Isosterism

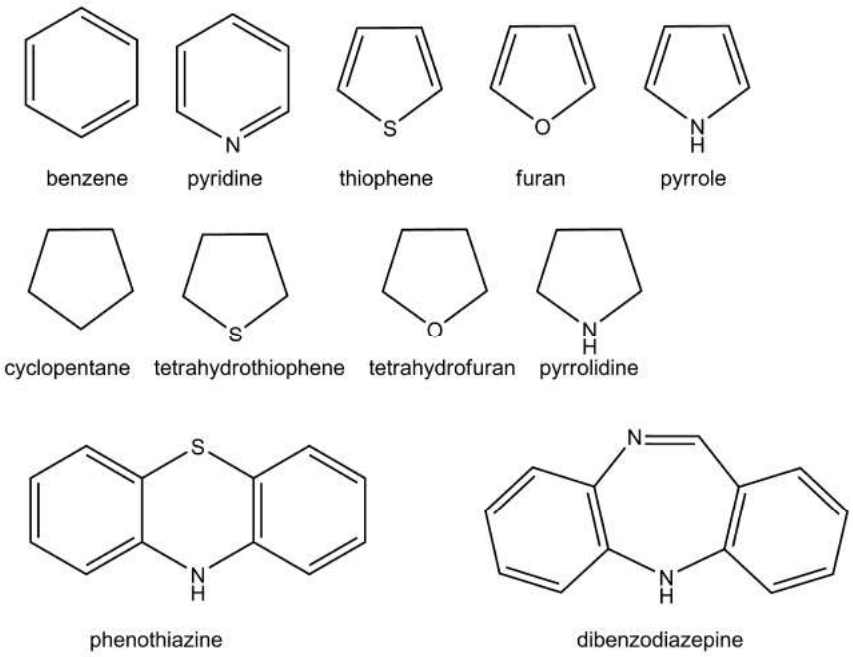
In the process of designing new pharmacologically active compounds, it is important to not restrict the definition of the structures to specific atoms. An important concept is ***isosterism***, a term that has been used widely to describe the selection of structural components—the steric, electronic, and solubility characteristics that make them interchangeable in drugs of the same pharmacological class.

Isosteres are compounds or groups of atoms having the same number and arrangement of electrons. Isosteres that were isoelectric (i.e., with the same total charge as well as the

same number of electrons) would possess similar physical properties. For example, the molecules N_2 and CO both possess 14 total electrons and no charge and show similar physical properties. Related examples were CO_2, N_2O, N_3^-, and NCO^- (Table below).

Groups of atoms that impart similar physical or chemical properties to a molecule because of similarities in size, electronegativity, or stereochemistry are now frequently referred to by the general term of *isostere*.

Commonly Used Alicyclic Chemical Isosteres					
A. Univalent atoms and groups					
(1)	$-CH_3$	$-NH_2$	—OH	—F	—Cl
(2)	—Cl	—SH			
(3)	—Br	—*i*—Pr			
B. Bivalent atoms and groups					
(1)	$-CH_2-$	—NH—	—O—	—S—	
(2)	$-COCH_2R$	—CONHR			
(3)	$-CO_2R$	—COSR			
C. Trivalent atoms and groups					
(1)	—CH═	—N═			



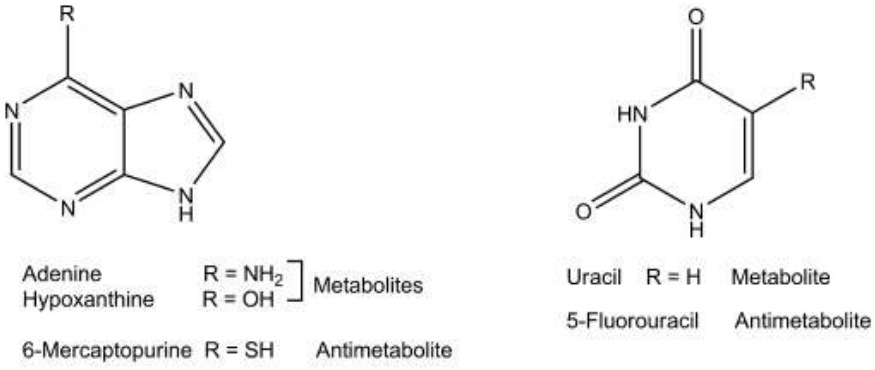
Examples of isosteric ring systems

Examples of isosteric pairs that possess similar steric and electronic configurations are the carboxylate (COO^-) and sulfonamide ($SO_2NR\_$) ions; ketone (C=O) and sulfone (O=S=O); chloride (Cl^-) and trifluoromethyl (CF_3); hydrogen (-H) and fluorine (-F); hydroxy (-OH) and amine ($-NH_2$); hydroxy (-OH) and thiol (-SH). Divalent ether (-O-), sulfide (-S-), amine (-NH-), and methylene ($-CH_2-$) groups, although dissimilar electronically, they are sufficiently alike in their steric nature to be frequently interchangeable in designing new drugs. Compounds may be altered by isosteric replacements of atoms or groups, to develop analogs with select biological effects or to act as antagonists to normal metabolites, but there are no general rules that predict whether biological activity will be increased or decreased.

