ISOSTERISM, BIOISOSTERISM, TARGET, LIGAND, RECEPTOR CONCEPTS, TRANSPORT SYSTEMS

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MOLECULAR MODIFICATION

Molecular modification is chemical alteration of a known and previously characterized **lead compound** for the purpose of enhancing its usefulness as a **drug**.

This could mean enhancing its specificity for a particular body target site, increasing its **potency,** improving its rate and extent of **absorption**, modifying to advantage its time course in the body, reducing its **toxicity,** changing its **physical** or **chemical properties (like solubility)** to provide desired features.

ISOSTERES

Isosteres are molecules or ions with the similar shape and often electronic properties.

It is usually employed in the context of bioactivity and drug development.

Such biologically-active compounds containing an isostere is called a bioisostere.

BIOISOSTERISM

In medicinal chemistry, bioisosteres are chemical substituents or groups with similar physical or chemical properties which produce broadly similar biological properties to another chemical compound.

In drug design, the purpose of exchanging one bioisostere for another is to enhance the desired biological or physical properties of a compound without making significant changes in chemical structure.

The study of bioisosters in medicinal chemistry is called as bioisosterism.

Bioisosterism is used to reduce toxicity, change bioavailability, or modify the activity of the lead compound, and may alter the metabolism of the lead.

In 1970, Alfred Burger classified and subdivided bioisoteres into two broad categories:

1. Classic Bioisoteres

1. Non Classic Bioisoteres


Dr.Alferrd Burger

Classical bioisosteres


Langnmuir

Classical bioisosterism was originally formulated by James Moir and refined by Irving Langmuir as a response to the observation that different atoms with the same valence electron structure had similar biological properties.

They have similarities in shape and electron configuration which they replace.

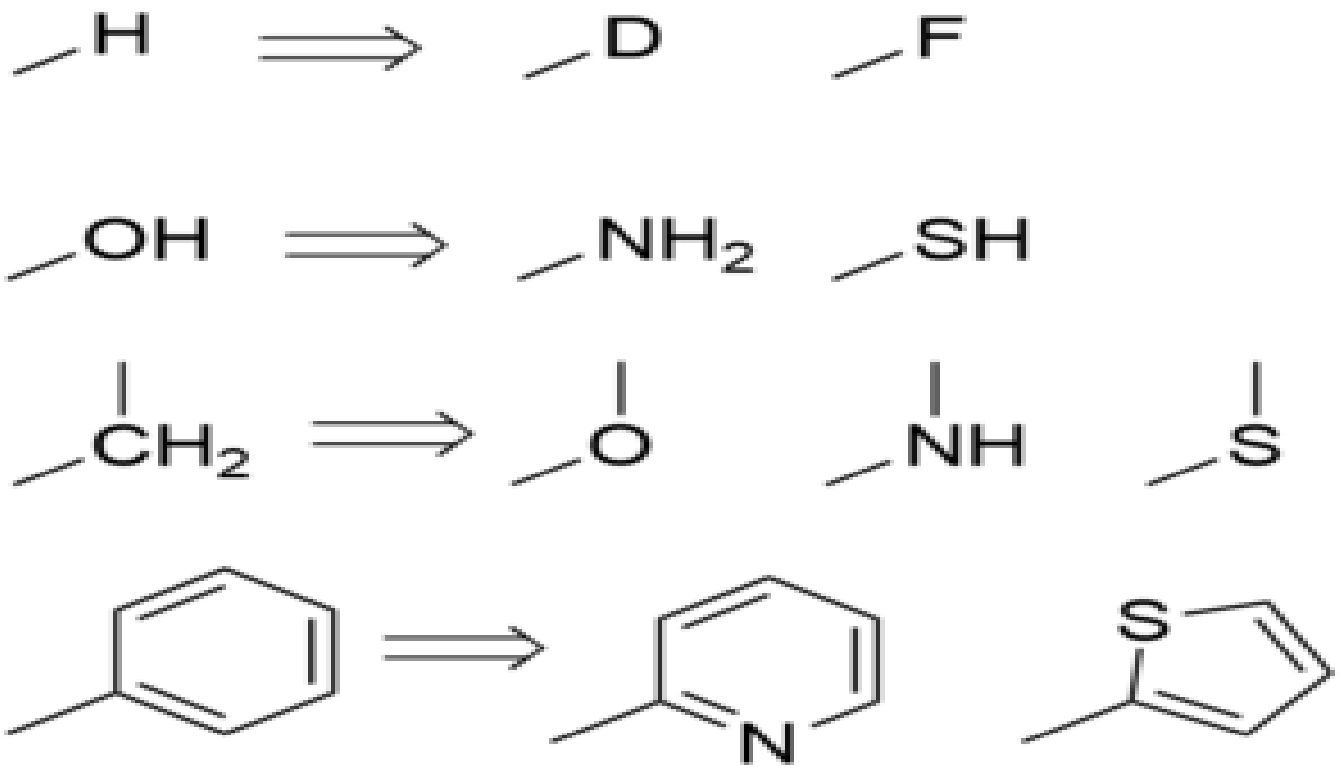
For example, the replacement of a hydrogen atom with a fluorine atom at a site of metabolic oxidation in a drug candidate may prevent such metabolism from taking place. Because the fluorine atom is similar in size to the hydrogen atom the overall topology of the molecule is not significantly affected, leaving the desired biological activity unaffected.

