Pharmaceutical Chem Vocabulary

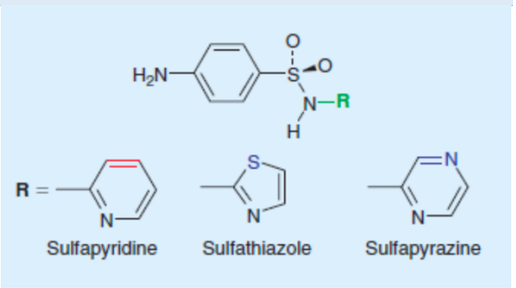
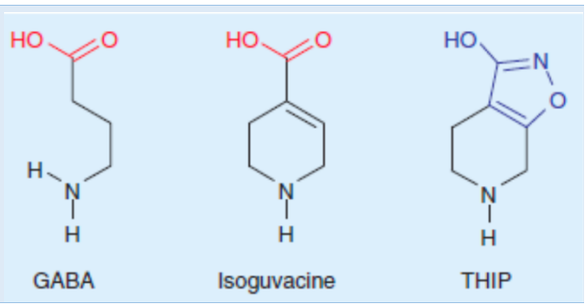
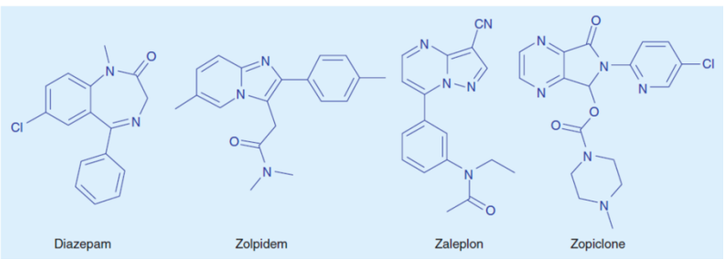
TERM	DEFINITION
Druggability	Chemicals are druggable when they have the right physicochemical properties to interact with the target, such as size, hydrophilicity/hydrophobicity ratio, metabolic stability
Ideal Drug	Patentable, maximum 4 steps for synthesis (90% yield per step ends in 35% loss after 4 steps), no heavy metal catalysts, or environmentally problematic waste, stable up to 70 C even in light, solid-state properties that allow it to be compacted into a tablet, solubility in water sufficient for production of stable blood-isotonic solutions, oral bioavailability >90%, very high activity and pharmacokinetic profile allowing once a day dosage of 5-10mg
Drug Development	High throughput screening → Hit Exploration → Hit to lead → lead profiling → Lead optimization (to here 24-36 months) → preclinical development candidate → Formulation and toxicology → Clinical Candidate (from millions of compounds, we end with one, if we are lucky)
Activity (of a drug)	The concentration of drug needed to produce the desired (or undesired) biological effect
Therapeutic Index	Quantitative measurement of the relative safety of a drug. It is a comparison of the amount of a therapeutic agent that causes the therapeutic effect to the amount that causes toxicity
Role of Medicinal Chemists	Synthesis, discover, study the mechanism of action, know the biochemistry, purification, structure of a drug.
Drug activity phases	Pharmaceutical phase → Pharmacokinetic phase → Pharmacodynamic phase
Pharmacokinetics	What the body does the molecule, ADME
Classification of drug	These slides are for pharmacists, I have never asked about this
Binding Groups	Functional groups able to form intermolecular interactions are called binding groups, HBA, HBD, Ionic binding group, or covalent binding group
HBD and HBA	HBD group is formed by a electron deficient hydrogen attached to a electronegative atom X-H, while HBA has a lone pair that can attack the H of the HBD. Some groups (OH, NH2) can act as HBD and HBA depending on the ligand, called hydrogen bond flip-flop
Coulombs Law	
Lennard-Jones Potential	
BioPhase	The effector site of the drug within the body
First Pass Effect	Orally and rectally administrator drugs which enter the GIT system undergo degradative attacks in the liver before entering the systemic circulation, therefor higher doses need to be used to achieve the same plasma concentration as intervenes or intermuscular.
Bioavailability	In pharmacology, bioavailability (BA or F) is a subcategory of absorption and is the fraction (%) of an administered drug that reaches the systemic circulation.
Personalized Medicine	
ADME(T)	Absorption, Distribution, Metabolism, Excretion (Toxicology).
Transcellular Drug Transport	Drugs that travel through cells, by passing through their membranes by passive deffusion, carrier mediated, or vesicular transport. These drugs have to be soluble in water, and also in fat to pass through the membrane
Paracellular Drug transport	Passing through gaps between cells
Hydrophobic Effect	Not as significant as in protein folding, because when water is displaced from the binding site by the drug, it becomes reordered in the acquis environment around the protein, in this case the enthalpy is almost zero since the order of the system is barely changed
Iceberg effect	Is the formation of an ordered structure around the hydrophobic solvent such that the enthalpy change of a drug binding is nearly zero (I didn't understand really but there's no good explanations online)
Fick's Law	-Passive diffusion is the spontaneous diffusion from high concentration to lower and is the main mechanism for passage of drugs through membranes. The rate of diffusion of the drug depends on the lipid/water coefficient (P), concentration gradient (C-out – C-in) membrane properties such as Area (A) and thickness (h) and diffusion coefficient (D) of the drug in the membrane, according to Fick's Law: Rate of Diffusion = [DAP(C-out – C-in)]/h

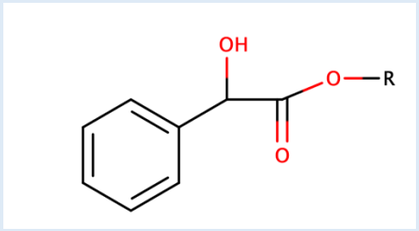
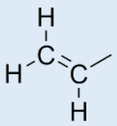
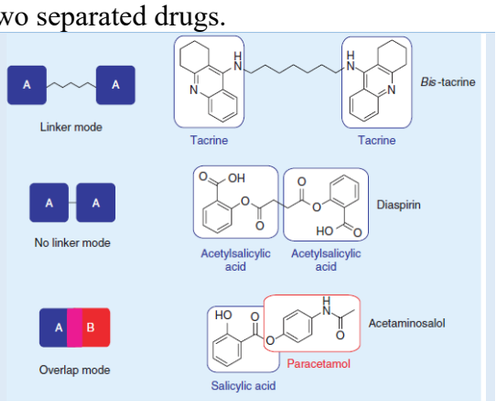
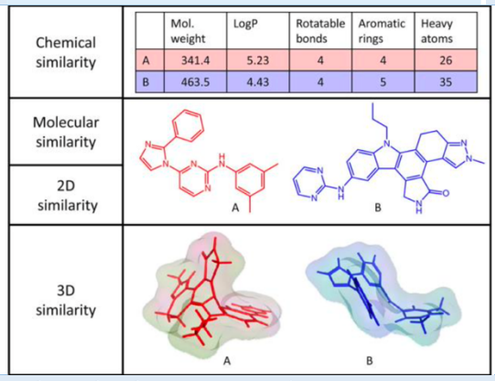
	-Remember the example about sugar dissolving in coffee, the area next to the sugar is where the sugar first diffuses, so we have a high Δ and in the far parts its low, so we mix the coffee and give the system kinetic energy - Ionized compounds are not able to pass through the fatty membrane, we have to use the Henderson Hasselbach equation to calculate the ratio of ionized/unionized drugs using the pKa
Ion Trapping	When pH is different on two sides of a barrier, therefor the concentration of ionized molecules and therefor total concentration will be much higher on one side of the membrane than the other, such as between blood plasms (pH 7.4) and stomach (pH 1-3)
Henderson-Hassel Bach equation	Gives us the percent ionixation of a molecule at a certain pH, used to give us hints about the solubility and concentration of a drug, ionized drugs are less absorbed into membranes.
Carrier Mediated	Facilitated diffusion does not require energy but uses some membrane proteins, active transport instead uses energy. Facilitated diffusion seems to play only a minor role with drugs
Vesicular Transport	Exocytosis and endocytosis, polio vaccine and other large proteins rely on this
Paracellular transport	Drugs that pass through small junctions between cells, proposed reason for celiac disease
Parenteral Routes	Injections: Intramuscular, Intra venous, Intra-arterial, Intra-cardiac and nihilation, rapid, higher bioavailability, less GIT disturbance
Enteral Routes	Oral, Sublingual, per rectum, pass through the liver
Lipinski's rule of 5	To determine if substances that are orally active had similar characteristics, Lipinski discovered orally active drugs are: Less than 500 MW, less than 5 HBD, less than 10 HBA, LogP less than +5
Rule of 5 Failures	Many orally active drugs such as atorvastatin, rosuvastatin, cidosporin do not obey rule of 5, the reason is that usually molecular weight correlates with increased bonding groups, but attempts are being made to calculate guidelines independent of molecular weight
Weber contributions	Weber thought Lipinski's rules are too rigid, so came up with the parameters: polar surface of < 140 A and < 10 rotatable bonds, OR < 12 HBD and HBA in total, and < 10 rotatable bonds, this is because too many degrees of freedom (rotatable bonds) decreases the oral bioavailability
Emulation	octanol and water smoothly mixed to calculate LogP, takes 2 days to separate, so LogP is only determined computationally instead of experimentally because it takes too long to separate
Microsomal Enzymes	Microsomes are formed when you break a piece of liver and break the ER to release the enzymes, then reforming into circular membranes containing degradative enzymes, but we do not contain microzymes in the body. Microszymes are responsible for the metabolism of drugs
Prodrugs	Drugs that are not active in vitro state and becomes active in vivo, if the drug is at all active in vitro, even less than in vivo it cannot be called a prodrug and is called a latenciated drug, a softened drug (idk). They can be activated by oxidation, reduction, or hydrolysis. This process is called bioactivation of the drugs
CYP	Cytochrome P450 enzymes responsible for most of the phase-I reactions. Called 450 because their heme group absorbs the maximum amount of light at the 450 wavelengths. The most important CYP are currently CYP2C9, CYP2D6 and CYP3A4 which treat most current drugs. These 3 accounts for 70% of drug metabolism, changing depending on population. Cytochromes modify the drugs chemically, by removing or adding groups called hard modifications
Phase-I	-Cytochromes modify the drugs chemically, by removing or adding groups called hard modifications. P450 are most important, non-specific enzymes can add polar function groups to a variety of drugs, making it more likely to be excreted when it goes through the liver. These reactions are generally oxidation, reduction, and hydrolysis, most occurring in the liver but some (hydrolysis of amides) in gut wall, plasma. -Cytochromes use NADPH as a cofactor: Drug-H + O2 + NADPH → Drug-OH + H2O + NADP, where NADPH donates an electron to the cytochrome, Reducing Fe3+ to Fe2+, which has a good affinity for oxygen. Oxygen then steals the electron from the Fe2+ to make it Fe3+, where it again is reduced to Fe2+ by NADH, creating a superoxide species. One oxygen forms water, the other to insert itself between X and H forming XOH. All cytochromes work in this cycle, cytochromes are selective based on the shape of the cytochrome, the heme is always the same -Cytochrome p450 (95%), Flavin containing monooxygenases, monoamine oxidases (MAO, connected to epinephrin absorption) -Phase one examples Page 1

