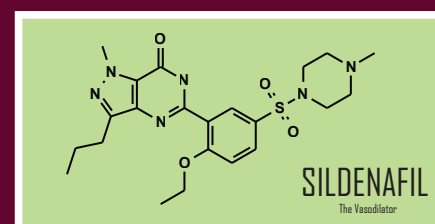
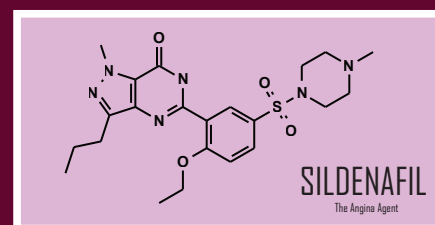
-This is where drug repositioning can come in

-Drug repositioning is the use of existing drugs in novel ways to treat different diseases that the ones initially developed for

-This can be helpful if the more optimal drug is difficult to synthesize or will not be synthesized due to patentability problems (in the case of orphan diseases)

-Sildenafil (otherwise known as Viagra) was an angina agent before it was more commonly used as a vasodilator

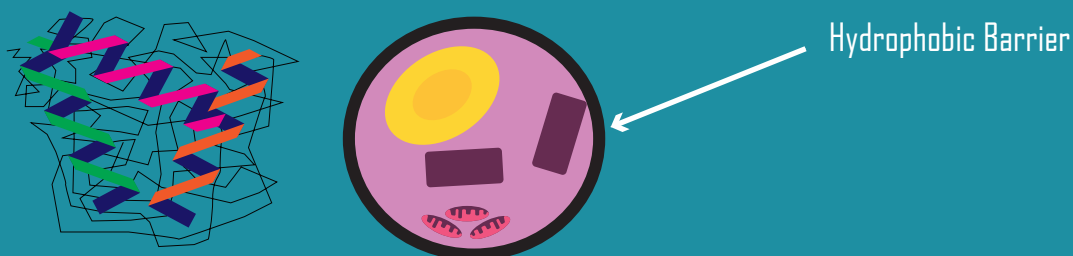
-Similarly, minoxidil was an antihypertensive drug before being used for hair loss treatment



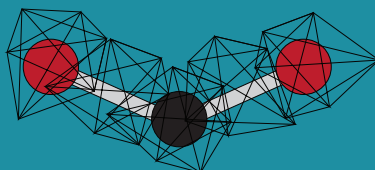
PHYSICOCHEMICAL PROPERTIES

PHYSICOCHEMICAL PROPERTIES

Hydrophobicity - This is determined by what is called a "partition coefficient" (which is found by taking the concentration of a drug in octanol over the concentration of the drug in an aqueous solution). Hydrophobicity is an important characteristic for drugs; this is because drugs generally need to cross hydrophobic barriers in order to reach their desired targets.

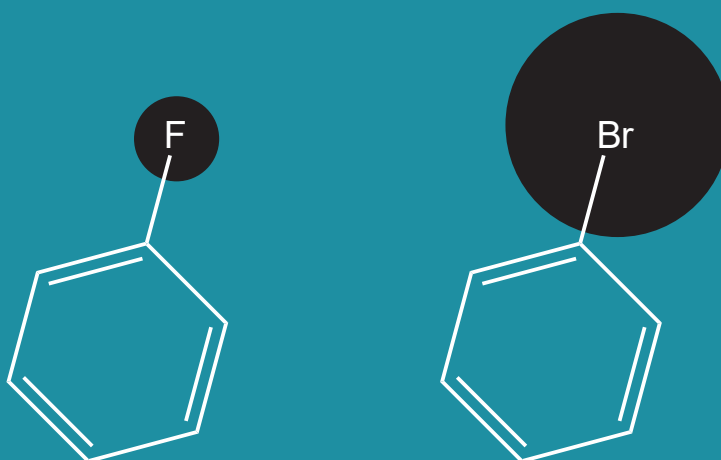


Electronic - A compound's electronic properties are oftentimes critical to consider. Introduction of a new group can have an inductive or withdrawing effect of electrons; this can affect, for example, ionization and polarity.



ELECTRON DENSITY
MAP

Steric - A compound's steric properties are about the shape and spatial arrangements of its atoms and how that affects its interactions with its surroundings.



The larger size of the bromine atom (compared to a fluorine) increases the steric properties of this molecule

DRUG MODIFICATIONS

WHY?

- After conducting tests (such as Lipinski's Rule of 5) it may become clear that a potential drug candidate is not suitable
- However all hope is not lost as one can use the concepts of bioisosterism and other properties to try and modify the existing candidate to achieve the desired properties
- It is usually done through the use of SAR (structure-activity relationships) where one analyzes and determines which parts of a chemical structure are essential for drug activity and function (based off the idea that structure relates to function), helping to guide discovery and attention on which parts of a molecule could be modified
- Before modifications are made, it is necessary to figure out which part of the molecule is the pharmacophore (i.e. which part will interact with the receptor); this can be done with SAR

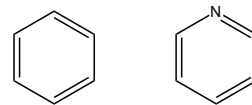
MODIFICATIONS AND PURPOSES

- Once a hit compound series has been found and some structure activity relationship calculations have been performed, one can begin thinking about refining the list and modifying some of the chemical compounds
- Then a core structure is highlighted and R group replacements are introduced to symbolize and show potential areas of improvement
- Some commonly used and pharmaceutically relevant group variations as well as other tools are discussed in the following boxes