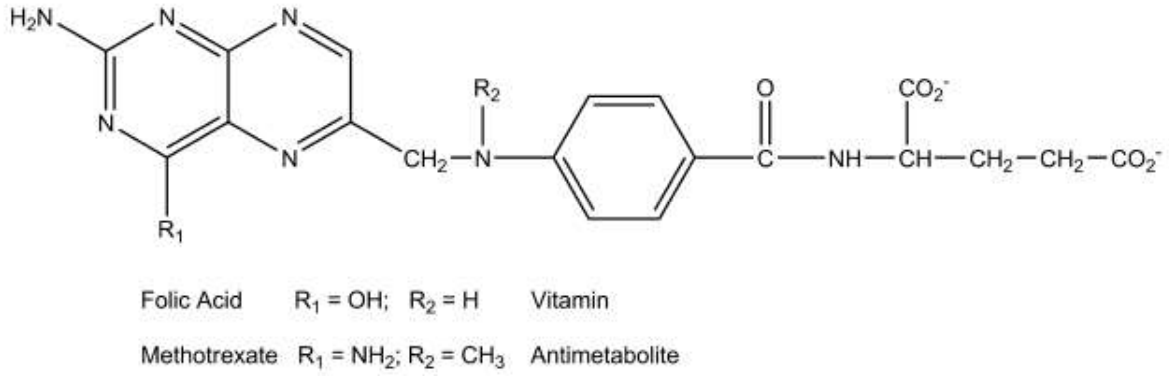
When a group is present in a part of a molecule in which it may be involved in an essential interaction or may influence the reactions of neighboring groups, isosteric replacement sometimes produces analogs that act as antagonists. The 6-NH_2 and 6-OH

groups appear to play essential roles in the hydrogen-bonding interactions of base pairs during nucleic acid replication in cells (Fig. below).

Adenine, **hypoxanthine** and the **antineoplastic 6-mercaptopurine** illustrate how substitution of the significantly weaker hydrogen-bonding isosteric sulfhydryl groups results in a partial blockage of this interaction and a decrease in the rate of cellular synthesis. Similarly, replacement of the hydroxyl group of pteroylglutamic acid (**folic acid**) by the isosteric amino group and addition of the methyl group to the *p*-aminobenzoate leads to the widely used **methotrexate**, a folate antimetabolite. Replacement of the hydrogen at the 5-position of **uracil** with the isosteric fluorine producing **5-fluorouracil** blocks the methylation step leading to thymine.



Examples of how isosterism produces drugs that inhibit the activity of the native metabolite



Examples of how isosterism produces drugs that inhibit the activity of the native metabolite

As a better understanding of the nature of the interactions between drug-metabolizing enzymes and biological receptors develops, selection of isosteric groups with particular electronic, solubility, and steric properties should permit the rational preparation of drugs that act more selectively. At the same time, results obtained by the systematic application of the principles of isosteric replacement are aiding in the understanding of the nature of these receptors.

METABOLIC CHANGES OF DRUGS AND RELATED ORGANIC COMPOUNDS

Metabolism plays a central role in the elimination of drugs and other foreign compounds (*xenobiotics*) from the body.

Most organic compounds entering the body are relatively lipid soluble (*lipophilic*). To be absorbed, they must traverse the lipoprotein membranes of the lumen walls of the gastrointestinal (GI) tract. Then, once in the bloodstream, these molecules can diffuse passively through other membranes and be distributed effectively to reach various target organs to exert their pharmacological actions.

Because of reabsorption in the renal tubules, lipophilic compounds are not excreted to any substantial extent in the urine. Xenobiotics then meet their metabolic fate through various enzyme systems that change the parent compound to render it more water soluble (*hydrophilic*). Once the metabolite is sufficiently water soluble, it may be excreted from the body.

If lipophilic drugs, or xenobiotics, were not metabolized to polar, readily excretable water-soluble products, they would remain indefinitely in the body, eliciting their biological effects. Thus, the formation of water-soluble metabolites not only enhances drug elimination, but also leads to compounds that are generally pharmacologically inactive and relatively nontoxic.