Phase-II	-Soft modifications that conjugate the drugs to make the drugs more hydrophilic and easily excreted. Also occurring mainly in the liver. Both sets of reactions are regio and stereoselective, meaning metabolic enzymes differentiate between identical functional groups in different positions (Regio), as well as different stereoisomers of chiral molecules (Stereo) -SAM, PAPs, UDPGA, Glutathione, Acyl-CoA, COA -Phase-II examples on page 2
Phase-III	Not well defined, phases of metabolism that occurs in a few number of drugs in which the drugs are reabsorbed and eliminated, or attacked by intestinal bacteria
Toxification	The process by which a safe compound becomes toxic by metabolism,
Biotransformation	Biotransformation means chemical alteration of chemicals such as nutrients, amino acids, toxins, and drugs in the body. It is also needed to render non-polar compounds polar so that they are not reabsorbed in renal tubules and are excreted. Biotransformation can be different between individuals and between populations, meaning different drugs need to be tested on various individuals and populations to make sure the secondary metabolites are safe
Glucuronic Acid	Conjugation with glucuronic acid is the most common of phase-II reactions, phenols, alcohols, and carboxylic acids form O-glucuronides, drugs that contain a nucleophilic point. Resulting conjugate is excreted in urine, or in bile if MW is over 300. He said FIX THIS IM MIND, you have to know this by chemistry (?)
Sulfate conjugation	Less common than GA and mostly restricted to phenols, alcohols, and catalyzed by sulfotransferases using the cofactor 3' phosphadenosine 5' phosphsulfate (PAPS) as a sulfate source. Primary and secondary amines, as well as secondary alcohols and phenols form stable conjugates, while primary alcohols form reactive sulfates acting as alkylating agents.
Metabolic Stability	Ideally drugs should be resistant to metabolism, as metabolites complicate things. For examples, metabolites of paracetamol cause liver toxicity. Other drugs such as codeine are metabolized by CYP2D6 into its active form of morphine. Codeine is ineffective in patients lacking this enzyme. Drug-Drug interactions also complicate the metabolism of drugs. -Many pharmaceutical companies only design drugs that cant interact with cytochromes
Hard/Soft Drugs	Hard drugs are resistant to the phase-I reactions, and remain unchanged in the body while soft drugs are designed to have a predictable, controlled metabolism. A group is normally added which is susceptible to metabolism, insuring the drug survives long enough to achieve its goal. These drugs are called antedrugs
Past Drug Development	-Trial and error process, testing natural compounds and often killing the patient because they were unpured, synthesis of drugs started in 1920-30 because organic chemistry was still too young
Alkaloids	The first drugs were alkaloids: A MOLECULE CONTAINING A BASIC NITROGEN
Drug Design	Identify SARs, Pharmacophore, Improve target interactions (pharmacodynamics) and pharmacokinetic properties
Orphan receptor	A receptor that we do not know the endogenous ligand (Ligand, neurotransmitter, hormone), or structure of . morphine acted on an orphan receptor until 10 years ago.
Orphan Drug	Definition given in 1984 as a drug intended to treat a condition affecting less than 200,000 people in the US, or which will not be profitable within 7 years of FDA approval. No company is going to invest the time to develop orphan drugs that treat rare disease, so state pays
Combinational Synthesis	thousands of compositionally varying samples are synthesized, processed, and screened in a single experiment to rapidly survey large materials phase spaces.
Parallel synthesis	Involves the small-scale synthesis of a large number of compounds at the same time, each reaction vial contains a different compound. Along with combinatorial, develops large libraries to run through HTS
Financial Return	Diseases are only studied that will promise a financial return for the company such as headaches, obesity, ulcers
Specificity	-How specific the drug is for its target, the ideal drug that only acts on its target is almost impossible. Drugs often need to be specific to tissues or organs, which is much harder than specific to host/non-host. - B-adrenergic receptors in the heart are mainly B1 whereas those in the lungs are B2, so drugs that can reduce blood pressure selectively inhibit B1 and not B2. They are isoforms and therefor highly similar so drugs need to be very selective to only one receptor. -Selectivity can also be dependent on a particular location, such as drugs targeting one dopamine receptor in the brain -Drugs designed against a specific target become less effective over time, the roadblock is bypassed by a different road
Selectivity	Selectivity looks at targets that are different between the target and others, penicillin targets cell wall biosynthesis enzymes not present in humans

Multi-target Drugs	Drugs that can activate against a range of specific and similar targets
Fail Fast, Fail Cheap	Drug development strategy that minimizes the risk of investing too much money in a drug that might fail, bioassays are important here but only the most promising ones are taken to in vivo assays
Agonistic Drugs	Those drugs that activate their targets, often targeting membrane proteins with G-linked receptors which induce a cellular signaling cascade, agonistic drugs are less well understood. Other agonists can be superneurotransmiteers which act as agonists and activate neuroreceptors at a greater rate
In Vitro Test	-In culture of cells, often measures the level of drug that can kill cells, and level of drug needed to kill the microbe, we should have a much higher toxic than clinical dose. In vitro tests also determine if the drug acts competitively or non-competitively, and IC50 values -In vitro tests are also used to determine pharmacokinetic properties by using microsomes and hepatocytes extracted from liver cells containing cytochrome P450 enzymes, and identify the likely metabolism of the drug and possible drug-drug interactions
In vivo test	Animals are treated to see if the drug alleviates the problem, transgenic animals are often used (animals with altered genetic codes, such as mouse genes replaced with human genes) to make the animal particularly susceptible to the disease. Many in vivo tests in animals are invalid, due to physiological differences between test animal and humans
HTS	High-throughput screening Involves the automated testing of large numbers of compounds versus a large number of targets, up to 1000s of compounds per day, but are very expensive. Medium throughput → 100s of compounds, Low throughput → 10s -HTS finds hit compounds, which can be later converted to lead compounds
Screening Methods	-NMR: Used to determine molecular structure of compounds -Affinity screening: Screen mixtures of compounds for their ability to bind the target -Virtual Screening: Use of computers assessing if lead hits a particular target, such as molecular docking -Surface Plasmon Resonance (SPR): Drug fixed on a gold plate, and tests if the target can be bound by the drug, but no information where and how it binds -Scintillon Proximity Assay (SPA): Visual method testing if the ligand binds the target, by using beads which release light upon binding, light is observed when the ligand binds the target(?) -Isothermal Titration Calorimetry (ITC): Used to determine the thermodynamic properties of drug-protein binding
Hit (1,000,000)	A hit is an active substance having a preferential activity for the target as a result of HTS, and has the following criteria: 1) reproducible activity in bioassay 2) confirmed structure and purity 3) specificity to target under study 4) Confirmed potential for novelty 5) chemically tracible structure, molecules presenting affinity for target, and not too aggressive and reactive
Hit Validation (1000)	Hit validation criteria are 1) active in vivo 2) not display hERG toxicity 3) analogues of hit must display clear SAR 4) Not contain chemically reactive functions 5) patent opportunity, if all five are validated, hit is now a lead
Human Ether-a-go-go	hERG related toxicity
Lead (10-1000)	Hit molecule that has been validated, undergoes additional SAR, ADME and toxicity studies to acquire clinical drug candidate status, where it can undergo toxicology studies in initial clinical studies (3-5 optimized leads/preclinical candidate), whole process takes no less than 3 years
Lead optimization	Finding analogues of the lead which have the desired specificity, activity stability etc..
SOSA	Selective optimization of side activities is used in drug development, a compound with an unintended side effect is used to study the side effect and optimize its activity towards that side effect. Choosing a known drug as a lead compound has many advantages as the lead is already drug like, and likely pharmacokinetically stable ect..
Me too, Me better	Many companies design drugs that are not included in the original patten of a company and can either do the same thing as the original drug (me too) or if accidentally finding a more potent or pure compound (me better)
Analog Design	Most popular strategy of drug design is synthesizing analogues of existing active molecules, the main drug of a medicinal chemist is creating analogues. The whole thing revolves around $$
Types of analogs	Structural analogues have the same chemical similarity, Functional analogues present different chemistry but similar pharmacological effects, True/Full analogues have the same chemistry and pharmacological effects