DRUG MODIFICATIONS

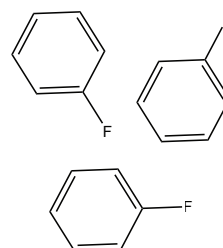
AROMATIC RINGS

- The specific point where a group binds (e.g. 5 v 6) to an aromatic ring can also be varied to help improve a ligand's performance
- This can have a significant affect on the electronic properties of a drug
- One could also change an aromatic ring to create better properties (e.g. making a benzene into a pyridine)
 - By doing this, one could increase the number of interactions by introducing the possibility of a hydrogen bond
- Fusing rings together can also improve steric properties (due to the increase in size) as well as through Van Der Waal Forces



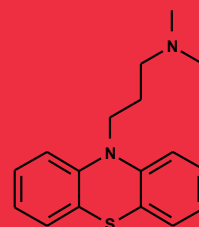
Above: Switching a benzene to a pyridine

Below: Changing the position of a fluorine on a benzene ring

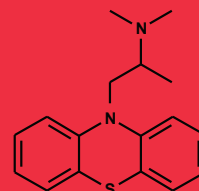


ALKYL CHAINS

Alkyl chains can improve the lipophilic properties. However adding or removing alkyl chains can drastically improve or reduce the strength of the activity of the ligand. If the chain is directly involved in interactions, an addition can drastically change the compounds' pharmacological properties. This is illustrated to the right with the compounds promethazine, an antihistamine, and promazine, an antipsychotic.



Promethazine



Promazine

DRUG MODIFICATIONS

METABOLIC/FUNCTIONAL GROUPS

- Certain compounds are more susceptible metabolic activity
- By swapping these parts out, one can either shorten or prolong the activity of a drug depending on one's goal for the specific drug
- For example, the methyl group is known to be lipophilic

TANIMOTO COEFFICIENT

- The Tanimoto coefficient is not a type of modification but a tool that is used for modifications
- It is a scoring method that allows one to compare the similarity between molecules
- As similar compounds may prove to have similar properties, this can be a useful tool for SAR but also to see if there are other compounds that may similar effects but have better properties or are easier to synthesize

DRUG MODIFICATIONS

BIOISOSTERES

Sometimes in the development of a drug, a very promising ligand is created, yet there might be poignant pharmacokinetic properties involving the drug. Bioisosteres help to resolve this problem by swapping out moieties with ones with a similar molecular shape and volume made possible due to the similarity in valence structure of these similar compounds. Yet structural differences made by the new compound help increase the molecule's electronic stability and change lipophilicity among other things. In turn, these changes can help, for example, by reducing the toxicity or strengthening the potency of the drug while maintaining its biological activity.

For example, a benzene, pyridine, and furan are considered to be bioisosteres of each other; one can try to swap one group for the other to improve properties.

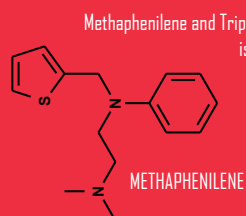
ISOSTERES

Isosteres are compounds with the same number of electrons in their valence shells, but will have varying electronic and steric properties. For example, fluorine, hydroxide, and methyl group are considered isosteres due to the fact they all have 7 electrons in their valence shells and similar sizes. Isosteres are important because they first helped scientists realize the ability to swap up certain groups while maintaining performance in certain areas (e.g. receptor interactions) but enhancing other areas such as potency and physiochemical properties.

Nowadays, the definition of isosterism has been slightly modified and broadened to include groups (or entire compounds) with similar physical properties and biological activity but varied physiochemical properties



Fluorine, hydroxide and methyl are considered isosteres because they all share 7 valence electrons in their valence shells and are similar in size

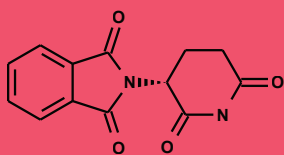


Methaphenilene and Triphenylamine are considered to be isosteres

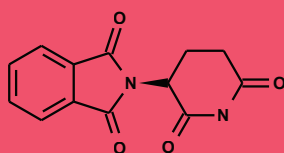


DRUG MODIFICATIONS

ISOMERS



(S)-Thalidomide



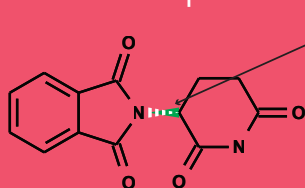
(R)-Thalidomide

DIASTEREODISOMERS

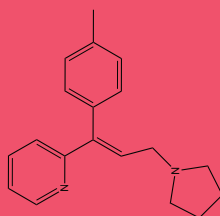
- Diastereoisomers are compounds that are nonsuperimposable
- However, they are also not mirror images of each other

ENANTIOMERS

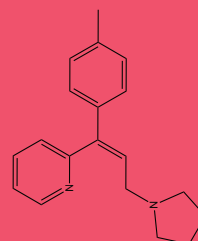
- Enantiomers are compounds that are nonsuperimposable upon their mirror image
- This means that if the compounds were aligned and overlayed upon each other an entirely new image would be formed, not a replica of either compound. In thalidomide, this is because of the difference in the planes for the C-N bond.



