LIMU

كلية الصيدلة
Faculty of Pharmacy

Pharmacophore and Bioisosteres

Presented by:

Khaled tajory
Hajer Farhate
Sondos Mohamed
2nd year PharmD students

Objectives

1 . Define pharmacophore.

2 . List pharmacophore types of functional groups.

3 . Describe pharmacophore modeling.

4 . Define bioisosteres.

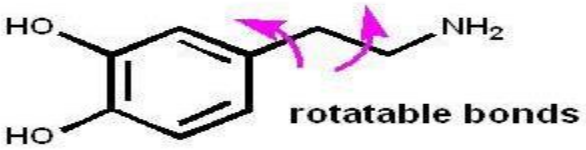
5 . Classify bioisosteres.

6 . Describe why bioisosteres are replaced.

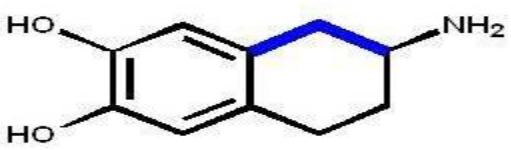

Pharmacophore

Definition of Pharmacophore

Is the region of the molecule containing the essential organic functional groups that directly interact with the receptor active site and, therefore, confers the biologic activity of interest.



Dopamine

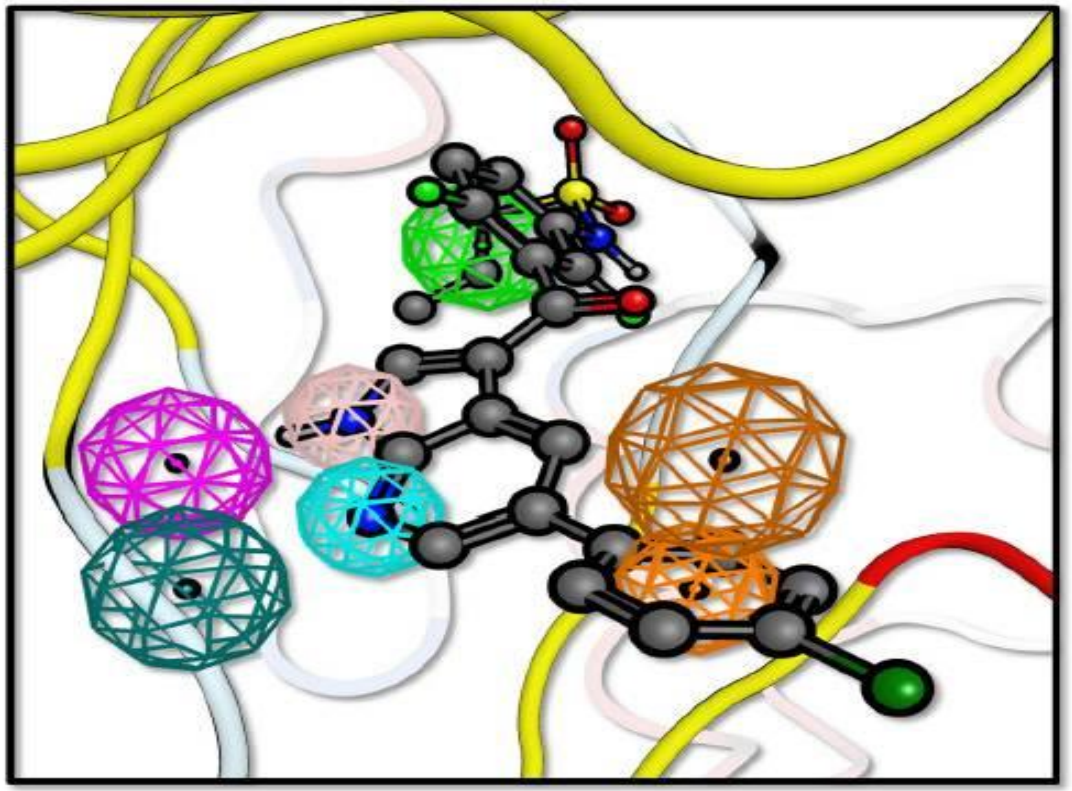


I

II

Locked bonds

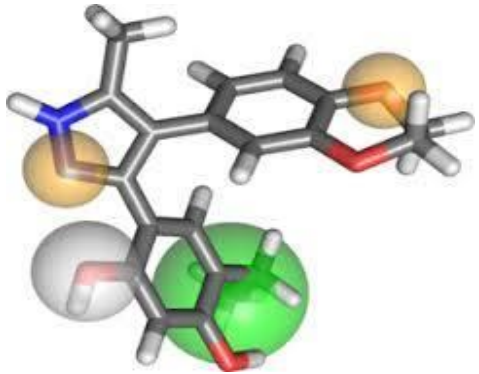
Pharmacophore Types of Functional Groups