Serendipity	-When something we don't expect happens, with a prepared mind and a little bit of chance we can recognize the luck. Frequently, new compounds arise from totally separate fields of chemistry. -Example: Clonidine was designed to be a nasal vasoconstrictant in nasal drops, but lead to marked fall in blood pressure and instead became an important antihypertensive
Crum Brown and Fraser (1869)	The first SAR, they observed tertiary amine containing molecules become muscle reactants when converted to a quaternary amine, morphine, nicotine, and atropine all became similar to tubocurarine when methylated, their hypothesis was wrong but was the first observation of chemical structure and biological activity. Likely because acetylcholine (natural neurotransmitter) also contains a 4 amide which stimulates muscle contraction
Xenobiotics	
Ehrlich	Developed the concept of drug receptors, he hypothesized that something in the cells are complementary to dyes or drugs allowing the two to interact, first to postulate existence of receptor and coined the term. He also coined the term "magic bullet" of the idea of a drug hitting the target somehow and modulating the behavior and restore some abnormalities.
Agonist	Binds receptor and activates it, can be full or partial agonist depending on its efficiency, morphine is an example of a full agonist
Reverse Agonist	Binds the receptor and produces the opposite effect as an agonist binding, for example if an antagonist binds and blocks activation , agonist binds and activate the reverse agonist will bind and deactivate. Reverse agonists are safer than antagonists because antagonists while binding can activate the receptor just once before inhibiting it.
Antagonists	Molecules that are able to bind the receptor in the same way as the endogenous ligand, but is generally much larger than the endogenous one and cannot activate it
SAR	Structure-activity relationship says that similar molecules exert similar biological actions in a qualitative sense, and that structural elements (functional groups) within a molecule often contribute in an additive manner to the physicochemical properties of the molecule.
pKa	A constant for any given molecule, the ratio of acid/base is determined by the pH of the solution. Ionization of a compound determines the absorption in different membranes
Blood Brain Barrier	Non-Polar drugs can pass and act on the CNS
Lemke Rule	An empirical approach to predict water solubility of molecules based on carbon-solubilizing potential of several organic functional groups, if the solubilizing potential of the functional groups exceeds the number of carbons the molecule is considered soluble. Functional groups that interact through hydrogen bonds, or ion-ion will decrease the solubilization. Charged groups are +20-30, alcohol, phenol 3-4, amine, carboxylic acid, ester 3
LogD	LogP is influenced by the pKa, so logD is better for ionizable compounds and is the LogP considering the ionizable parts of the drug $AH \rightleftharpoons A^- + H^+$ $P_0 = \frac{[AH]_{octanol}}{[AH]_{water}}$ $P_{-1} = \frac{[A^-]_{octanol}}{[A^-]_{water}}$ $D = \frac{[AH]_{octanol} + [A^-]_{octanol}}{[AH]_{water} + [A^-]_{water}}$
ClogP	The fragmental approach to calculating log P similarly to Lempke, we use a table containing the π value of each individual component, and can be + of -
Log(1/C)	Measure of potency of a substance, C stands for Conc. of compound required to produce a standard response in each t.
Stereoisomers	Can be enantiomer (non-superimposable mirror images, only separated by polarizable light) or diastereoisomers (not enantiomers, including geometric, double bonds, or ring systems. Easy to separate as their physicochemical properties usually differ)
Eutomer	Since the proteins and biological molecules are asymmetric, one sterioisomer of a drug can act differently than another considering the special placement of its functional groups, the eutomer of a drug is the most important enantiomer, and the less favorable is called distomer
Racemic Mixture	Equal amount of enantiomers and do not polarize light
Easson-Stedman Hypothesis	Drugs containing chiral centers which are given as enantiomers, there must always be one that is more active and one that is less, because the need for at least three points to fit into the receptor, one enantiomer will not be able to present the same groups at the same time.
Pharmacophore	-First definition: The determination of the 3D position of the most important functional groups around the molecular scaffold that might interact with the (unknown) receptor.
Alteration of Alkyl Chains	Chain length, Branching, rings can be added to a molecule to change its physiological activities, for example morphine goes from Analgesic (CH3) to Agonist (CH2CH3) to antagonist (CH2CH2CH3) . Functional group position can also be varied to create different biological activities

Isosterism	First observed by Allen in 1918, observed that two molecules having the same molecular number share many parameters. Isosterism was introduced by Langmuir in 1919, who focused on the similarities of electronic and steric arrangement of atoms, groups and radicals. N2O and CO2 are examples of isosteres which contain almost identical viscosity, density, solubility.
Bioisosterism	Bioisosters include all atoms and molecules which fit the broadest definition of isosteres and elicit the similar biological activity, used as a research tool in analogue design. Bioisosterism has a very broad application, and is unpredictable depending on the organism and process.
Grimm's Hydride Displacement Law	From carbon we can create isosteres for any atom next to it by simply adding a H, such as N-CH, or O-NH-CH2 and so on. In some form we can expect that these isosteres have some properties that resemble the other isosteres in their group (not always the case), and even some analogues which have more favorable properties.
Langmuir	Independently from Allen, defined the concept of isosterism as those molecules containing the same number and arrangement of electrons, most importantly in their outer shell. He identified 21 groups of isosteres based on this definition: Na+, NH4+ and K+ are all isosteres considering Langmuir and Allen definitions **TABLE 15.1** Groups of Isosteres as Identified by Langmuir Groups: 1 — Isosteres: H^-, He, Li^+ Groups: 2 — Isosteres: O^{2-}, F^-, Ne, Na^+, Mg^{2+}, Al^{3+} Groups: 3 — Isosteres: S^{2-}, Cl^-, Ar, K^+, Ca^{2+} Groups: ↓ — Isosteres: ↓ Groups: 8 — Isosteres: N_2, CO, CN^- Groups: 9 — Isosteres: CH_4, NH_4^+ Groups: 10 — Isosteres: CO_2, N_2O, N^{3+}, CNO^-
Heinsberg	Applied the concept of isosterism to entire molecues, developed the concept of ring equivilants.
Burger (Great medicinal chemist)	Expanded the definition of bioesteres: "Bioisosteres are Compounds or groups that possess near-equal molecular shapes and volumes, approximately the same distribution of electrons, and which exhibit similar physicochemical properties." And transformed a purly chemical concept into a medicinal chemestry concept, from a chemical application it evolved into a statistical application 
Non-Classical Bioisosters	Any bioisoster that does not conform to the normally defined definitions of bioisoster, example is Isopropeteronol and soterenol, replacing m-OH with sulfonaminde works in this case. Very broad concept, bioisosters are defined in literature experiementally through trial and error 
Scaffold Hopping	Scaffold hopping is illustrated by the molecule diazepam, zolpidem and other molecules acting on GABA-A receptors, and is used recursivly to discover structurally novel ($) compounds from a known biologically active compound 
Homologous series	Introduced by Gerhardt, in medicinal chemestry it describes molecules differeing by only a methylene group. Most common are: monoalkylated derivitives(R-CH2-X), Difunctional, molymethlenic (X-(CH2)n-Y), Cyclopolymethylenic (), Substituted cationic heads (R-N-(CH3)3). Most homologous series are a bell shaped, where potency increases to a point then decreases. Sometimes drugs have an ideal length in order to interact with its pharmacophore elements
Potency	How much of the drug is needed to create the biological activity, that is how much affinity it binds, you cant say a drug is more active, only it is more potenent. If a drug can bind, it is active.