Overlay of the enantiomers of thalidomide



(E)-triprolidine
Active



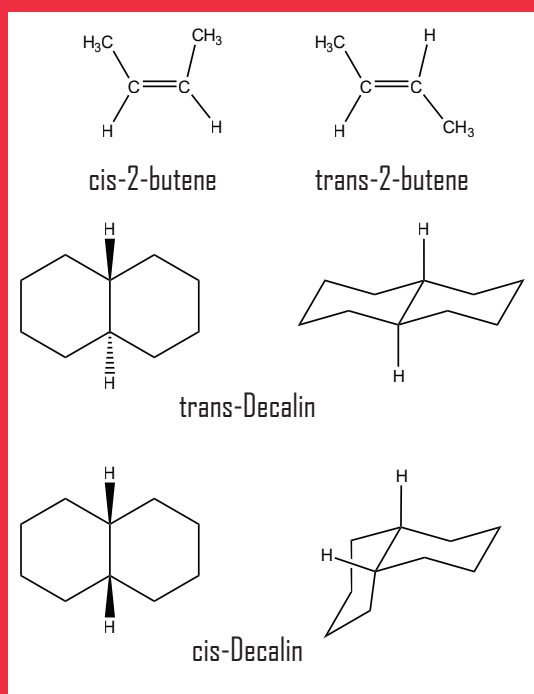
(Z)-triprolidine
Inactive

DRUG MODIFICATIONS

CIS & TRANS ISOMERS

Cis - elements are the same on either side

Trans - elements are different on either side



CONFORMATIONAL ISOMERS

-Conformational isomers are compounds that have the same molecular formula and connectivity yet differ on the rotation of their bonds.

-This can also affect the steric properties of the ligand because the size and the shape of the compound will have changed and thus can affect pocket binding

RACEMIC

-Chiral drugs are very important

-However, it is oftentimes difficult to synthesize and then isolate one enantiomer from another

-As a result, things such as a "racemic mixture", a mixture with both enantiomers can occur

-Many drugs on the market currently are racemic mixtures (only around a 1/3 of drugs are sold as single enantiomers)

-Ibuprofen is one of them!

-However, this can become problematic when one enantiomer is harmless and provides great therapeutic effects but the other enantiomer is extremely dangerous

-This was the case with thalidomide. In order to differentiate between the pharmacologically important chirality and the other chirality, the following terms are used

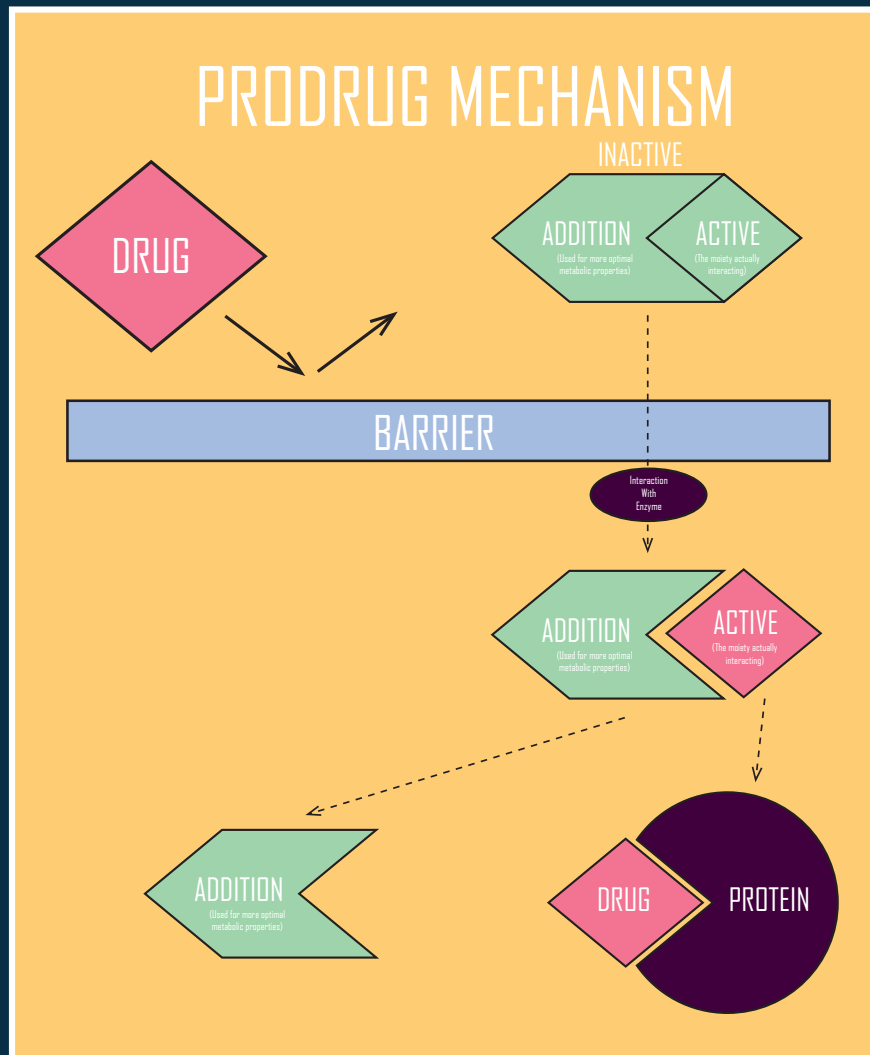
Eutomer - the active enantiomer

Distomer - the inactive enantiomer

EUDYSMIC RATIO

The eudysmic ratio is a ratio of the pharmacological activity between two enantiomers (the eutomer versus the distomer). It allows one to mathematically see this difference in activity.