However, with a blocked pathway for metabolism, the drug candidate may have a longer half-life.

Procainamide, an **amide**, has a longer duration of action than **Procaine**, an **ester**, because of the isosteric replacement of the ester **oxygen** with a **nitrogen** atom.

Procainamide is a classical bioisostere because the valence electron structure of a disubstituted oxygen atom is the same as a trisubstituted nitrogen atom, as Langmuir showed.

Classical bioisosteres



Classic Bioisosteres

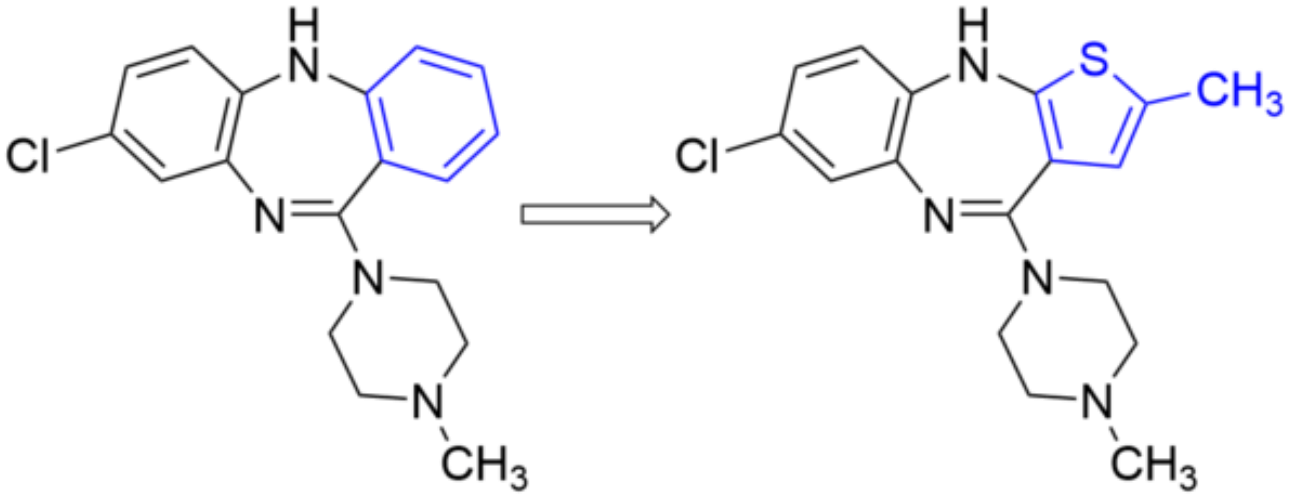
1. Monovalent atoms or groups: -OH, -NH_2, -CH_3, -OR
   -F -Cl, -Br, - I, -SH,
   -Si_3, -SR