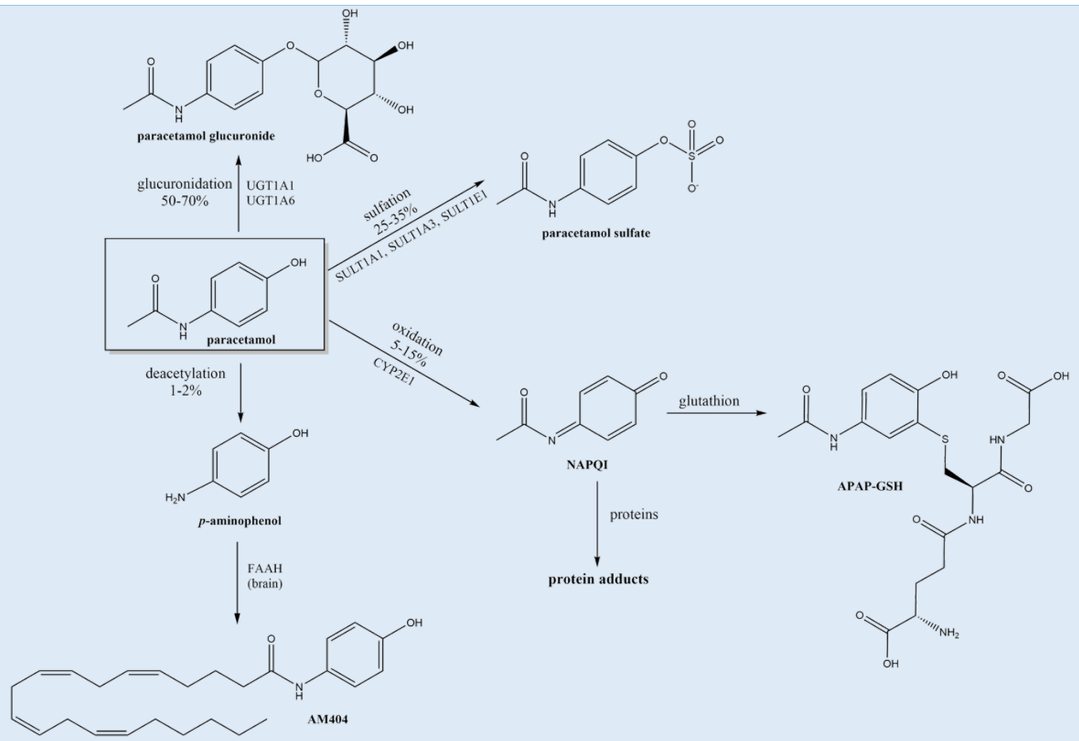
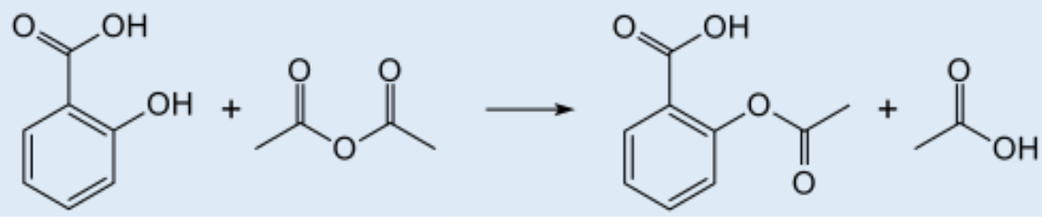
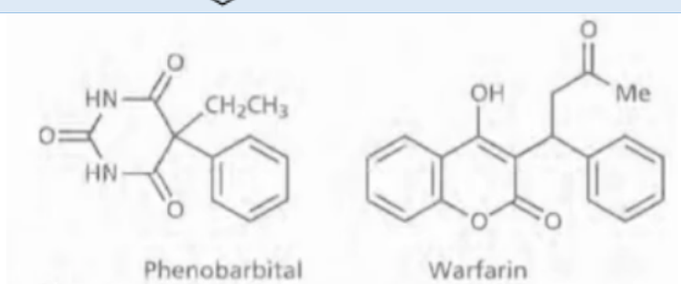
Biological Response Curves	Most commonly in homolgous series we have a bell shaped curve (A), but we can also have the cases of: Increasing without any particular rule (B), Zig-Zaging (C), increasing then plateau (D), decrease regularly, especially in toxicity (E), and lastly inverson of pharmacological activity accompanying increase in carbons (F) -Add some examples -Spasmolytic comounds increase in activity as their chain is extended 
Carbamate Group	
Vinylogues	Vinylogy is a way to design analogues by inserting a vinyl group. Vinyl group plays a role of electron-conducing channel between carbonyl group and hydroxyl group (mesomeric effect). A doule bond is needed to create the interaction. The goal is to create a dipole-dipole interaction between the terminal CH2 group and a possible site on the receptor Ex. Formylacetone has similar acidic properties to acidic acid CH2-CO-CH2-CHO → CH2-CO-CH=CH-OH This principle isoften unpredictable but is sometimes used to design bioisosters. 
Mesomeric Effect	It is defined as the polarity produced in the molecule by the interaction of two pi bonds or between a pi bond and lone pair of electrons present on an adjacent atom.
Benzologues	Similarly to vinylogues, except a benzyl group is added instead of vinyl
Twin Drug Approach	-Drugs containing two pharmacophoric groups covalently bounded are called twin drugs. The association of two identical pharmacophoric enti ties will generate an "identical twin drug" which is equivalent to a homodimer derivative. A compound, where two different pharmacological entities are bounded, is called a "non-identical twin drug" or heterodimer. The aim of the first approach is the production of a more potent and/or more selective drug compared to the single entity. The second strategy consists of an association of two different pharmacophores. In this case, the new compound will possess both initial pharmacological activities. The administration of twin drugs can be favourable compared to the two separated drugs.
Combination modes	
Chemical Similarity	-Based primarily on the physicochemical characteristics of compounds (e.g., solubility, boiling point, log P, molecular weight, electron densities, dipole moments, etc.) - Two Vascular Endothelial Growth Factor Receptor 2 ligands and different ways to assess their similarity. 
Molecular Similarity	Focuses primarily on the structural features (e.g., shared substructures, ring systems, topologies)
Neighborhood Principle	-Given a molecule of known biological activity, compounds that are structurally similar to it are likely to exhibit the same activity.de -There are many exceptions to the principle but it is an excellent rule- of-thumb in the absence of more detailed knowledge
Similarity Measure	In order to be able to quantify the similarity between two molecules, a similarity searching method requires two components: -a set of numerical descriptors that can be used to compare molecules; -a similarity coefficient which provides a way of quantifying the degree of similarity based on the descriptors. -1D properties: MW, logP, PSA -2D properties: fingerprints, topological indices -Maximum Common Substructures -3D properties: molecular fields, shape

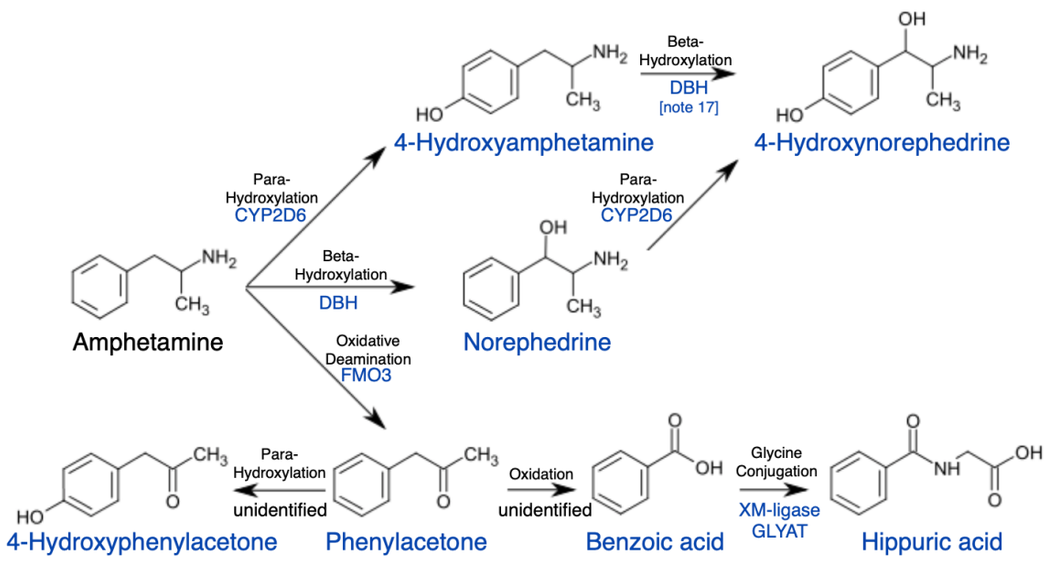
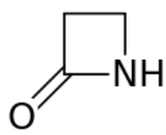
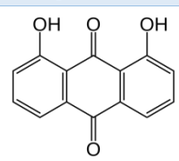
Molecular Descriptor (chemical)	0D: bond counts, molecular weight, atom counts 1D: fragment counts, H-Bond acc/don, Crippen, PSA, SMARTS 2D: topological descriptors (Balaban, Randic, Wiener, BCUT, kappa, chi) 3D: geometrical descriptors, surface properties, COMFA 4D: 3D coordinates + conformations
Molecular Fingerprints (Structural)	Lots of types, indicates the presence or absence of a structural feature, can be 166-4096 bits+, and usually compares using tanimoto metric
LBDD (Indirect)	Designing potential drugs with only the knowledge of the ligand, we do not know the structure of the receptor and therefore predicting the receptor is outside of our applicability domain. Purpose is to speed up hit and lead finding, reducing possibility of failure, animal toxicity. Includes QSAR, Pharmacophore approach, and 3DQSAR
SBDD	
Applicability Domain	We can only predict things that we are studying, used as the example in LBDD that we can NEVER predict the structure of the receptor based only on ligands
Pharmacophore (1979, LB or SB if known)	-"A pharmacophore is the ensemble of steric and electric features that are necessary to insure optimal supramolecular interactions with a specific biological target and to trigger (or block) a biological response" This IUPAC definition contains two errors; 1) "supramolecular interactions" assumes we know the interactions with the biological target, we don't. 2) "Biological target" for the same reason, we don't know anything about the target except it exists. We can build a pharmacophore but never assume anything about the structure of the target. -The result is an array of points connected in space by distances and angles, there is no chemistry here, just features that give an idea of the geometry of potentially biologically similar molecules
Pharmacophore components	-Pharmacophores are made of 1) Aromatic Rings or hydrophobic 2) HBD from N or O with at least one H attached and formal charge ≥ 0 3) HBA from N or O with at least one accessible lone pair, and formal charge ≤ 0 4) Formally charged atoms -We need at minimum 3 points to define a pharmacophore
Active Analogue approach	States that if a molecule fits the pharmacophore, it might be active. A way of filtering active vs not active compounds
BDZ Cook Model	Studied benzodiazepine receptor (GABA receptor), discovered pharmacophore for GABA agonists, inverse agonists, and antagonists could be defined by same receptor applying different pharmacophoric elements. In this way, Cook defined a multiclass model for a single pharmacophore
QSAR History	Even older than pharmacophore, 1863- Cros found toxicity of alcohols increases as solubility of alcohol decreases -1890-Meyer and Overton independently noted toxicity of organic compounds depends on lipophilicity -1938-Hammet introduces the electric parameter σ -1952-Taft introduces Es the steric parameter -1964-Hansch introduces hydrophobic parameters π and LogP
Es	Steric Parameter, introduced by Taft in 1952, $Es = \log kX - \log kO$ where kx represents the rate of hydrolysis of an aliphatic ester bearing the substituent X and ko represents the rate of hydrolysis of the reference ester.
σ	Electronic parameters, also called **Hammett substituent constant (1938).** This is a measure of the electron- withdrawing or electron-donating ability of a substituent and has been determined by measuring the dissociation of a series of substituted benzoic acids compared with the dissociation of benzoic acid itself.
LogP	-Logarithm of the molecule's partition coefficient (1-octanol/water), LogP is highly correlated to drug absorption, toxicity. ClogP and MlogP are particular ways of calculating LogP. Optimal LogP is between 3-5 which allows passage of drugs between plasma membrane. Total range Is from -3 – 7, non-polar molecules mainly enter octenol so the LogP is large -https://docs.chemaxon.com/display/docs/logp-and-logd-calculations.md#src-1806711-logpandlogdcalculations-definitionoflogpandlogd
LogD	LogP is influenced by the pKa, so logD is better for ionizable compounds and is the LogP considering the ionizable parts of the drug $AH \rightleftharpoons A^- + H^+$ $P_0 = \frac{[AH]_{octanol}}{[AH]_{water}}$ $P_{-1} = \frac{[A^-]_{octanol}}{[A^-]_{water}}$ $D = \frac{[AH]_{octanol} + [A^-]_{octanol}}{[AH]_{water} + [A^-]_{water}}$
ClogP	The fragmental approach to calculating log P similarly to Lempke, we use a table containing the π value of each individual component, and can be + of -