DRUG MODIFICATIONS



PRODRUGS

Prodrugs are biologically inactive that become biologically active through a conversion in the body. They are used to improve metabolic properties and permeability of compounds

1) Permeability - prodrugs can help ensure the ligand is able to cross a cell membrane even when its functional groups may have proved this to be problematic (e.g. in the case of a hydroxyl). In this case for example, an ester group may be added to the compound, to help make it more lipophilic and allow it to cross the cell membrane

2) Prolong activity - sometimes compounds may prove to act well but act too quickly, prodrugs can help facilitate a slower diffusion and allow for a more sustained pharmacological activity. This could be brought about through a change of electron withdrawal on a heterocyclic group

3) Targeting - sometimes compounds may need to pass through the multiple parts of the body before reaching their intended target. By adding prodrug properties that make the compound degrade once it encounters areas with a certain level of acidity, it can better target the disease it is after.

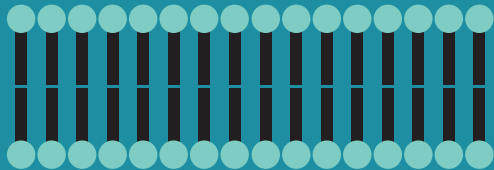
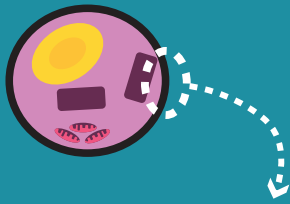
4) Toxicity - sometimes compounds may be associated with unpleasant side effects, and prodrugs can be used to help minimize these effects. This can even be seen with aspirin. Aspirin, whose active part is salicylic acid has an acetyl (another ester) which helps to lower the harmful effects of the drug

HOW DO DRUGS WORK?

DRUG INTERACTIONS

-While we discussed in greater detail how drugs interact with proteins, they are not the only way drugs can interact in the body

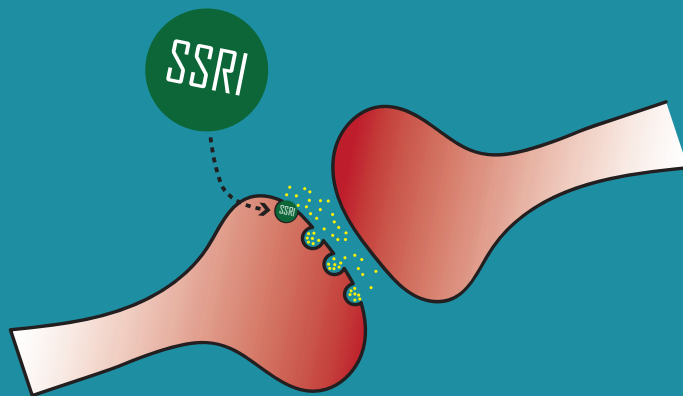
-Below are some various other targets and ways drugs can interact with the body



LIPIDS

-Drugs that directly interact with the lipid layer are interested with disrupting and changing the structure and property of the membrane

NEURONS

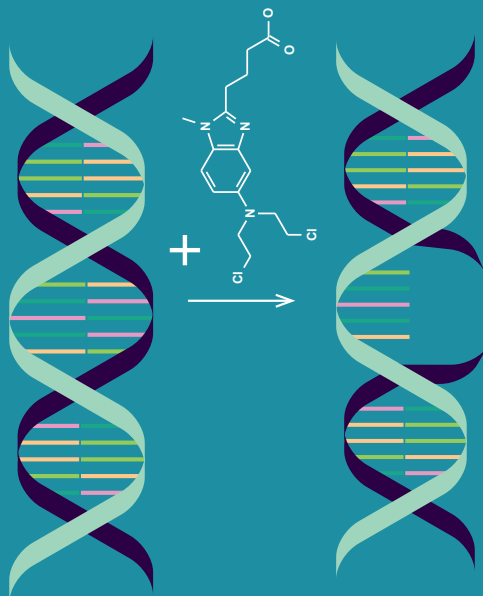


-Drugs that affect neurological function will often try to focus on the interaction between neurons, the transmitting and receiving of messages
-While there are many different types of neuron receptors, for the autonomic nervous systems, two of the main classes are cholinergic and adrenergic receptors

Cholinergic are the receptors for the neurotransmitter acetylcholine

Adrenergic are the receptors for the neurotransmitter norepinephrine

Primary Target for: psychotic medication, antidepressants



NUCLEIC ACID

-Drugs interact with nucleic acids by primarily messing with the structure of DNA or its reproduction

