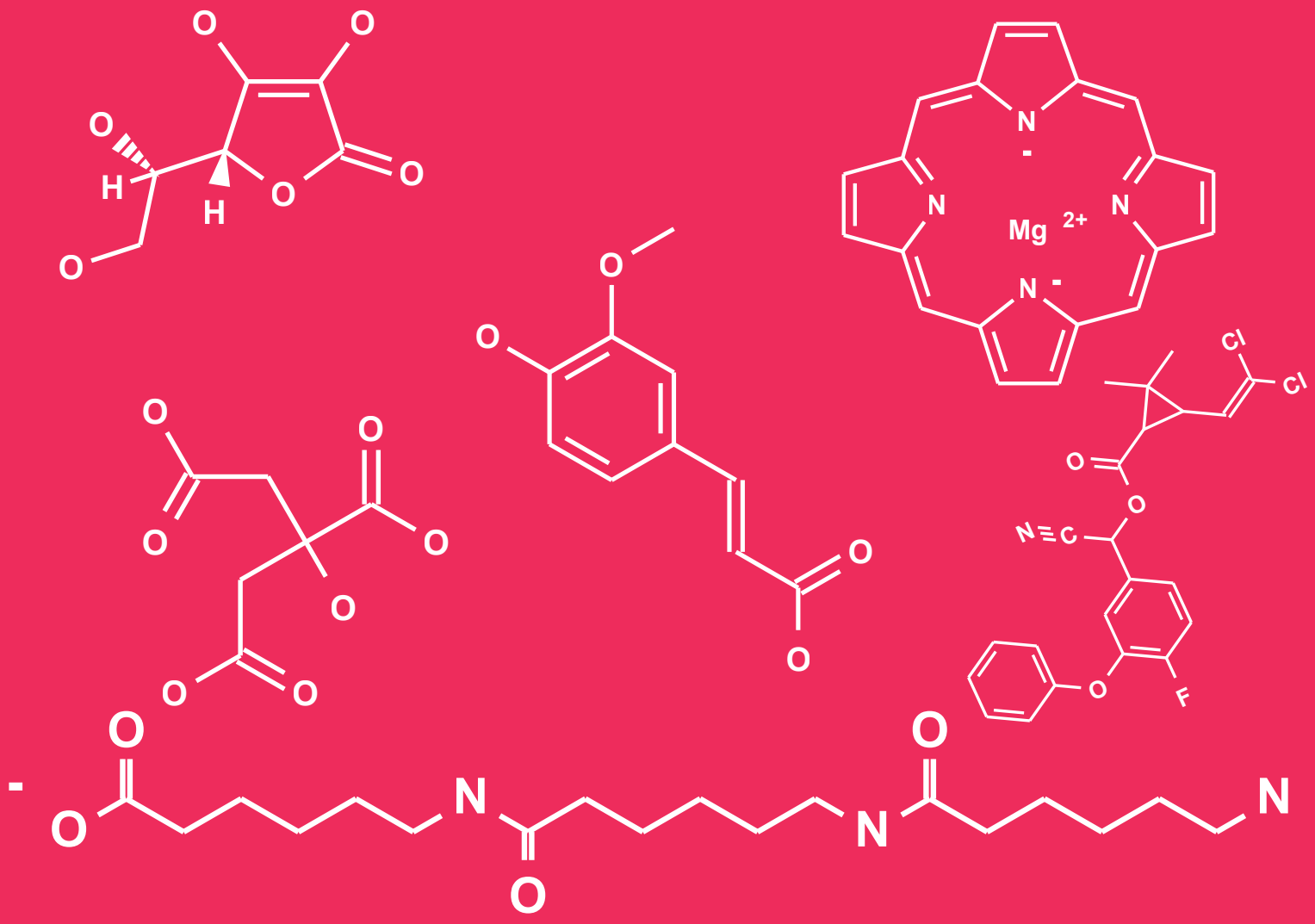
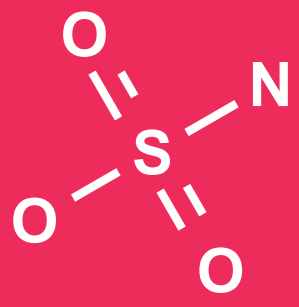
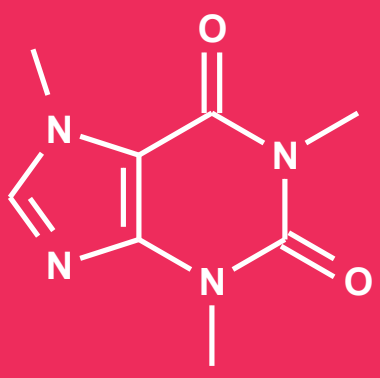
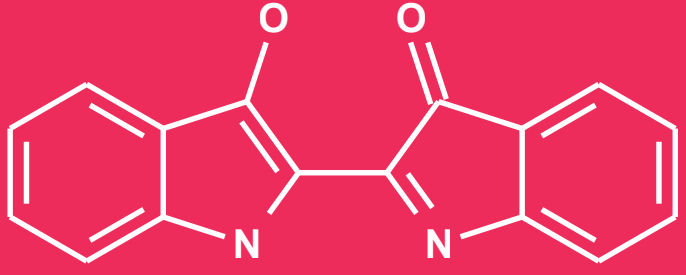


MEDICINAL CHEMISTRY







STAGES OF DRUG DEVELOPMENT

THE DRUG DEVELOPMENT PROCESS

Here are the steps of a possible drug development scenario. These steps will be discussed in further detail later on but for now this is a broad overview of the process.

BEGINNING

-In the beginning, scientists utilize computers (in silico) to help speed up their process. They begin by choosing what information they have and go from there:

1) Structure based screening - this is used when the structure of protein or receptor site is known. Sets of ligands are tested at the protein's binding site and binding affinity and thermodynamic favorability are calculated.