π	By Hansch (1964), considers the individual substituents contribution to the hydrophobicity of the whole molecule. The π factor measures the hydrophobicity of a specific region on the drug's skeleton and, if it is present in the QSAR equation, it could emphasize important hydrophobic interactions involving that region of the molecule with the binding site. In other words the LogP associated with a specific functional group
Log(1/C)	Measure of potency of a substance, C stands for Conc. of compound required to produce a standard response in each t.
QSAR	Quantitative Structural Activity Relationship, while pharmacophore tells is if a substance might be active, QSAR tells us how active it might be
Ki	Inhibition coefficient, the smaller the Ki, the greater the binding affinity and the smaller amount of medication needed in order to inhibit the activity of that enzyme.
IC50-Ex	The actual concentration needed to produce a 50% of the biological effects of a drug
IC50-Calc	Since we can only plot in 2D, instead of comparing IC50-Ex to any one parameter, IC50-Calc is used to incorporate all the parameters used into a single function which allows us to plot QSAR graphs in 2D
Hansch Equation	Originally postulated in 1969 as log Ki = k1 (ΔGLogP) +k2 (ΔGσ) + k3 (ΔGEs), not real QSAR because there are no STRUCTURES and instead studied how parameters effected the ΔG of a reaction, estimated by Ki
Hansch-Fujita approach	Also called linear free energy approach, comes from the idea that the ΔG of a reaction (In this case drug action) is made up for several smaller ΔG's for measurable parameters such as hydrophobicity, steric, electric etc.., where each parameter is weighted by a coefficient depending on its contribution strength to form a linear regression equation, most often needs to be calculated by a computer

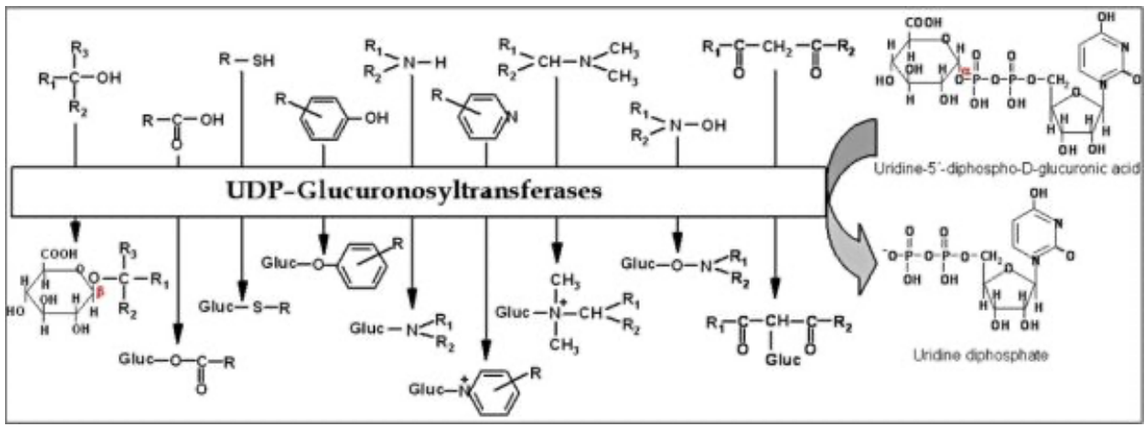
Drugs and Molecules

Clarithromycin	A small molecular change in Clarithromycin (a semisynthetic derivative of erythromycin) blocks the hemiketal formation making the drug stable in the acid stomach (pH 2)
Erythromycin 2-ethylsuccinate	A small molecular change in Erythromycin 2-ethylsuccinate (a semisynthetic derivative of erythromycin) leads to elimination of bitterness, important as its used in children.
Articaine	Dental local anesthetic, the ester group is hydrolyzed after 15 minutes so the life is short. We could add an amide instead of an ester, or a ketone, which are both similar to the ester but more resistant. But it could be too toxic.
Statins	Covalently binding drugs, the most sold drug class worldwide
Vancomyosine	Antibiotic that needs to only work in the intestine, fortunately because it is toxic to humans, but is trapped in the acidic pH of the stomach instead of diffusing into the blood
Dimethyl ether	Like water but with methyl instead of H, therefor it is insoluble in water because it cannot make hydrogen bonds
Propranolol	Occupies the B-adrenergic receptor, decreasing heart rate and anxiety. Used as example of drug metabolism, can become a huge number of different secondary metabolites produced through biotransformation
Paracetamol (Acetaminophen)	Glucuronic acid, Sulfidation, Glutathione conjugation (Indirectly), Oxidation (CYP2E1) and Deacetylation

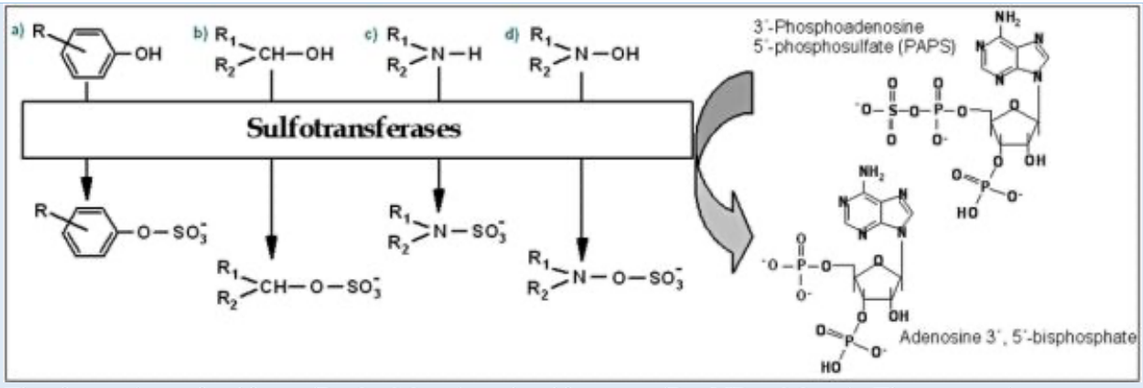
	
Codeine	
Aspirin	-Prodrug, not activated in vitro but activated in vivo. -R-Serine-OH is not able to acetylate in vitro. -Synthesis of Aspirin: The synthesis of aspirin is classified as an esterification reaction. Salicylic acid is treated with acetic anhydride, an acid derivative, causing a chemical reaction that turns salicylic acid's hydroxyl group into an ester group (R-OH → R-OCOCH3). This process yields aspirin and acetic acid, which is considered a byproduct of this reaction. 
Warfarin-Phenobarbital	Drug to Drug interaction example, Warfarin is an anticoagulant, and Phenobarbital (Barbiturate) activates cytochrome 450S, accelerating the metabolism of Warfarin and making it less effective 
Chloroform	Toxification by CYP and NADPH to phosgene (Toxic)
Amphetamine	The primary active metabolites of amphetamine are 4-hydroxyamphetamine and norephedrine; at normal urine pH, about 30–40% of amphetamine is excreted unchanged and roughly 50% is excreted as the inactive metabolites (bottom row). The remaining 10–20% is excreted as the

	active metabolites.Benzoic acid is metabolized by XM-ligase into an intermediate product, benzoyl-CoA, which is then metabolized by GLYAT into hippuric acid. 
Fluoxetine	Choosing a drug target, fluoxitine is a tricyclic antidiperession very popular due to its lack of many side effects
Caspases	Recent drug target as caspases are involved in inflammation, cancer development
Penicillin	Acts specifically on bacteria and not humans, Penicillin is a beta lactam.
Beta Lactam	A four membered cyclic amide ring. Beta lactams are named because the nitrogen in the ring is attached to the beta carbon relative to the carbonyl. The simplest beta lactam is 2-azetidinone. Nearly all these antibiotics work by inhibiting bacterial cell wall biosynthesis. Beta lactams open their lactam ring when bound to the target, and are there for a suicide inhibitor 
Fluconazole	One of the most potent antifungal drugs, inhibits a fungal demethylase enzyme involved in steroid biosysnthsis. The enzyme is also present in humans, but different enough to not be targeted. Unfortunatly because the durg tarets the heme structure of the demethylase, they also inhibit human cytochromes
Sorafenib	Optimized lead example, two modifications (removal of acetyl and addition of phenol) produced two molecules that were inactive, but when done together they produced an optimized lead that was a powerful anticancer agent (by inhibiting Raf-1 kinase) eventually sold as sorafenib. IC50 dropped from 17uM to 0.012 uM increasing the potency by over 1000
Artemisinin	Antimalerial drug with extreamly unstable looking trioxane ring that no chemest would dream of synthisising, was first observed in nature and inspired the idea of new chemical entity
Dantron	Derived from the natural source of rubarb, is used to treat GIT problems, exampled of leads from natural sources and from medical folklore as a purgative for many centeries and is now used as a laxtative 
Progesterone and Testosterone	Structural analogues, the two are chemically very similar but totally different biological functions
Sulfonamide and Tolbutamide	Sulfanimides inhibit bacterial formation of folate, a essectial substance in humans diets. Sulfanimide was seen to have a undesirable effect for antibacterial drugs of lowering glucose levels, Through SOSA the antidiabetic agent tolbutamide was achieved.
Salbutamol	Designed as an agonist of B-adrenergic receptors by studying the natural ligand of the receptor, in this case adrenaline and nerodrenaline
Benzodiazepines	Bind to a regulatory site on the GABA receptor, and was later discovered a class fo natural peptides exists that binds in the same site and mannor as benzodiazepines, sometimes drugs help us discover phesyology
Dectain	Cis-Trans Isomer importance, add
Acetylcholine	Due to its flexability, can act on different receptors depending on its conformation, example of confirmational isomers and biological activity. Interacts with nicotiner, and muserinic receptors, while the venylacetylcholine interacts only with the nicotentic receptor but not the muserinic
Methadone	By usinf the pharmacophore and SAR of morphine, methadone was developed through refinement of the lead structure