2. Divalent atoms or groups: -CH_2-, -O-, -S-, -Se-, -Te-

3. Trivalent atoms or groups: =CH-, =N-, =P-, =As-, =Sb

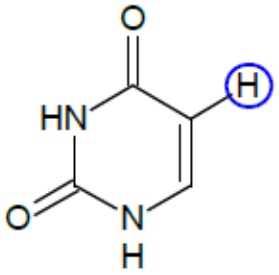
4. Tetrasubstituted atoms: =C=, =Si=, =N^+=, =P^+=, =As^+=, =Sb^+=

5. Ring equivalents: benzene and thiophene,
   benzisoxazole rings and the indole nucleus

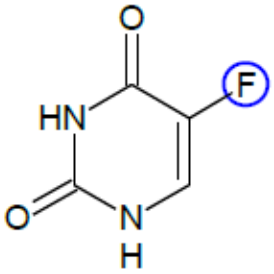


Benzene ring → **Thiophene ring**

1. Monovalent bioisosters

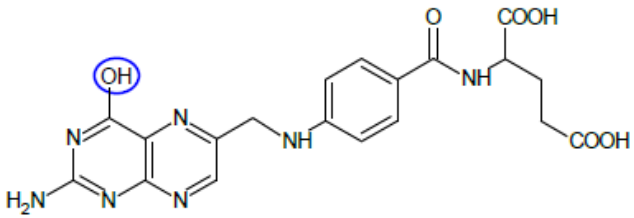


Uracil

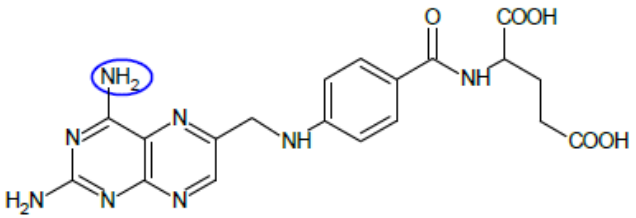


5-fluorouracil

- Replacement of monovalent –H atom in uracil by monovalent –F atom results in anticancer drug 5-fluorouracil, which is uracil antagonist.



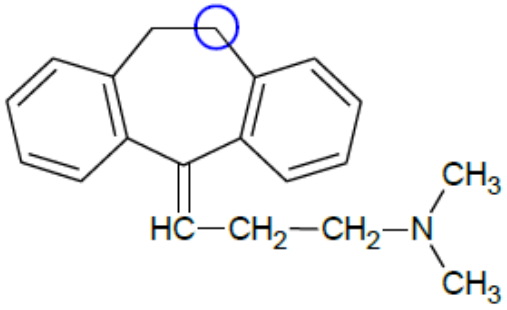
Folic acid



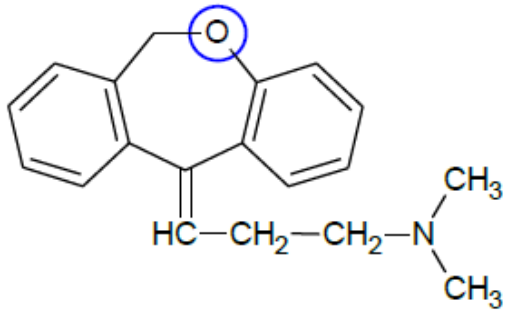
Aminopterine

- Replacement of monovalent –OH group in folic acid by monovalent –NH_2 group results in anticancer drug aminopterine, which is folic acid antagonist.