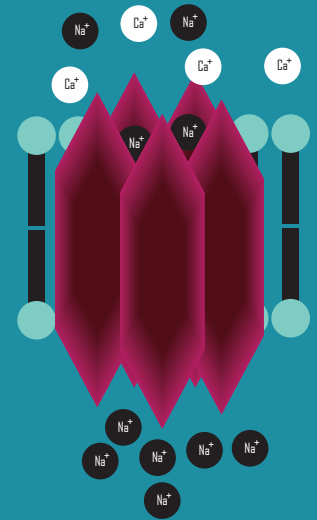
-This can occur through cross-linking or through the mismatching of the nucleic acids or through transcription

Primary Target for: cancer, steroids

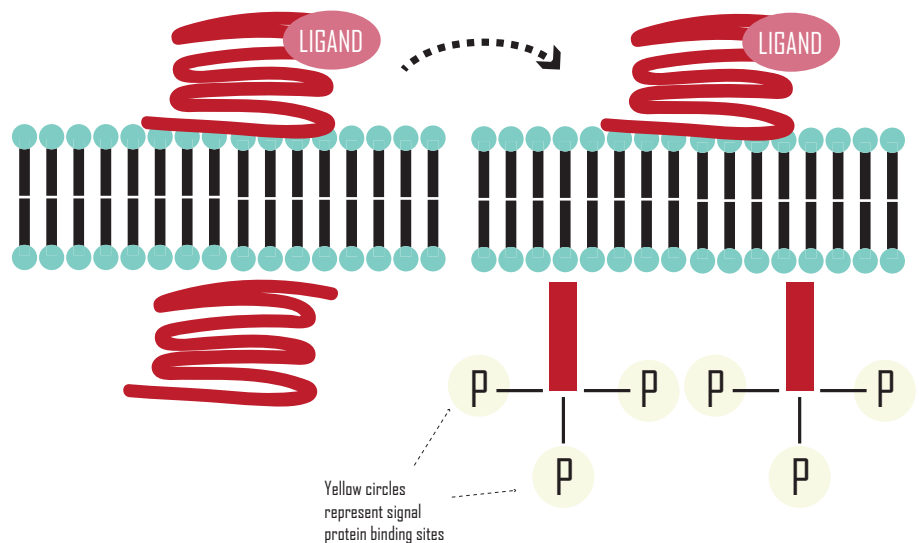
PROTEIN RECEPTORS

ION CHANNELS

- Ion channel receptors typically consist of five protein subunits
- A ligand will bind to a subunit which will then cause the ion channel gate to open; this leads to a depolarization of the cell
- This causes a signal to be sent to the cell