Glucuronic Acid (UDP-GA)

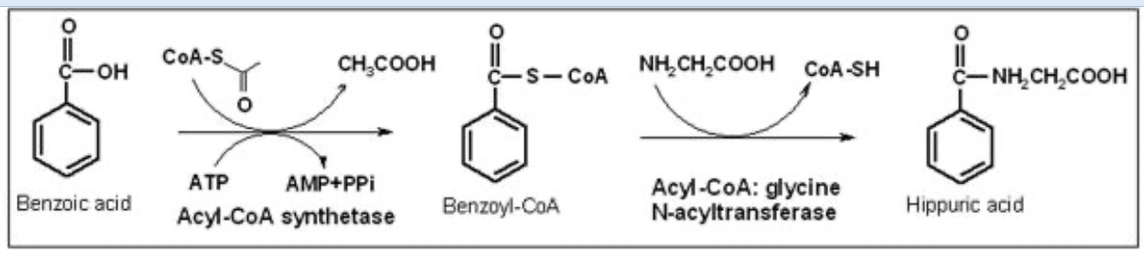


Sulfotransferases (PAPs)

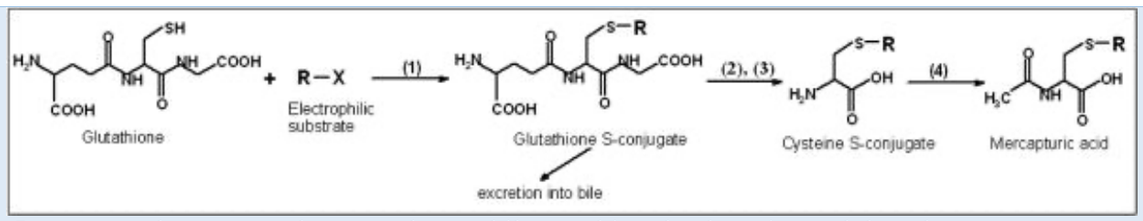


The formation of sulfates (R–O–SO_3^-) and sulfamates (R_1–NR_2–SO_3^-). These reactions are catalyzed by 3'–phosphoadenosine 5'–phosphosulfate (PAPS)–dependent sulfotransferases.

Hippuric Conjugation /Amino Acid Conjugation (Acyl-CoA)

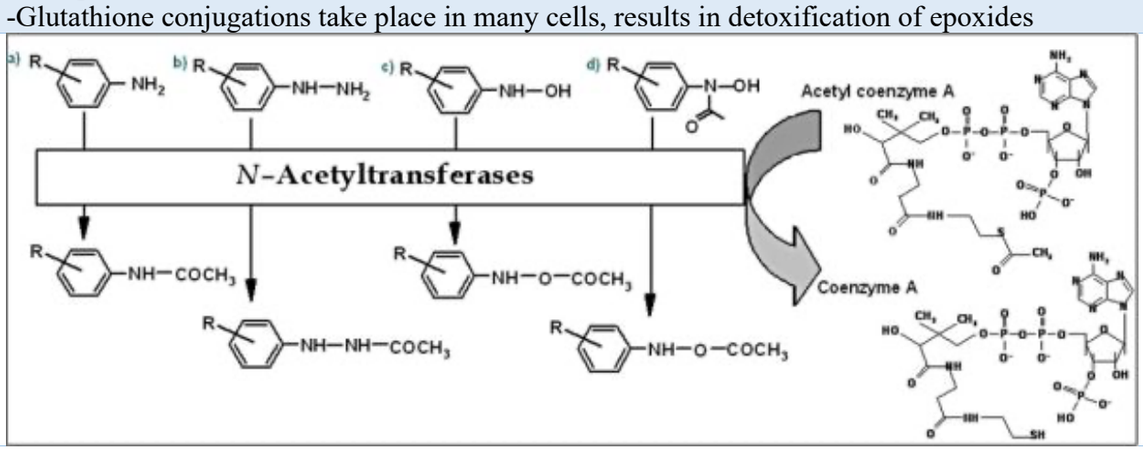


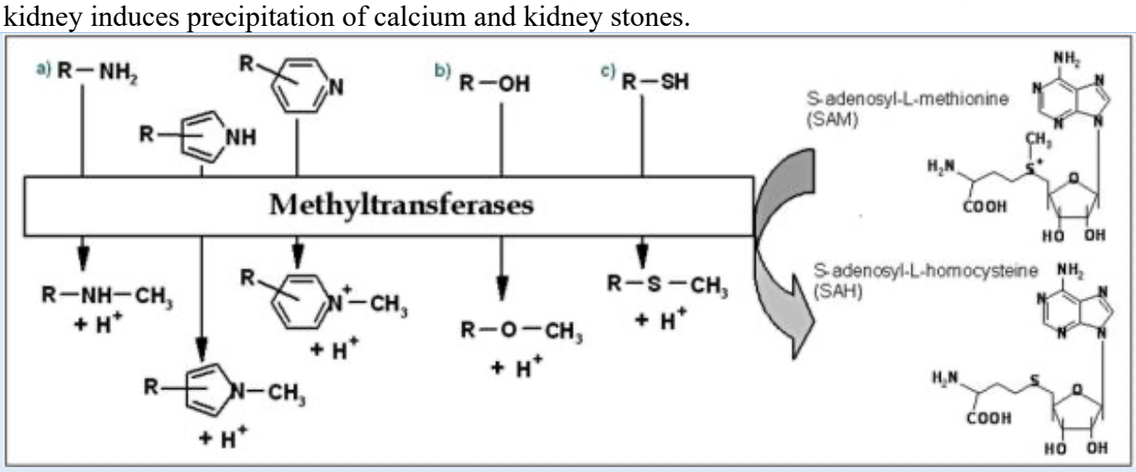
Glutathione Conjugation (Glutathione)



-Importance because we have an electrophile attacking the drug, instead the others are nucleophile, Sulfur is the reaction center, sulfur is a good neutrophile because it has a large orbital, so its lone pairs attack the carbon containing a good escaping group, and the carbon is the electrophile.
-Glutathione S–transferase (1) catalyzes the conjugation between glutathione and various endogenous or xenobiotic electrophilic compounds. Subsequently, the resulting glutathione S–conjugate is broken down to a cysteine S–conjugate by γ-glutamyl transpeptidase (2) and dipeptidases (3). Finally, cysteine S–conjugate N–acetyltransferase (4) catalyzes formation of mercapturic acid.
-Glutathione conjugations take place in many cells, results in detoxification of epoxides

N-Acetyl Transferases (AcetylCoA, CoA)



	Always leads to less polar compounds, important in antibacterial drugs derived from sulfonyl amide which is a good antibacterial that blocks THF synthesis in bacteria, an essential vitamin in humans but biosynthesized in bacteria. This drugs are no longer used because the pH of the kidney induces precipitation of calcium and kidney stones.
Methylation (SAM)	 Methylation and acetylation are not to make the drugs more polar and can be problematic by rendering the molecule even less polar keeping the drug in out body longer.

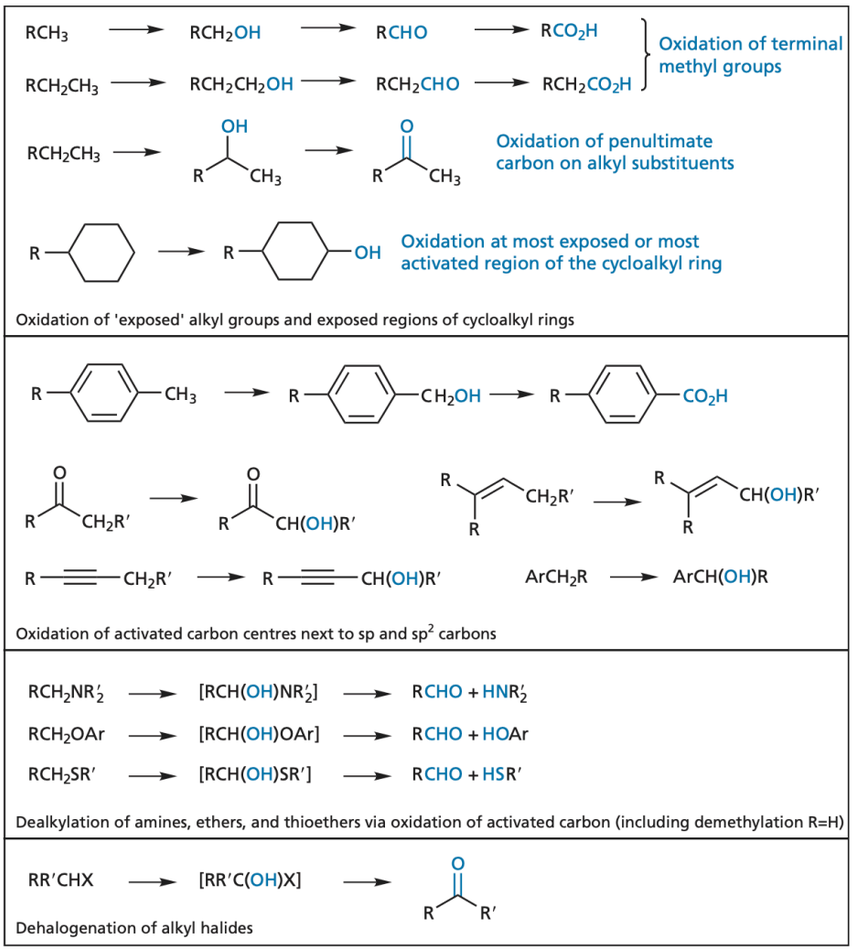


FIGURE 11.4 Oxidative reactions catalysed by cytochrome P450 enzymes on saturated carbon centres.