2. Divalent bioisosters



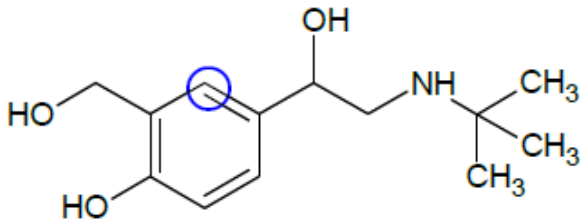
Amitriptyline



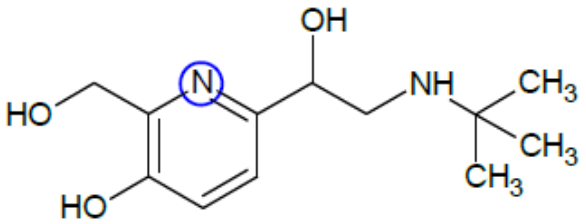
Doxepine

- Replacement of divalent -CH_2- group in antidepressant drug amitriptyline by divalent -O- atom results in doxepine, which is also having antidepressant activity.

3. Trivalent bioisosters



Albuterol (Salbutamol)



Pirbuterol

- Replacement of trivalent group –CH= in β_2-agonist albuterol by trivalent atom –N= results in pirbuterol, which is also having β_2-agonistic activity.

Non-classical bioisosteres

1. Cyclic vs Noncyclic

2. Functional groups

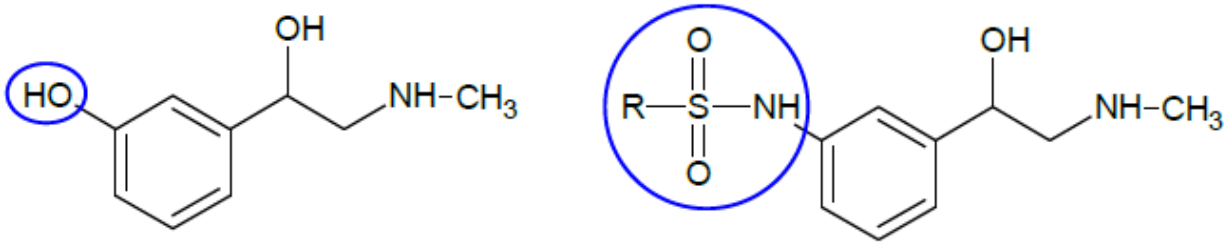
Non-classical bioisosteres may differ in a multitude of ways from classical bioisosteres, but retain the focus on providing similar **sterics** and **electronic** profile to the original functional group.

Whereas classical bioisosteres commonly conserve much of the **same structural properties**, non-classical bioisosteres **are much more dependent on the specific binding needs of the ligand** in question and may substitute a linear functional group for a cyclic moiety, an alkyl group for a complex heteroatom moiety, or other changes that go far beyond a simple atom-for-atom switch.

For example, a chlorine -Cl group may often be replaced by a trifluoromethyl -CF_3 group, or by a cyano -C≡N group, but depending on the particular molecule used the substitution may result in little change in activity,

or either increase or decrease affinity or efficacy depending on what factors are important for ligand binding to the target protein.

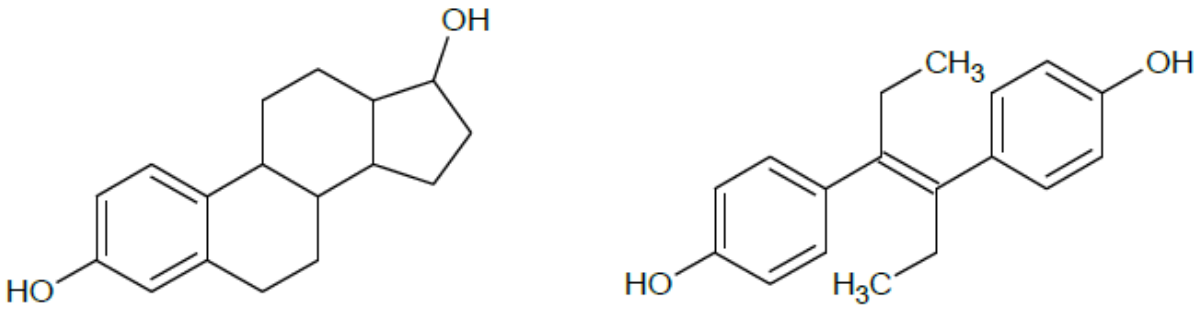
1. Exchangeable groups



Phenylephrine

The phenolic –OH group in phenylephrine may be replaced by alkylsulfonamido group. Some of the resulting compounds are agonists whereas, others are antagonists.