PROTEIN KINASE RECEPTORS

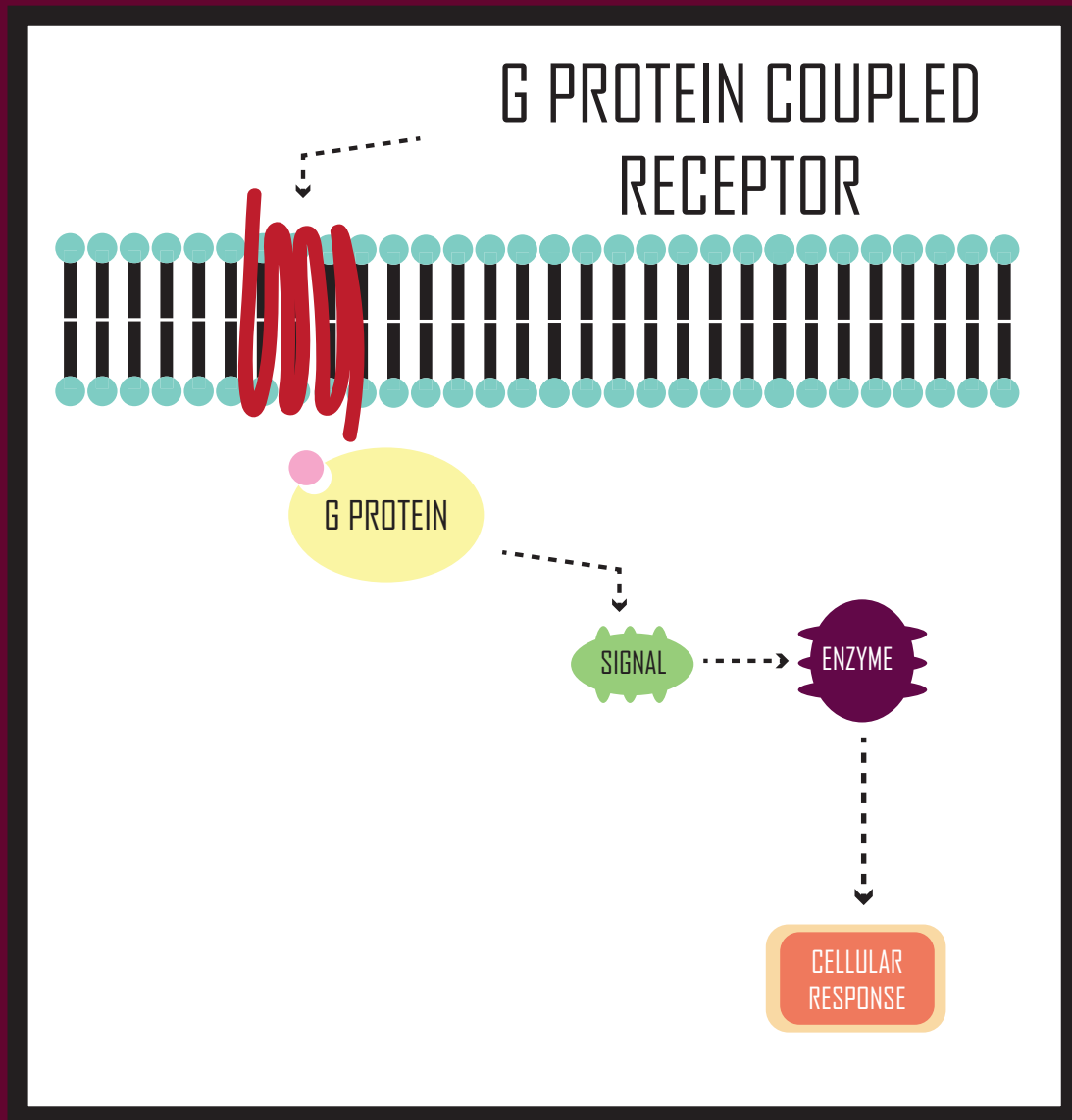


TYROSINE KINASE PROTEINS

- Kinase protein receptors require a ligand to be bound to the receptor to activate tyrosine kinase, a catalytic enzyme
- It will then convert ATP into ADP and undergo phosphorylation
- The phosphotyrosine binding region can then be occupied by a wide variety of signal proteins which tell the cell to do or initiate certain tasks

PROTEIN RECEPTORS

G PROTEIN COUPLED RECEPTORS



- Interestingly, G protein coupled receptors are similar in structure
- Yet, a wide variety of compounds bind to G-protein coupled receptors.
- Some of these include acetylcholine, serotonin, dopamine, and other monoamines, lipids, and nucleotides, among others.
- The G protein receptor initiates the G protein which then initiates an enzyme and as a result, a cellular response will occur

DRUG CLASSES

DRUG CLASSES

There are dozens of classifications of drugs and dozens more of subsets of those classifications. Here, several of the most common drug classes are listed and an example is given of each class and its mechanism, use, drawbacks as well as several other types of drug types in the classes.

ANALGESICS

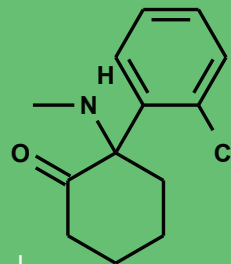
μ Agonists

Use: It is used to treat pain

Major Drawbacks:

Addictive -> tolerance and withdrawal problems

Other Types: μ Agonists, μ Antagonists
Antidiarrheal agents, Cough suppressants



KETALAR

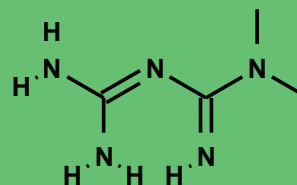
ADRENOCORTICOIDS

Biguanides

Use: It is used to treat diabetes

Major Drawbacks: nausea, upset stomach, diarrhea, other gastrointestinal problems

Other Types: glucocorticoids, mineralocorticoids, adrenocorticoid antagonists



METFORMIN
(Biguanide)

DRUG CLASSES

CHEMOTHERAPY

Tubulin Inhibitors

Use: Tubulin inhibitors are a type of chemotherapy drug. They act by binding to and preventing tubulin from being created normally either through "polymerization" or "depolymerization" agents that either cause the shape tubulin to be formed incorrectly or cause the resulting size to shrink

As a result, this prevents the cell from undergoing mitosis and stops the spread of cancerous tumors

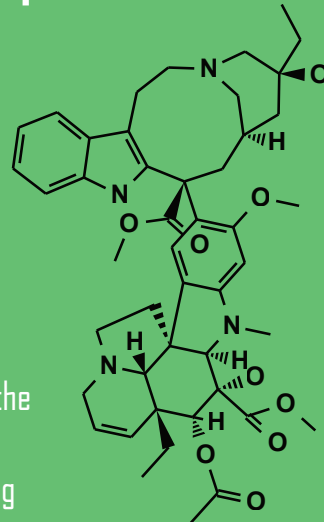
Major Drawbacks:

Cytotoxicity

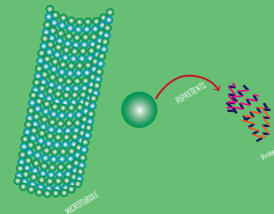
Drugs do not discriminate;

Neurotoxicity, cardiotoxicity (10%)

Other Types: DNA Cross-Linking Agents, Topoisomerase Poisons, DNA Demethylators



VINBLASTINE
(Tubulin Inhibitor)



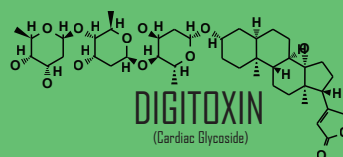
CARDIAC AGENTS

Calcium Channel Blockers

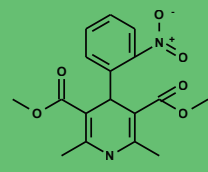
Use: Treatment of Angina, Arrhythmia, and Hypertension