2) Ligand based screening - ideal if you have a chemical compound in mind that you would like to work with or a compound derived from nature that showed biological activity. It is also used when the receptor site that the ligand will bind with is unknown. Similar compounds can be found using libraries online (such as the ZINC library) and similarity can be calculated by using a Tanimoto Score

IDENTIFYING THE TARGET

-Scientists need to determine what to focus their efforts on
-They need to identify that their biological target (a gene or protein) has a possible role in the disease that they are trying to remediate
-If there are not any models for the protein in a research database, X-ray crystallography may need to be used to create a model of the protein from experimental data
-They may also need to figure out which site of the protein is most favorable for their desired outcome
-Target validation also needs to occur to ensure that the target they are focusing on has the potential to be adjusted to result in medicinal effects
-They can also see if the protein has good druggability, or the ability or potential to bind well with a ligand
-After ensuring their target, screenings can be carried out

HIT-TO-LEAD

Once scientists are able to identify their target, screenings can occur to try and identify which ligands show the most promise based off of binding affinities as well as other chemical factors such as the molecule's polar surface area and the molecule's ability to donate or accept a hydrogen bond
Once the hundreds of thousands (if not millions) of ligands have been filtered to a much more feasible number (e.g. around a 100), structure activity relationships need to be done to see what are the critical moieties in the structure for interaction with the protein and what affect adding or subtracting certain ligands have on protein interaction
SAR studies also need to be done to identify the critical moiety (pharmacophore) of the ligand compounds

OPTIMIZATION/TESTING

-After desirable lead compounds have been chosen, scientists need to figure how to adjust or optimize them for various purposes
-They will also test the ligands by conducting "in vitro" or assay screenings on cell cultures and if the ligand is promising enough, "in vivo" tests on animals
-There is also a big gap between theoretical calculations done on the computer and experimental results
One of the reasons that account for this is the fact that in order to perform computer screening in a practical amount of time, receptor models are oftentimes static and do not represent the accurate dynamic configuration of a receptor that is found
-Other problems may include that the compound may bind very well but may cause unwanted side effects or the compound may be too costly or difficult to synthesize for the market

FURTHER TESTING, TRIALS, & PRODUCTION

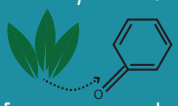
-Once this stage has been reached, significant computational testing has been done as well as some experimental testing and has proved to be favorable. By now just a handful of compounds have been identified as worthy enough to continue on testing, specifically clinical testing.
-Even after rigorous testing, 90% of the candidates selected for clinical testing do not pass
-In the end, several years would have been spent researching, developing, and testing the drug and close to a billion dollars have been spent to develop the drug

FINDING LEAD COMPOUNDS

TRADITIONAL MEANS

Traditional Knowledge

- Traditional knowledge is vital for discovering new medicines as it can oftentimes be a launch pad for discovering new treatments
    - Some of these sources may include the Ayurveda, Chinese medicine, Arabian medicine, or even folklore



- Pharmacognosy

- Pharmacognosy is deriving drugs from compounds from plants
- Other sources in nature for potential drug candidates include microorganisms, marine life, animal sources, and even venom (e.g. from snakes or spiders)

RATIONAL DRUG DESIGN

Functional Groups/Bioisosterism - The idea of functional groups is grounded in the principle that specific chemical groups will exhibit specific biological properties regardless of the molecular structure they are in.

Fragment Based Drug Discovery - Researchers use nuclear magnetic resonance spectroscopy (NMR) to find out and see how a ligand binds to a protein

COMPUTATIONAL METHODS

-Through technological advancements and computational methods, the drug discovery process has rapidly been sped up

-Scientists can now employ computers (sometimes referred to as "in silico" methods derived from the fact that silicon is used in computer chips) to help get a jumpstart at sifting through and finding promising drug candidates

-Instead of relying on luck or previous knowledge, once they have identified a viable protein binding site ("target identification) scientists can now sift through libraries of chemical compounds (oftentimes with tens of millions of compounds) to find promising ones (ligands) that would likely show strong affinity for a given protein

-This is known as High Throughput Screening

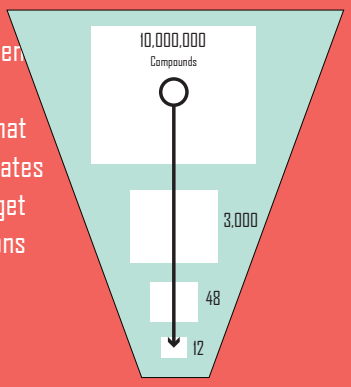
There are various other methods used to help facilitate the discovery process. These include:

-Homology Models, Molecular Docking, QSAR, Pharmacophore Screening

-While this process may seem miraculous, it does have its limitations. They are primarily due to:

-Inaccuracy with computational models and methods

-Limited computational power due to limited hardware capabilities.



REPRESENTATION OF THE SCREENING PROCESS

OTHER APPROACHES

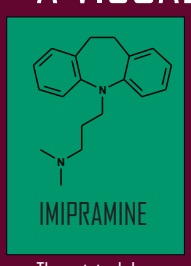
"MeToo" Drugs

Sometimes drug companies will take an already known and successful drug and make small changes to it. By doing this, these companies will be able to commercially synthesize and sell the drug because it will be considered a "new" drug and won't infringe on existing patents, even if their modifications result in hardly any change of the effect of the drug.

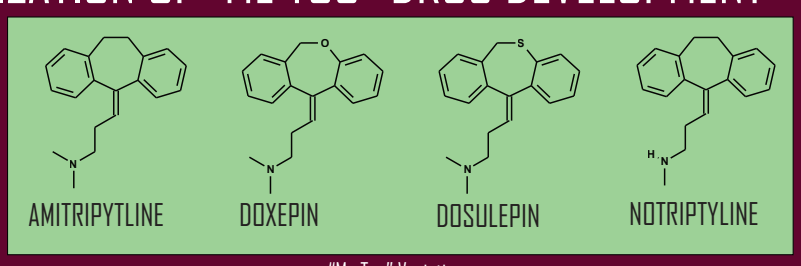
Drug Repositioning

Existing drugs are investigated for use in new ways. This will be discussed in more detail later.