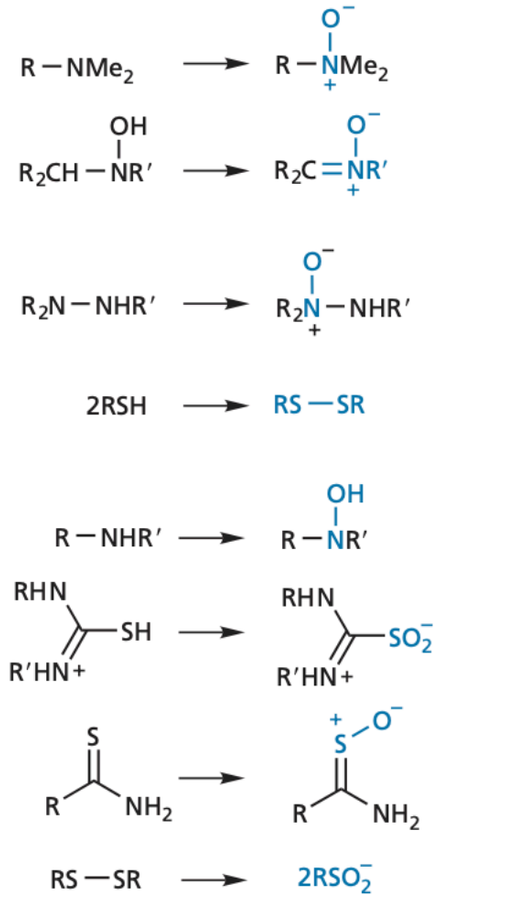


FIGURE 11.6 Phase I reactions catalysed by flavin monooxygenases.

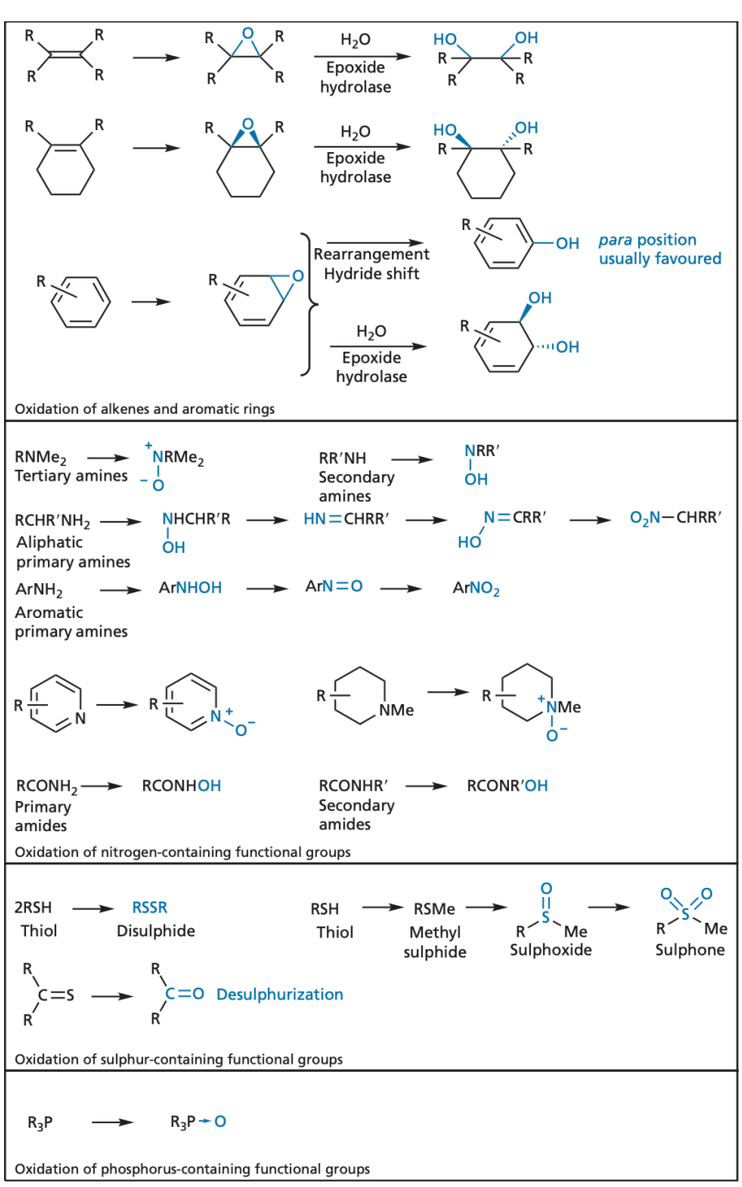


FIGURE 11.5 Oxidative reactions catalysed by cytochrome P450 enzymes on heteroatoms and unsaturated carbon centres.

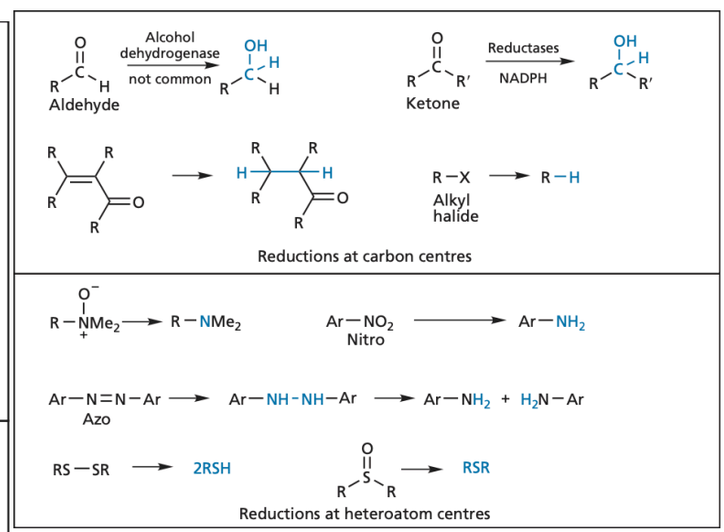


FIGURE 11.8 Phase I reductive reactions.

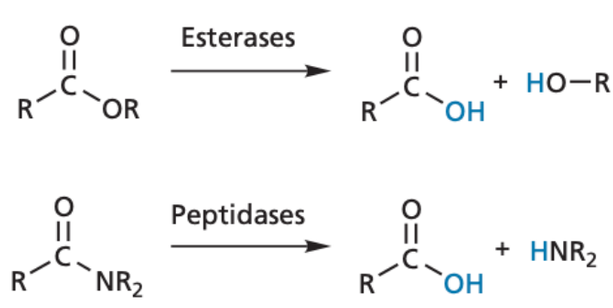


FIGURE 11.9 Hydrolysis of esters and amides.

Similarity Measures

Name	Formula for continuous variables	Formula for binary (dichotomous) variables
Tanimoto (Jaccard) coefficient)	$S_{AB} = \frac{\sum_{i=1}^{N} x_{iA}x_{iB}}{\sum_{i=1}^{N}(x_{iA})^2+\sum_{i=1}^{N}(x_{iB})^2-\sum_{i=1}^{N}x_{iA}x_{iB}}$ Range: -0.333 to $+1$	$S_{AB} = \frac{c}{a+b-c}$ Range: 0 to 1
Dice coefficient (Hodgkin index)	$S_{AB} = \frac{2\sum_{i=1}^{N} x_{iA}x_{iB}}{\sum_{i=1}^{N}(x_{iA})^2+\sum_{i=1}^{N}(x_{iB})^2}$ Range: -1 to $+1$	$S_{AB} = \frac{2c}{a+b}$ Range: 0 to 1
Cosine similarity (Carbó index)	$S_{AB} = \frac{\sum_{i=1}^{N} x_{iA}x_{iB}}{\left[\sum_{i=1}^{N}(x_{iA})^2 \sum_{i=1}^{N}(x_{iB})^2\right]^{1/2}}$ Range: -1 to $+1$	$S_{AB} = \frac{c}{\sqrt{ab}}$ Range: 0 to 1
Euclidean distance	$D_{AB} = \left[\sum_{i=1}^{N}(x_{iA}-x_{iB})^2\right]^{1/2}$ Range: 0 to ∞	$D_{AB} = \sqrt{a+b-2c}$ Range: 0 to N
Hamming (Manhattan or City-block) distance	$D_{AB} = \sum_{i=1}^{N}\lvert x_{iA}-x_{iB}\rvert$ Range: 0 to ∞	$D_{AB} = a+b-2c$ Range: 0 to N
Soergel distance	$D_{AB} = \frac{\sum_{i=1}^{N}\lvert x_{iA}-x_{iB}\rvert}{\sum_{i=1}^{N}\max(x_{iA},x_{iB})}$ Range: 0 to 1	$D_{AB} = \frac{a+b-2c}{a+b-c}$ Range: 0 to 1