Major Drawbacks: Dizziness, Hypotension, Headache, Peripheral and Pulmonary Edema

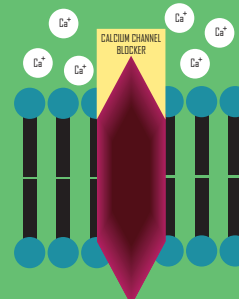
Other Types: Statins, ACE Inhibitors, Cardiac Glycosides, Antianginal, Antiarrhythmic, Vasodilators



DIGITOXIN
(Cardiac Glycoside)



NIFEDIPINE
(Calcium Channel Blocker)



DRUG CLASSES

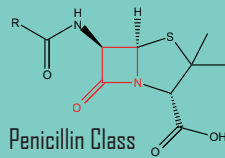
ANTIBIOTICS/ANTIMICROBIALS

Penicillins

The penicillins are a type of β -lactam antibiotic due to the fact their molecule's structure contains the β -lactam group

Uses:

In the treatment of infections

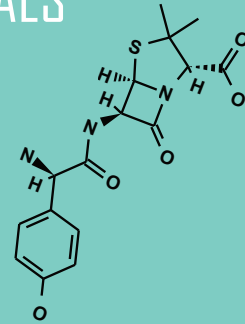


Major Drawbacks:

Around 10% of the population is allergic to β -lactam antibiotics
They have become less and less effective against bacteria due to growing antibiotic resistance over the years partly due to the overprescription of them

Other Types of Antibiotics:

Sulfonamides, Quinolones, Penicillins, Nitroheteroaromatic compounds



(Penicillin)

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Profens are 2-arylpropionic acid derivatives

Uses:

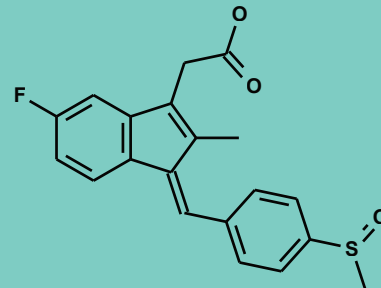
In the treatment of inflammation namely rheumatic diseases such as arthritis

Major Drawback:

Significantly increase the risk for a heart attack; can also cause adverse gastric events such as ulcerations and stomach and intestinal perforation

Other Types of NSAIDs:

Salicylates, COX-2 Inhibitor



("Profens")

ANTIDEPRESSANTS

Serotonin Reuptake Inhibitors

Serotonin reuptake inhibitors aim to prevent the reuptake of serotonin, a hormone which helps in mood stabilization and content; by preventing the reuptake, more of it can cross the synapse and reach further neurons

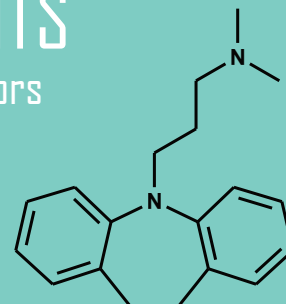
Uses: In the treatment of depression, mood swings, anxiety

Major Drawbacks:

May increase suicidal risk

Other Types of Antidepressants:

Dopamine and norepinephrine reuptake inhibitors, serotonin antagonist/reuptake inhibitors, monoamine oxidase inhibitors



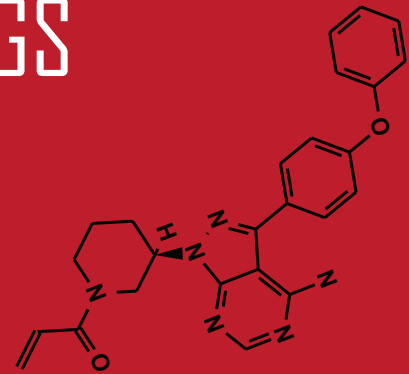
(Serotonin Reuptake Inhibitors)

DRUG CLASSES

ORPHAN DRUGS

Orphan drugs are drugs used to treat relatively rare diseases

These drugs are oftentimes supported by grants or increased patent protection to incentivise the innovation of novel drugs oftentimes in a market with little incentive due to the lack of people affected. To illustrate this, Imbrutinib is used to treat chronic lymphocytic leukemia and mantle cell lymphoma; there are approximately only 20,160 cases of chronic lymphocytic leukemia per year and only 4,200 new cases for mantle cell lymphoma per year



IMBRUTINIB
(Kinase Inhibitor)