A VISUALIZATION OF "ME TOO" DRUG DEVELOPMENT



The original drug



"Me Too" Variations

CHEMICAL TESTING

IMPORTANCE AND REASONS

-So now we have identified a whole slew of potential lead compounds either via computational methods or pharacognosy, but how do we identify which compounds truly show promise and which ones are merely false hopes?

-There are various requirements that a drug must pass through before a drug is sent to market

-These requirements are vital in the development of the drug as, without them, major safety problems can go overlooked causing great harm to thousands of people

-This can be seen with the case and catastrophe of the children of Thalidomide

-So why might a once promising drug candidate become rejected during the development process? Here are some major reasons:

SAFETY

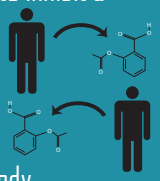
Therapeutic Index

-Refers to a drug's safety; the ratio of desirable versus undesirable effects

-Safety of drug metabolites (compounds made through body and drug interaction)

IC_{50} - refers to the amount of substance needed to inhibit a process by 50%

KI - inhibition constant



Pharmacodynamics

-Refers to how a drug interacts with a person's body

ACTIVITY

-Lipinski's Rule of 5

-Guidelines for how well a drug will work or how well it will be absorbed

-It is used as a rule of thumb, specifically with how well a particular compound may work as an oral drug

Water Solubility

-This can be predicted by measuring logP

Similarly, **Jorgenson's Rule of Three** is another rule of thumb on the absorption of a drug

ADME

ADME stands for absorption, distribution, metabolism, and excretion

-Refers to how a person's body interacts with the drug or pharmacokinetics

BIOLOGICAL TESTING

"In vitro" testing -- "in vitro" testing refers to tests done with assays

"In vivo" testing -- refers to testing with live animals

These are tests in increasingly more complex organisms to ensure that the functionality of the compound in question remains experimentally and when put up against organisms that are more similar to humans (this is particularly true in in vivo testing)

MISC.

-The ligand may be very promising and bind very well to a protein

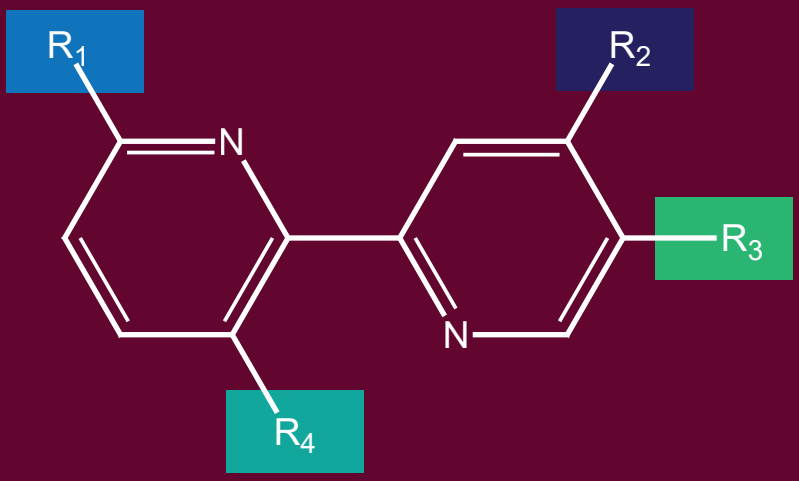
-However, if the drug is too difficult to synthesize or is not commercially feasible it may be rejected

-This has happened with multiple drugs over the years; while one ligand may have a stronger affinity, it is too difficult to feasibly synthesize so a chemical with an inferior affinity but with a greater ease of production is chosen

INSIGHTS

STRUCTURE-ACTIVITY RELATIONSHIPS

-Structure-activity relationships are one of the most important tools a medicinal chemist has, and they rely on the principle that the structure of a compound determines its functionality
-Structure-activity relationships can be useful when conducting a virtual screening
-The hit series of ligands can be analyzed to see which groups the hit ligands have in common and this can act as the "backbone" structure in guiding modifications and narrowing of the promising ligands
-However, SAR is a very helpful tool in the lead optimization stage, where it is most used
-SAR is employed by swapping out different groups with structures with known properties (lipophilicity, high metabolic rate, etc.)
-They help scientists find patterns, better visualize a given compound and what aspects of the compound are favorable and are interacting well with the target
-SAR also allows scientists to hypothesize and identify which physiochemical properties of the ligand that are more critical than others (e.g. if they swap out methyl group for a trifluoromethyl, and there is not a significant change in the favorability of the interaction, electronic properties may not play a huge role, specifically in that part of the molecule's interactions with the protein. However, if they fused two benzene rings together and created a naphthalene ring, and there was a sizeable favorability change in the protein interaction, they can hypothesize that for this receptor steric properties are significant.



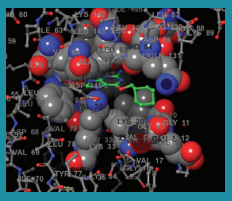
QSAR

QSAR - Quantitative Structure-Activity Relationships

QSAR is a type of structure activity relationship where molecular descriptors or molecular characteristics are taken from a set of compounds and the data used helps to make predictions about the favorability of certain compounds. It is structure optimization based on quantitative data of physiochemical properties. For example, if one has data for a set of compounds on logP, a characteristic of water solubility, one can then see how adding different groups will change the water solubility of the compounds and seeing patterns in this data can help elucidate which groups are most beneficial to this and allows one to make predictions on novel compounds to test. This helps speed up the drug development process and permits one to see how multiple physiochemical properties are affected when introducing a certain functional group.