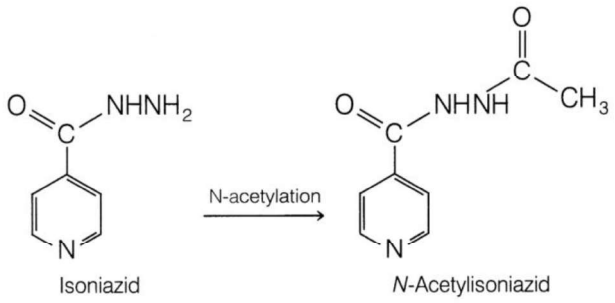
Detoxication (or *detoxification*) processes is regarded as drug metabolism reactions. It is incorrect to assume that drug metabolism reactions are always detoxifying since many drugs are biotransformed to pharmacologically active metabolites, and these metabolites may have significant pharmacological or toxicological effect(s) attributed to the parent

drug, whereas other parent compound is inactive when administered and must be metabolically converted to a biologically active drug (metabolite). These types of compounds are referred to as *prodrugs*.

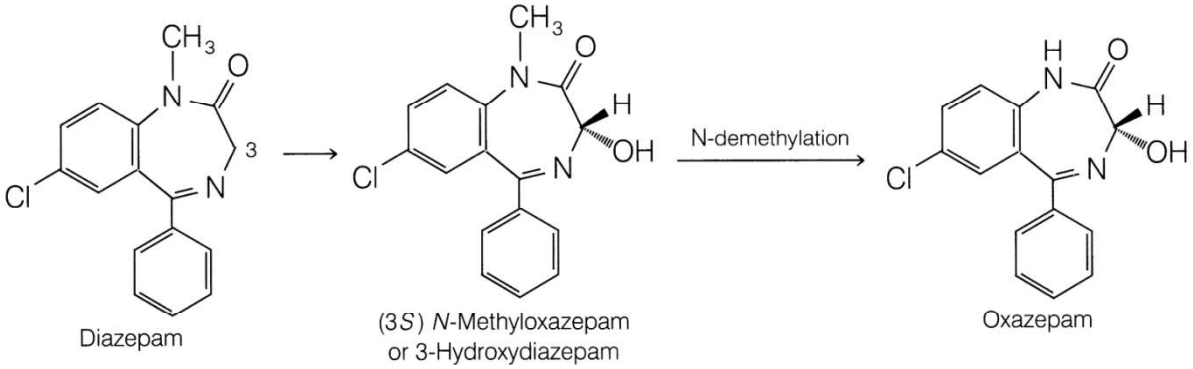
Indeed, many adverse effects (e.g., tissue necrosis, carcinogenicity, teratogenicity) of drugs and environmental contaminants can be attributed directly to the formation of chemically reactive metabolites that are highly detrimental to the body. This concept is more important when the patient has a disease state that inhibits or accelerates xenobiotic metabolism.

Purposes of metabolism in regarding to drug molecule

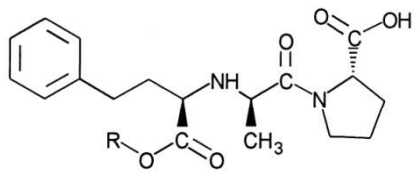
1. Inactivation of drug: example isoniazide used as antituberculosis can be inactivated by acetylation, by addition of acetyl derivation to produce inactive compound.



2. Maintain or enhance of drug activity: example diazepam this drug is active undergo several steps of metabolism, like demethylation of amine and hydroxylation of third position of the compound convert it from active compound to more active form.



3. Initiate activity of some drugs: when drug taken is inactive, but is activated inside the body called (prodrug). Example enalapril. It is taken in ester form, when reached to liver, deesterification occurs, turning it to active form.



Enalapril: R = C_2H_5
Enalaprilic Acid: R = H

General Pathways of drug metabolism:

Drug metabolism reactions have been divided into two categories: phase I (*functionalization*) and phase II (*conjugation*) reactions.

1. Phase I, or functionalization reactions,:

include oxidative, reductive, and hydrolytic biotransformations (Table 3.1). The purpose of these reactions is to introduce a functional polar group(s) (e.g., OH, COOH, NH_2, SH) into the xenobiotic molecule to produce a more water-soluble compound. This can be achieved by

a. direct introduction of the functional group (e.g., aromatic and aliphatic hydroxylation)
b. By modifying or "unmasking" existing functionalities e.g.
    1. reduction of ketones and aldehydes to alcohols;
    2. oxidation of alcohols to acids;
    3. hydrolysis of ester and amides to yield COOH, NH_2, and OH groups;
    4. reduction of azo and nitro compounds to give NH_2 moieties;
    5. oxidative *N*-, *O*-, and *S*-dealkylation to give NH2, OH, and SH groups.