"OTHER" INTERACTIONS

DRUG INTERACTIONS

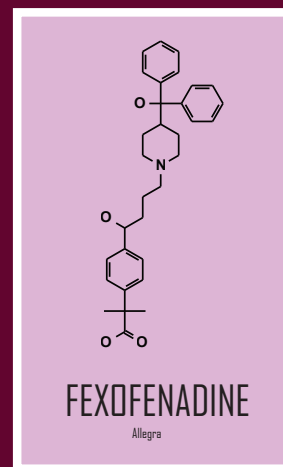
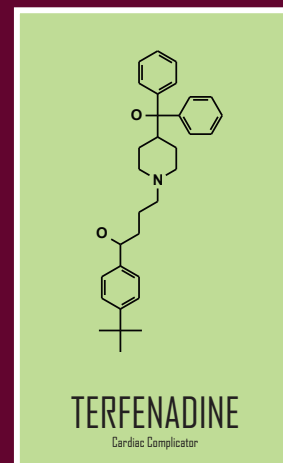
- Drugs are miraculous things
- Yet, the human body is very complex, dynamic, and it is oftentimes difficult to predict it perfectly or in its entirety
- While drugs have the potential to do great good they also have the possibility of doing great harm, most often unbeknownst to researchers and manufacturers
- Drugs can interact with other drugs in the body
 - This will oftentimes result in pharmacokinetic changes of the drug
 - These are oftentimes resulted from enzyme inhibition or induction in the liver; two particularly important and common enzymes are called "CYP450" and "CYP3A4"
 - Enzyme inhibition or induction messes up with metabolic properties and increase toxicity
 - Terfenadine (also discussed below) was taken with a CYP3A4 inhibitor resulted in ventricular arrhythmia (these however was not its only problem)

- However, drugs can also interact with food
- Drug pharmacokinetics can be affected by the amount of fat in certain foods
- MAO inhibitors have been reported to have caused severed hypertensive reactions when taken with cheese (due to a high amount of amine tyramine)
- A more extensive example a food-drug interaction is given below



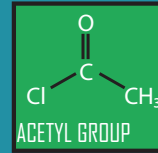
DRUG-DRUG INTERACTIONS, GRAPEFRUIT JUICE, & THE CREATION OF ALLEGRA

- You may have seen that certain medications advise against taking the medication with grapefruit juice
- At first this seems rather random and odd, grapefruit does not seem particularly special: it is not the most acidic fruit or the sweetest
- Yet these warnings are not without reason, this is because grapefruit can significantly enhance the oral bioavailability of a drug
- This is because drinking grapefruit leads to the inhibition of the P450 enzyme which causes a reduction in presystemic metabolism, resulting in the greater bioavailability
- While this may be less of a concern with drugs that already have a high bioavailability, it can still be very concerning
- It was reported by the Tampa Bay Times in 1997 that a Michigan man who was in good health collapsed after taking the antihistamine, terfenadine (otherwise known by its brand name, Seldane), along with two cups of grapefruit juice. Terfenadine was later recalled for its adverse drug-drug interactions (specifically causing cardiac complications). Later, a safer form was created (from active ingredient isolation). This was antihistamine fexofenadine, more commonly known now was Allegra.
- Terfenadine ended up causing 125 cardiac related deaths in the U.S. and 14 in the U.K. and serves as a somber reminder of the importance of drug-drug as well as food-drug interactions.



DRUG DISCOVERY CASE EXAMPLE

ASPIRIN



- While Aspirin™ has become a ubiquitous name, it had humble origins
- It had been known for thousands of years that willow bark has some restorative properties
- In the 1800s, scientists were able to extract the active ingredient which came to be known as salicylic acid
- While the discovery of salicylic acid was great, with its use, there would be gastric unpleasantness
- In 1853, a French chemist, Charles Gerhardt, improved on this development by adding an acetyl group creating acetylsalicylic acid to try and remove some of these unwanted side effects
- While Gerhardt did not do anything with this discovery, later a scientist working for the Bayer company took this and was able to convince Bayer to start selling the drug, commercializing the first creation of Aspirin

IMPERFECTIONS

- Soon Aspirin became a wonder drug, specifically gaining prominence in the Spanish Flu outbreak for alleviating symptoms of influenza
- However no drug is perfect
- In the early to mid 20th century it became known that aspirin was causing problems, notably gastritis and Reye's syndrome in children (which is why it is not recommended for children)

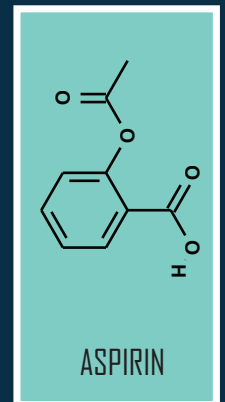
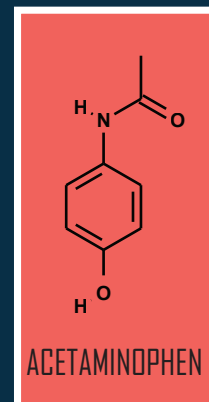
TRICKINESS

- Upon the miraculous discovery of aspirin, its creator, Felix Hoffman, decided to apply the same principle of its creation to another drug, morphine
- The powerful properties of this drug were reflected in its name: coming from "heroish", or powerful in German, heroin. Heroin, however, ended up being highly addictive
- While the acetylation of one drug was highly successful, the acetylation of another proved to be extremely dangerous

MORPHINE

LATER

- Over the decades, aspirin slowly fell out of favor, mainly due to the fact that aspirin had to be given in high doses which increased the risk for bleeding and allergic reaction and due to the rise of better substitutes such as ibuprofen and acetaminophen
- However, while its favorability had slightly fallen, aspirin continued to play a valuable role specifically in the 1980s and 1990s when it caught the attention of scientists for its antiplatelet forming effects
- Thus, the drug was later repositioned as a platelet aggregation inhibitor
- There have also been research with aspirin as a stroke prevention drug and for use in treating some hematological diseases



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