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 ides 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?

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

Common methods include:

-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

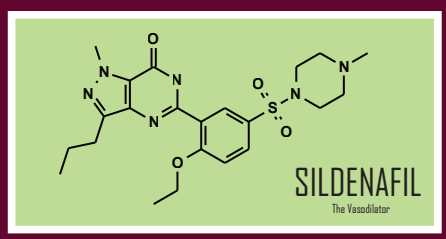
-This is where drug repositioning can come in

-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 particality problems (in the case of orphan diseases)

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

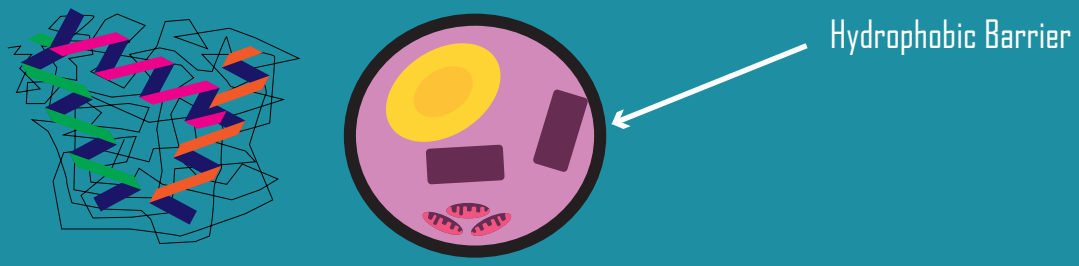
-Similarly, minoxidil was an antihypertensive drug before being used for hair loss treatment



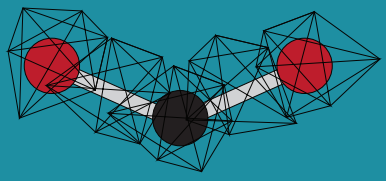
PHYSICOCHEMICAL PROPERTIES

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.

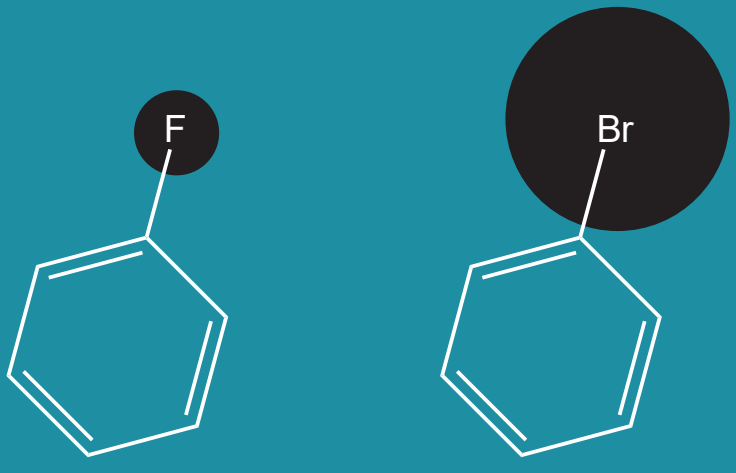


Electronic - A compound's electronic properties are oftentimes critical to consider. Introduction of a new group can have an inductive or withdrawing effect of electrons; this can affect, for example, ionization and polarity.



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 bioisoterism 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

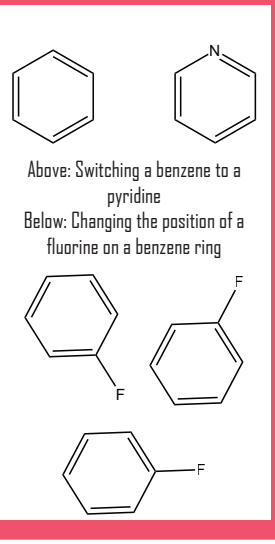
MODIFICATIONS AND PURPOSES

-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

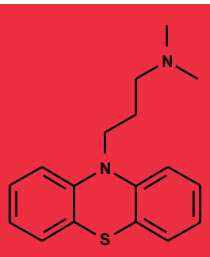
-The specific point where a group binds (e.g. 5 v 6) to an aromatic ring can also be varied to help improve a ligand's performance
-This can have a significant affect on the electronic properties of a drug
-One could also change an aromatic ring to create better properties (e.g. making a benzene into 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



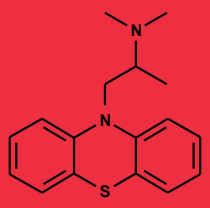
Above: Switching a benzene to a pyridine
Below: Changing the position of a fluorine on a benzene ring

ALKYL CHAINS

Alkyl chains can improve the lipophillic 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 antipyschotic.



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

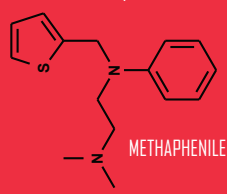
Sometimes in the development of a drug, a very promising ligand is created, yet there might be poignant pharmacokinetic properties involving the drug. Bioisosteres help to resolve this problem by swapping out moieties with ones with a similar molecular shape and volume made possible due to the similarity 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.