Although phase I reactions may not produce sufficiently hydrophilic or inactive metabolites, they generally tend to provide a functional group that can undergo subsequent phase II reactions.

2. phase II reactions:

The purpose of phase II reactions is to form water-soluble conjugated products by attaching small, polar, and ionizable endogenous compounds such as **glucuronic acid**, **sulfate**, **glycine**, and other amino acids to the functional groups of phase I metabolites or parent compounds that

already have suitable existing functional groups. Conjugated metabolites are readily excreted in the urine and are generally devoid of pharmacological activity and toxicity in humans.

Other phase II pathways, such as **methylation** and **acetylation**, terminate or attenuate biological activity, whereas **glutathione** (GSH) conjugation protects the body against chemically reactive compounds or metabolites. Thus, phase I and phase II reactions complement one another in detoxifying, and facilitating the elimination of, drugs and xenobiotics.

General Summary of Phase I and Phase II Metabolic Pathways

Phase I or Functionalization Reactions

Oxidative Reactions
Oxidation of aromatic moieties
Oxidation of olefins
Oxidation at benzylic, allylic carbon atoms, and carbon atoms α to carbonyl and imines
Oxidation at aliphatic and alicyclic carbon atoms
Oxidation involving carbon–heteroatom systems:
- Carbon–nitrogen systems (aliphatic and aromatic amines; includes *N*-dealkylation, oxidative deamination, *N*-oxide formation, *N*-hydroxylation)
- Carbon–oxygen systems (*O*-dealkylation)
- Carbon–sulfur systems (*S*-dealkylation, *S*-oxidation, and desulfuration)

Oxidation of alcohols and aldehydes
Other miscellaneous oxidative reactions

Reductive Reactions
Reduction of aldehydes and ketones
Reduction of nitro and azo compounds
Miscellaneous reductive reactions

Hydrolytic Reactions
Hydrolysis of esters and amides
Hydration of epoxides and arene oxides by epoxide hydrase

Phase II or Conjugation Reactions

Glucuronic acid conjugation
Sulfate conjugation
Conjugation with glycine, glutamine, and other amino acids
Glutathione or mercapturic acid conjugation
Acetylation
Methylation

Sites of Drug Biotransformation:

Liver is the most important organ in drug metabolism and detoxification of endogenous and exogenous compounds. Liver, a well-perfused organ, is particularly rich in almost all of the drug-metabolizing enzymes. Orally administered drugs that are absorbed into the bloodstream through the GI tract must pass through the liver before being further distributed into body compartments.

Therefore, they are susceptible to hepatic metabolism known as the ***first-pass effect*** before reaching the systemic circulation. Depending on the drug, this metabolism can sometimes be quite significant and results in decreased oral bioavailability. For example, in humans, several drugs are metabolized extensively by the first-pass effect. Some of those drugs are:

Isoproterenol, **Morphine**, **Propoxyphene**, **Lidocaine (**not effective orally**)**, **Nitroglycerin (**given bucally or sublingually**)**, **Propranolol**, **Meperidine**, **Pentazocine**, and **Salicylamide**.

Another important site, especially for orally administered drugs, is the **intestinal mucosa**. Intestinal mucosa contains the CYP3A4 isozyme and P-glycoprotein that can capture the drug and secrete it back into the **intestinal tract**.

- For example, in humans, orally administered **isoproterenol** undergoes considerable sulfate conjugation in the intestinal wall. Several other drugs (e.g., **levodopa**, **chlorpromazine**, and **diethylstilbestrol**) are also metabolized in the GI tract.
- **Esterases** and **lipases** present in the intestine may be particularly important in carrying out hydrolysis of many ester prodrugs.
- Bacterial flora present in the intestine and colon appear to play an important role in the reduction of many aromatic azo and nitro drugs (e.g., sulfasalazine).
- Intestinal-glucuronidase enzymes can hydrolyze glucuronide conjugates excreted in the bile, thereby liberating the free drug or its metabolite for possible reabsorption (enterohepatic circulation or recycling).

  Although other tissues, such as **kidney**, **lungs**, **adrenal glands**, placenta, **brain**, and **skin**, have some drug metabolizing capability, the biotransformations that they carry out are often more substrate selective and more limited to particular types of reaction (e.g., oxidation and glucuronidation).