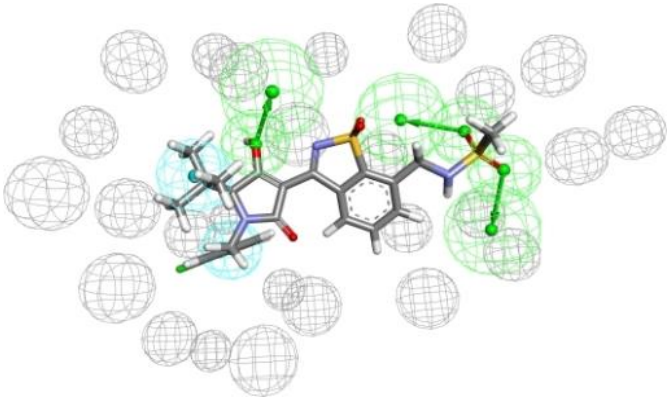
Pharmacophore Modeling

Pharmacophore

Ligand Based



Structure Based



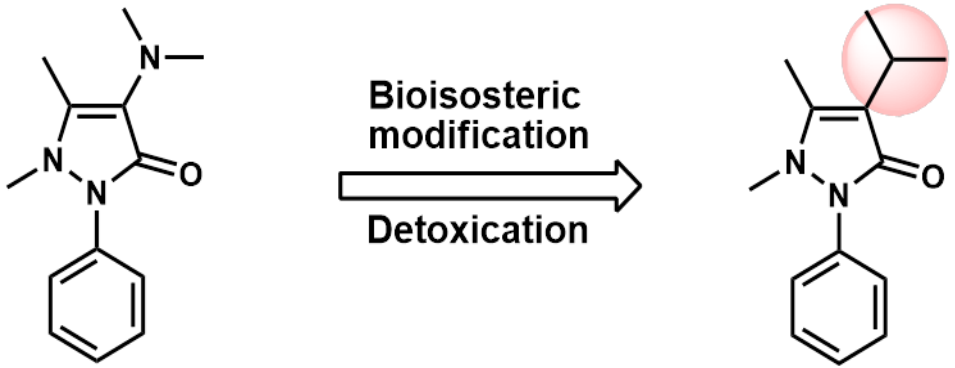
Pharmacophore Molecule Feature

- **3D: (Hydrophobic group, charged ionizable group, H donor or acceptor).**
- **2D: (Substructures).**
- **1D: (Physical or biological properties).**

Bioisosteres

Definition of Bioisosteres

Is the replacement or modification of specific pharmacophore (functional) groups with other groups having similar properties is known as "isosteric replacement" or "bioiosteric replacement."



Aminopyrine **Propylphenazone**

Classification

Classical Bioisosteres

Classical bioisosteres represent the result of a nearly appreciation of the concept and encompass structurally simple atoms or groups.

Monovalent bioisosteres

F, H

OH, NH_2

F, OH, NH_2 or CH_3 for H

SH, OH

Cl, Br, CF_3

Divalent bioisosteres:

—C=S, —C=O, —C=NH, —C=C—

Trivalent atoms or groups:

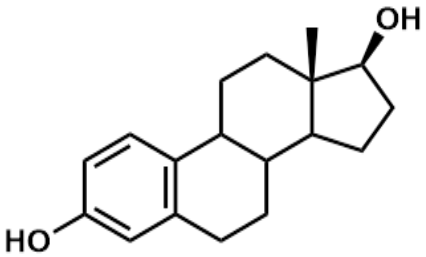
Tetrasubstituted atoms:

Ring equivalents:

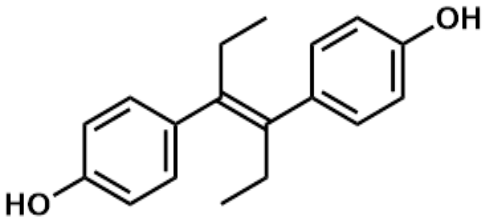
Non-Classical Bioisosteres

Non classical bioisosteres are structurally distinct, usually comprised of different number of atoms and exhibit different steric and electronic properties.

1) Cyclic and noncyclic isostere



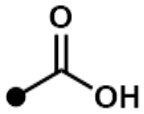
Estradiol

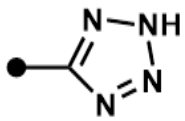


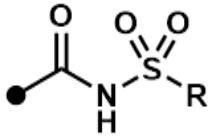
Diethylstilbestrol
(Artifical female hormone)

2) Exchangeable group

ex.) Carboxylic acid isosteres







Bioisosteres are replaced, Why ?!

Improved selectivity

Fewer side effect

Decreased toxicity

Improved pharmacokinetics

Increase stability

Patented lead compounds

All the bioisosteric not produce utilization biologic activity.

- True
- False

Summary

✓Pharmacophore : it is the group of atoms in the molecule of a drug responsible for the drug's action.

✓Ligand-based and structure-based methods have been developed for improving pharmacophore modeling .

✓bioisosterism" to describe functional groups related in structure that have similar biologic effects.

✓There are two general types of bioisosteres: classical and non- classical.

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

References

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Thank you..