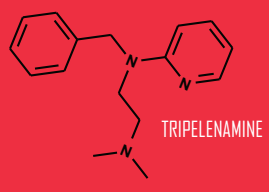
ISOSTERES

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

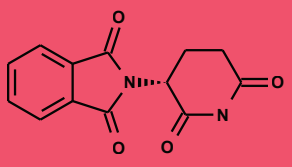
Methaphenilene and Tripelenamine are considered to be isosteres



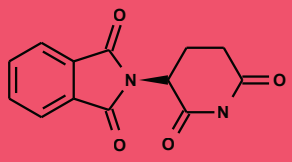


DRUG MODIFICATIONS

ISOMERS



(S)-Thalidomide



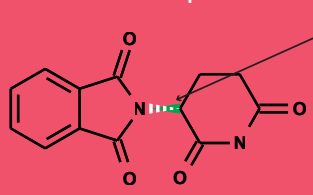
(R)-Thalidomide

DIASTEREOISOMERS

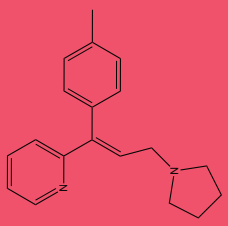
-Diastereoiosomers are compounds that are nonsuperimposable
-However, they are also not mirror images of each other

ENANTIOMERS

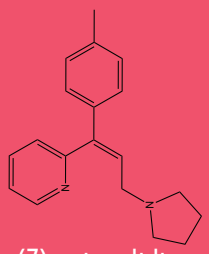
-Enantiomers are compounds that are nonsuperimposable upon their mirror image
-This means that if the compounds were aligned and overlayed upon each other an entirely new image would be formed, not a replica of either compound. In thalidomide, this is because of the difference in the planes for the C-N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



Overlay of the enantiomers of thalidomide



(E)-triprolidine
Active



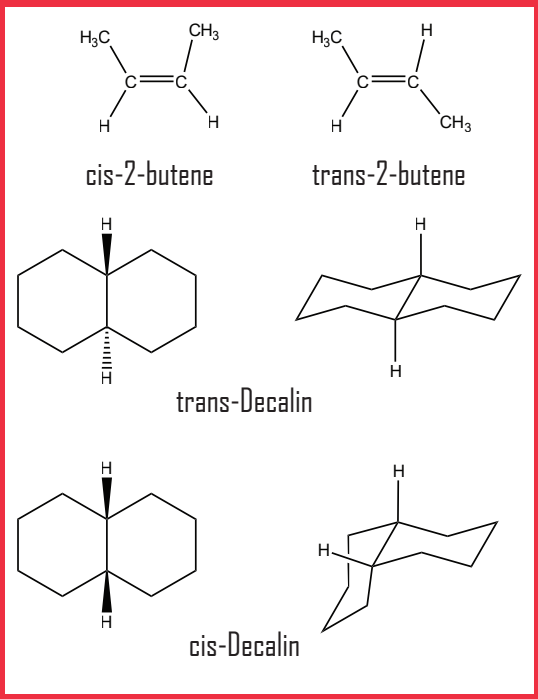
(Z)-triprolidine
Inactive

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

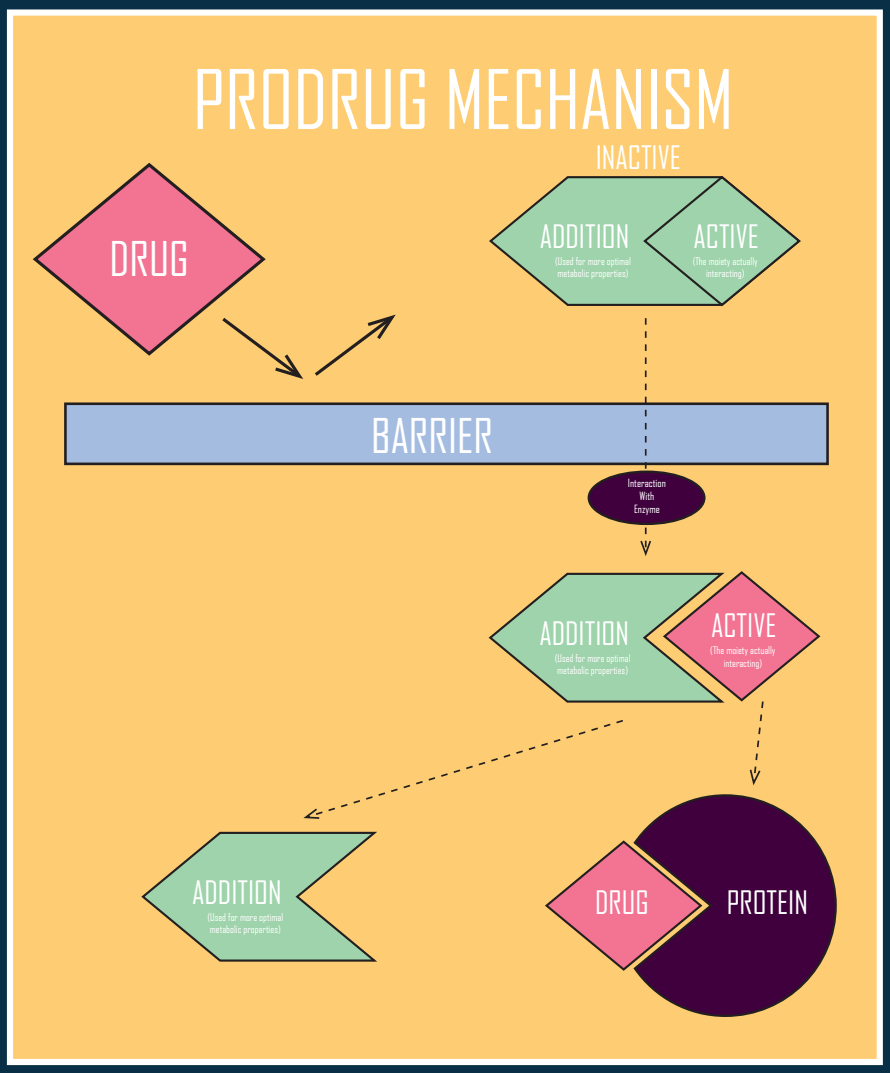
Eutomer - the active enantiomer

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 hydroxl). In this case for example, an ester group may be added to the compound, to help make it more lipophillic 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.