2. Cyclic and noncyclic structures



Estradiol **Diethylstilbesterol**

Estradiol is cyclic structure, while diethylstilbesterol is noncyclic structure. Both have estrogenic activity. Thus they are bioisosters.

What is Receptor?

A receptor is a biological molecule that yield a biological response upon interaction with a drug molecule

Biological response is produced by the interaction of a drug with a functional or organized group of molecules, which may be called the biologic receptor site.

Ligand ;

A (usually small) molecule that binds to a biological macromolecule

Enzyme;

An endogenous biocatalyst that can transform one or more substrates into one or more products

Substrate;

A ligand that is a starting material for an enzymatic reaction

Inhibitor;

A ligand that prevents the binding of a substrate either directly (competitive) or indirectly (allosteric), reversibly or irreversibly

How Binding Takes Place

- Binding occur through points of attachment, for a chemical compound they are the functional groups.
- Functional groups use their electronic & shape characters in the binding process.
- Bonds could be inter-molecular or intra-molecular.
- If we talk about reversible binding, binding of drug to receptor should be in equilibrium state.

Receptor-drug interaction

- Receptors are mostly membrane-bound proteins that selectively bind small molecules called ligands which results in physiological response.

- They are difficult to isolate because they exist in tiny amount and if isolated it will be difficult to purify.

Receptor-drug interaction

- The driving force for drug-receptor interaction is the low energy state of the drug-receptor complex.
- The biological activity is related to the drug affinity for the receptor, i.e the stability of the complex.
- Dissociation constant of the drug-receptor complex gives an idea a bout how potent is the drug

Classes of Receptors

- Lipoproteins or Glycoproteins
- Enzymes
- Nucleic Acids
- Lipids

Drug Transport (Diffusion) Systems

- Active Transpot
- Passive Transport
- Facilitated Diffusion
- Pinocytosis

Active transport

Active transport is the movement of molecules across a membrane from their lower concentration to higher concentration.

Unlike passive transport, which uses the kinetic energy and natural entropy of molecules moving down a gradient, active transport uses cellular energy to move them against a gradient, polar repulsion, or other resistance.

Passive transport

Passive transport is a movement of ions and other molecular substances across cell membranes without need of energy input.

Unlike active transport, it does not require an input of cellular energy. The rate of passive transport depends on the permeability of the cell membrane, which, in turn, depends on the organization and characteristics of the membrane lipids and proteins.

Facilitated Diffusion

Facilitated diffusion, also called carrier-mediated osmosis, is the movement of molecules across the cell membrane via special transport proteins that are embedded within the cellular membrane.

Large, insoluble molecules, such as glucose, vesicles and proteins require a carrier molecule to move through the plasma membrane.

Therefore, it will bind with its specific carrier proteins, and the complex will then be bonded to a receptor site and moved through the cellular membrane.

Facilitated diffusion is a passive process: the solutes move down their concentration gradient and do not require the expenditure of cellular energy for this process.

Pinocytosis

Pinocytosis is a mode of **endocytosis** in which small particles are brought out to the mitochondria and then expelled from the cell, forming an **invagination**, and then suspended within a small **vesicle**.

These pinocytotic vesicles subsequently fuse with **lysosomes to hydrolyze** (break down) the particles. This process requires energy in the form of **adenosine triphosphate** (ATP), the chemical compound mostly used as energy in the majority of animal cells.