Symbol	Description	
$onlyA$	number of bits set "on" in fingerprint A but not in B	A 1 0 1 1 1 0 0 0 B 1 1 0 1 1 0 1 0
$onlyB$	number of bits set "on" in fingerprint B but not in A	A 1 0 1 1 1 0 0 0 B 1 1 0 1 1 0 1 0
$bothAB$	number of bits set "on" in both fingerprints	A 1 0 1 1 1 0 0 0 B 1 1 0 1 1 0 1 0
$neitherAB$	number of bits set "off" in both fingerprints	A 1 0 1 1 1 0 0 0 B 1 1 0 1 1 0 1 0
$\lvert A\rvert$	number of bits set "on" in fingerprint A	
$\lvert B\rvert$	number of bits set "on" in fingerprint B	

Formula:

$$Sim_{Euclid}(A,B) = \sqrt{\frac{bothAB+neitherAB}{onlyA+onlyB+bothAB+neitherAB}}$$

Range:

$$[0.0 - 1.0]$$

Example:

A 1 0 1 1 1 0 0 0
B 1 1 0 1 1 0 1 0

$$\sqrt{\frac{bothAB+neitherAB}{onlyA+onlyB+bothAB+neitherAB}} = \sqrt{\frac{3+1}{1+2+3+1}} = \sqrt{\frac{4}{8}} = 0.707$$

	Coefficient	Symbol	Equation	Limits
1	Squared Correlation Coefficient	R^2 or r^2	$r^2 = 1 - \frac{\sum_{i=1}^{N}(Y_{exp,i}-Y_{calc,i})^2}{\sum_{i=1}^{N}(Y_{exp,i}-\bar{Y})^2}$	$0 \le r^2 \le 1$
2	Cross-Validated R^2	Q^2 or q^2	$q^2 = 1 - \frac{\sum_{i=1}^{N}(Y_{exp,i}-Y_{pred,i})^2}{\sum_{i=1}^{N}(Y_{exp,i}-\bar{Y})^2}$	$\infty \le q^2 \le r^2$ or 1
3	Y-scrambling	r^2_{ys} and q^2_{ys}		$r^2_{ys} \le r^2$ $q^2_{ys} \le q^2$
4	Prediction Error	SDEP	$SDEP = \sqrt{\frac{\sum_{i=1}^{N}(Y_{exp,i}-Y_{pred,i})^2}{N}}$	As low as possible

Formula:

$$Sim_{Tanimoto}(A,B) = \frac{bothAB}{|A|+|B|-bothAB} = \frac{bothAB}{onlyA+onlyB+bothAB}$$

Range:

$$[0.0 - 1.0]$$

Example:

A	1	0	1	1	1	0	0	0
B	1	1	0	1	1	0	1	0

$$\frac{bothAB}{onlyA+onlyB+bothAB} = \frac{3}{1+2+3} = \frac{3}{6} = 0.5$$

Test Questions:
2020

May 2021
1) smiles ⇔ structures
2) Hit to lead definitions and criteria
3) SAM structure and it's interaction (example with drug)
4) pharmacophore definition and draw pharmacophore from example ligands
5)
   a) calculated parameters needed for QSAR
   b) calculated parameters can be used for QSAR
   c) calculated parameters are used for QSAR

June 2021
1 smiles
2 lempke rules
3 transition analogues example with proteases
4 UDPGA and example
5 List of all the SBDD techniques

During his exam he might ask for an example of metabolism of one drug, it's important to know one of these pathways really well. Or give me an example of toxification coming from metabolites or the environment. Or give me an example of any drug that could be transformed by PAPs, and we would need to suggest why a drug would be metabolized in a way. Or what is a drug that can undergo a glutathione transformation.

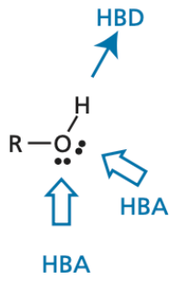
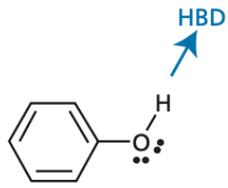
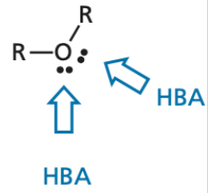
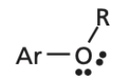
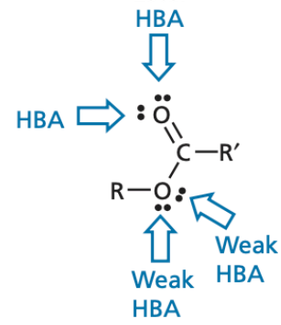
We need to learn an example really well for the exam of isosterism. The question could be: give me a compound and its isostere.

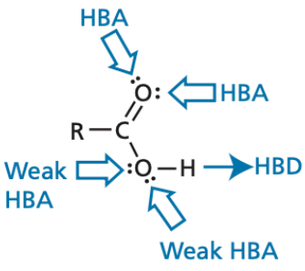
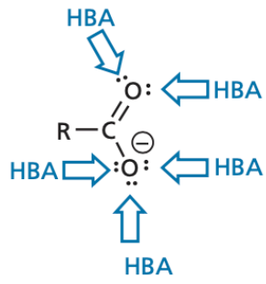
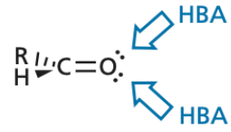
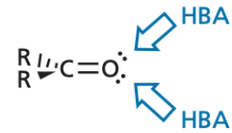
Scritto:

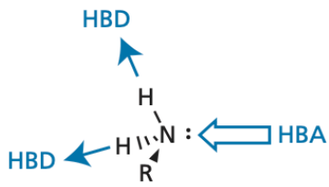
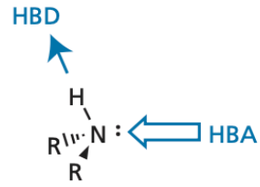
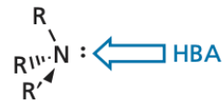
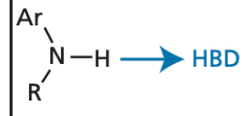
- Choose a drug, drow it on marvin sketch and write down its SMILE. Indicate lipinki's parameters.
- Choose two drugs and parameters to calculate timoto similarity
- Equation of q2 and its role in 3dQSAR
- Grimms law application
- Gluthathione structure and mechanism of action in detoxification.
- list receptor molecules (drug targets)
- steps of drug discovery
- suicide substrates and inhibitors
- y scrambling
- henderson-hesselbach equation, importance and meaning
- similarities enumeration

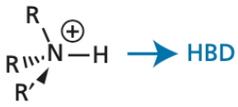
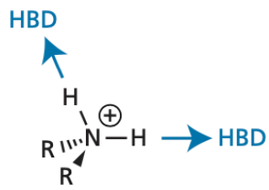
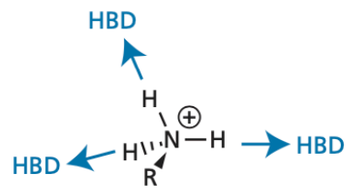
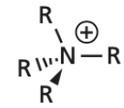
Orale

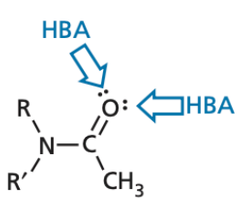
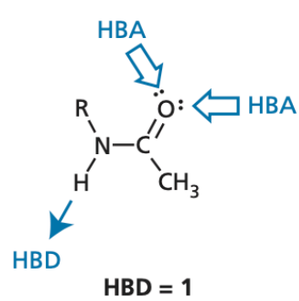
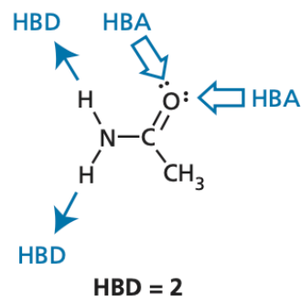
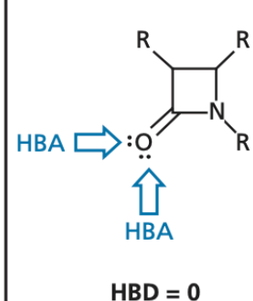
- scritto correzione
- q^2
- UDPGA (structure and example)
- docking
- phase1 and phase2

Alcohol	Phenol	Ether	Aromatic ether	Ester
				
HBD = 1 HBA = 1	HBD = 1 HBA = 0	HBD = 0 HBA = 1	HBD = 0 HBA = 0	HBD = 0 HBA = 1

Carboxylic acid	Carboxylate ion	Aldehyde	Ketone
			
HBD = 1 HBA = 1	HBD = 0 HBA = 2	HBD = 0 HBA = 1	HBD = 0 HBA = 1

Primary amine	Secondary amine	Tertiary amine	Aromatic 2° amine
			
HBD = 2 HBA = 1	HBD = 1 HBA = 1	HBD = 0 HBA = 1	HBD = 1 HBA = 0

Aminium ions			Quaternary ammonium ion
			
HBD = 1 HBA = 0	HBD = 2 HBA = 0	HBD = 3 HBA = 0	HBD = 0 HBA = 0

Primary amide	Secondary amide	Tertiary amide	β-Lactam
			
HBD = 0 HBA = 1	HBD = 1 HBA = 1	HBD = 2 HBA = 1	HBD = 0 HBA = 1