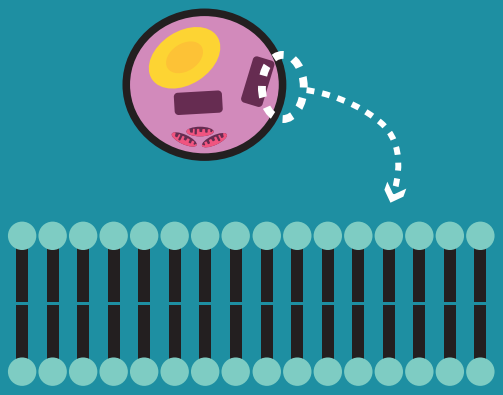
4) Toxicity - sometimes compounds may be associated with unpleasant side effects, and prodrugs can be used to help minimize these effects. This can even be seen with aspirin. Aspirin, whose active part is salicylic acid has an acetyl (another ester) which helps to lower the harmful effects of the drug

HOW DO DRUGS WORK?

DRUG INTERACTIONS

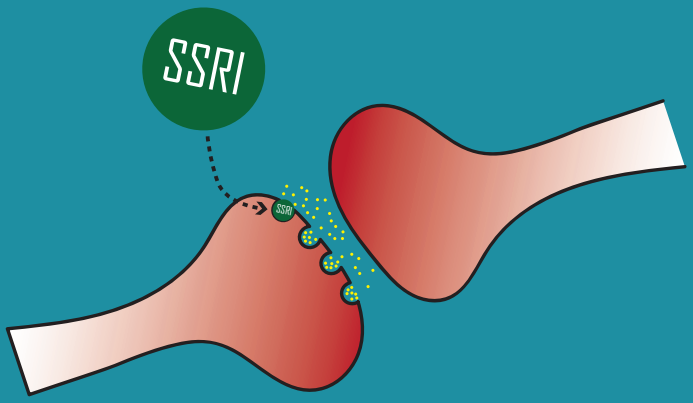
-While we discussed in greater detail how drugs interact with proteins, they are not the only way drugs can interact in the body

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



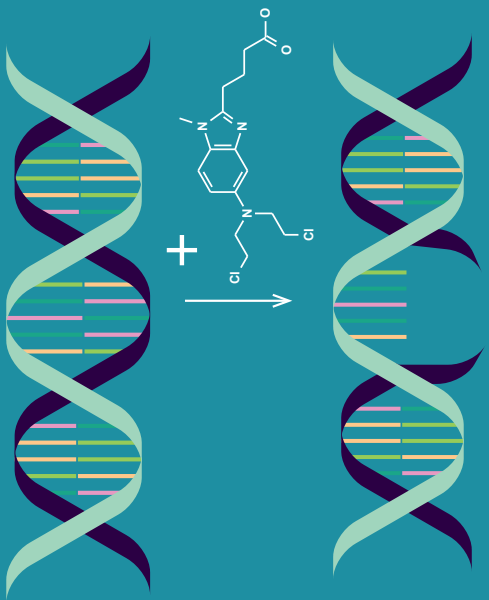
LIPIDS

-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

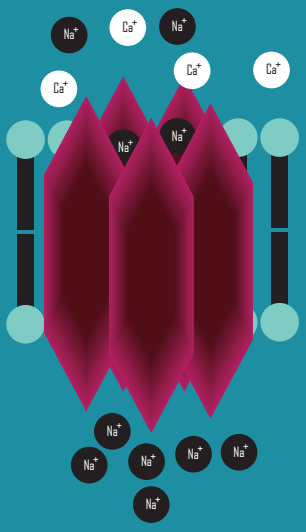


NUCLEIC ACID

-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

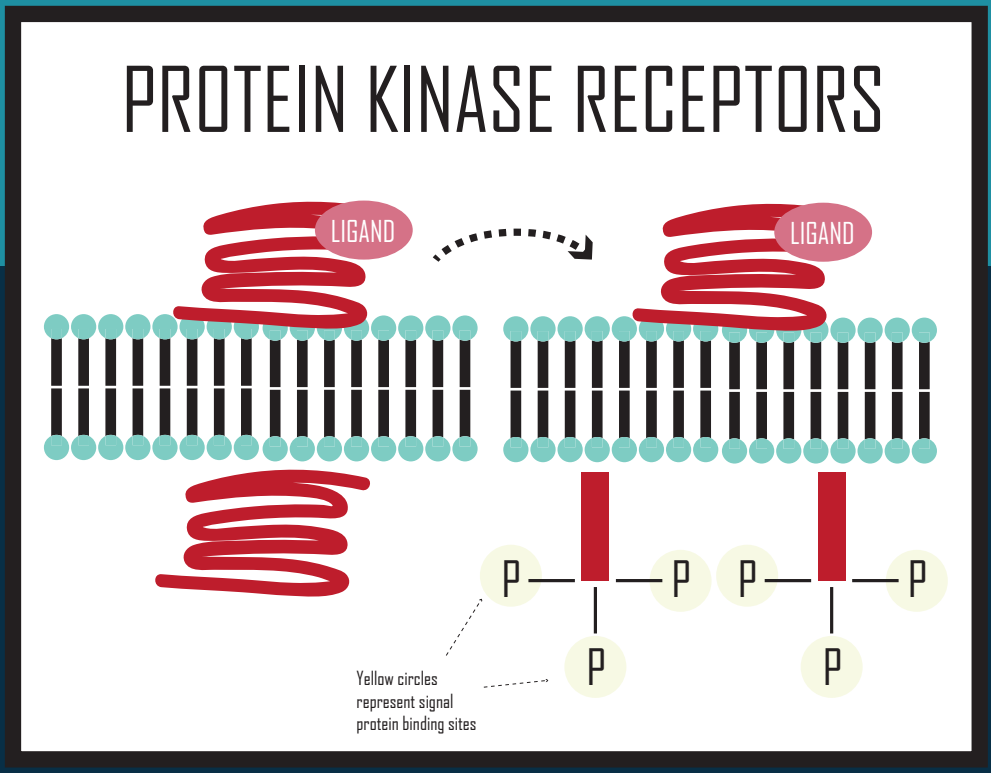
PROTEIN RECEPTORS

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

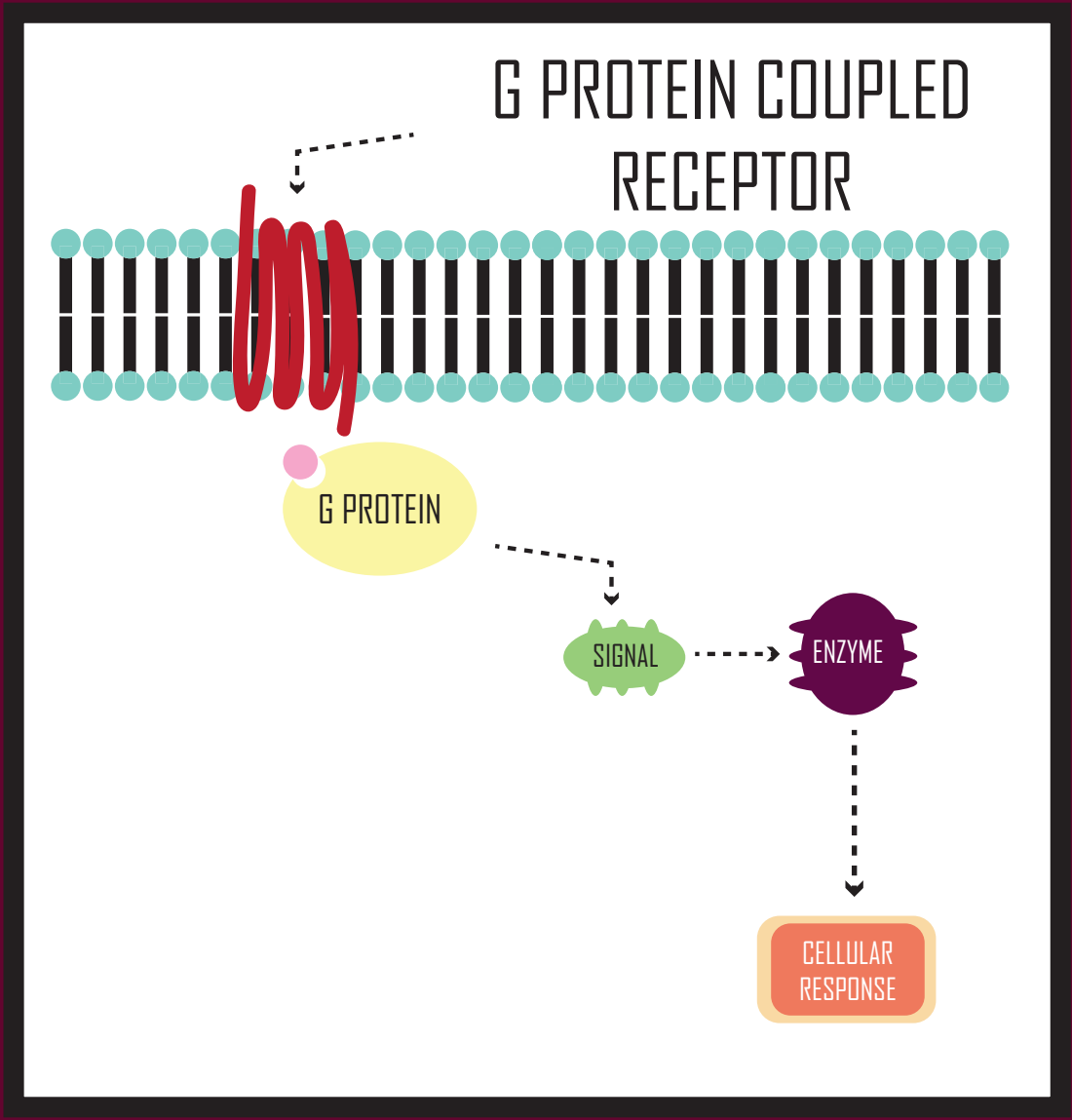
TYROSINE KINASE PROTEINS



-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

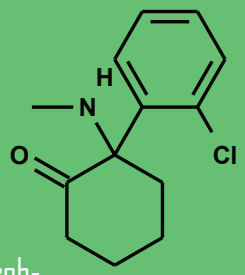
DRUG CLASSES

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



KETALAR

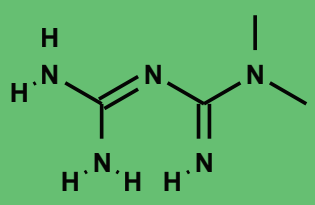
Major Drawbacks:
Addictive -> tolerance and withdrawal problems

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

ADRENOCORTICOIDS

Biguanides

Use: It is used to treat diabetes



METFORMIN
(Biguanide)

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

Other Types: glucocorticoids, mineralocorticoids, adrenocorticoid antagonists

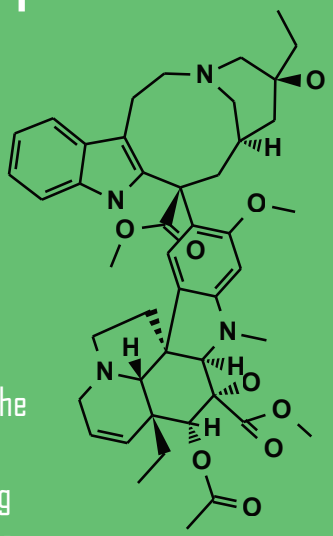
DRUG CLASSES

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

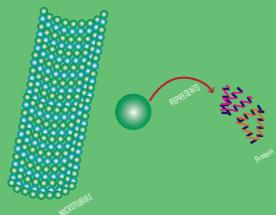


VINBLASTINE
(Tubulin Inhibitor)

Major Drawbacks:

Cytotoxicity

Drugs do not discriminate;
Neurotoxicity, cardiotoxicity (10%)



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

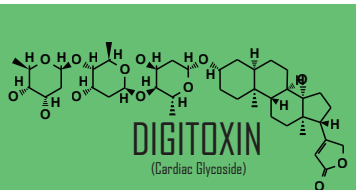
CARDIAC AGENTS

Calcium Channel Blockers

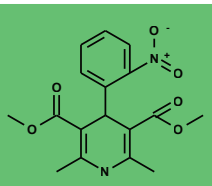
Use: Treatment of Angina, Arrhythmia, and Hypertension

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

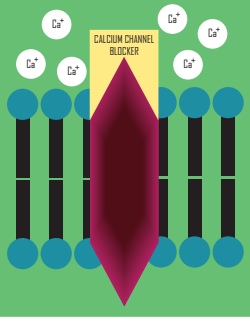
Other Types: Statins, ACE Inhibitors, Cardiac Glycosides, Antianginal, Antiarrhyth-mic, Vasodilators



DIGITOXIN
(Cardiac Glycoside)



NIFEDIPINE
(Calcium Channel Blocker)



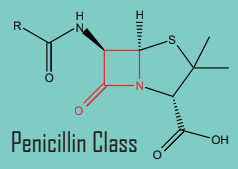
DRUG CLASSES

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

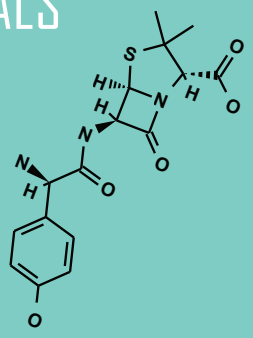
Uses:
In the treatment of infections



Penicillin Class

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



AMOXICILLIN
(Penicillin)

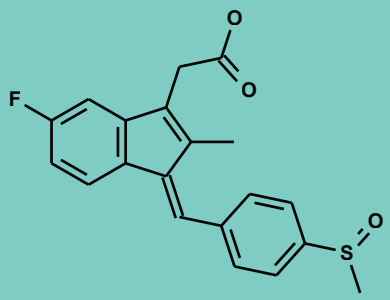
NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

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



SULINDAC
("Profens")

ANTIDEPRESSANTS

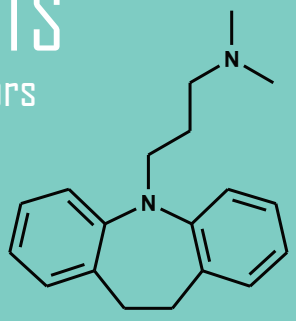
Serotonin Reuptake Inhibitors

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 Anti-depressants:
Dopamine and norepinephrine reuptake inhibitors, serotonin antagonist/reuptake inhibitors, monoamine oxidase inhibitors



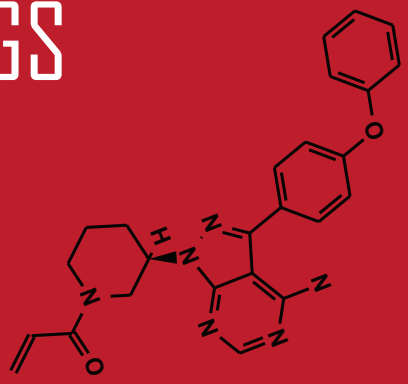
IMIPRAMINE
(Serotonin Reuptake Inhibitors)

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

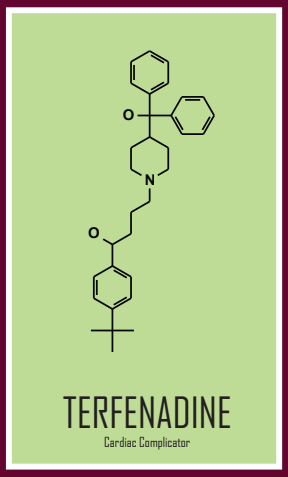
DRUG INTERACTIONS

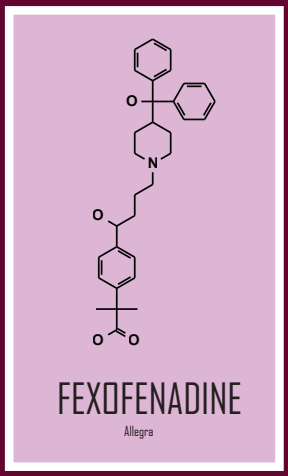
-Drugs are miraculous things
-Yet, the human body is very complex, dynamic, and it is oftentimes difficult to predict it perfectly or in its entirety
-While drugs have the potential to do great good they also have the possibility of doing great harm, most often unbeknownst to researchers and manufacturers
-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

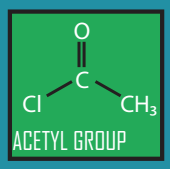
-You may have seen that certain medications advise against taking the medication with grapefruit juice
-At first this seems rather random and odd, grapefruit does not seem particularly special: it is not the most acidic fruit or the sweetest
-Yet these warnings are not without reason, this is because 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

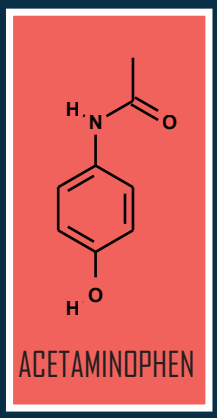
TRICKINESS

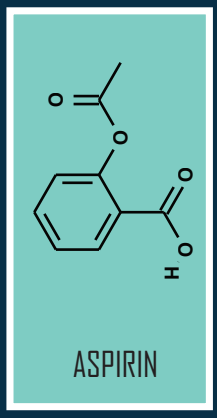
-Upon the miraculous discovery of aspirin, its creator, Felix Hoffman, decided to apply the same principle of its creation to another drug, morphine
-The powerful properties of this drug were reflected in its name: coming from "heroish", or powerful in German, heroin. Heroin, however, ended up being 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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