Bioisosterism

Bioisosteres - substituents or groups with chemical or physical similarities that produce similar biological properties. Can attenuate toxicity, modify activity of lead, and/or alter pharmacokinetics of lead.
Bioisosterism allows modification of physicochemical parameters

Multiple alterations may be necessary:

If a bioisosteric modification for receptor binding decreases lipophilicity, you may have to modify a different part of the molecule with a lipophilic group.

Where on the molecule do you go to make the modification?
Classical Isosteres

1. Univalent atoms and groups
   a. CH₃, NH₂, OH, F, Cl
   b. Cl, PH₂, SH
   c. Br, i-Pr
   d. I, t-Bu

2. Bivalent atoms and groups
   a. \(-\text{CH}_2-\), \(-\text{NH}-\), \(-\text{O}-\), \(-\text{S}-\), \(-\text{Se}-\)
   b. \(-\text{COCH}_2R\), \(-\text{CONHR}\), \(-\text{CO}_2R\), \(-\text{COSR}\)

3. Trivalent atoms and groups
   a. \(-\text{CH}=\) \(-\text{N}=\)
   b. \(-\text{P}=\) \(-\text{As}=\)

4. Tetravalent atoms
   a. \(\text{C}=\) \(\text{Si}=\)
   b. \(\text{C}=\) \(\text{N}=\) \(\text{P}=\)

5. Ring equivalents
   a. \(-\text{CH}=\text{CH}-\) \(-\text{S}-\) (e.g., benzene, thiophene)
   b. \(-\text{CH}=\) \(-\text{N}=\) (e.g., benzene, pyridine)
   c. \(-\text{O}-\) \(-\text{S}-\) \(-\text{CH}_2-\) \(-\text{NH}-\) (e.g., tetrahydrofuran, tetrahydrothiophene, cyclopentane, pyrrolidine)
Non-Classical Isosteres

Do not have the same number of atoms and do not fit steric and electronic rules of classical isosteres, but have similar biological activity.
4. Ester group

![Ester group diagram]

5. Hydroxyl group

![Hydroxyl group diagram]

6. Catechol

![Catechol diagram]

7. Halogen

![Halogen diagram]

8. Thioether

![Thioether diagram]

9. Thiourea

![Thiourea diagram]
10. Azomethine

\[ \text{N} \equiv \text{C} \]

11. Pyridine

\[
\begin{align*}
\text{N} & \quad \text{NO}_2 \\
\text{NR}_3 & \\
\text{N} & \\
\end{align*}
\]

12. Benzene

\[
\begin{align*}
\text{N} & \quad \text{O} & \quad \text{R} \\
\text{N} & \quad \text{O} & \quad \text{R} \\
\text{R} & \quad \text{N} & \quad \text{O} \\
\end{align*}
\]

13. Ring equivalents

\[
\begin{align*}
\text{N} & \quad \text{O} & \quad \text{R'} & \quad \text{R} \\
\text{N} & \quad \text{O} & \quad \text{R} & \quad \text{R'} & \quad \text{O} \\
\text{R} & \quad \text{N} & \quad \text{O} & \quad \text{H} & \quad \text{R} \\
\text{R} & \quad \text{N} & \quad \text{O} & \quad \text{H}_3 & \quad \\
\text{R} & \quad \text{N} & \quad \text{O} & \quad \text{NH} & \quad \text{NH}_2 \\
\end{align*}
\]

14. Spacer group

\[ \text{(CH}_2)_3 \]

15. Hydrogen

\[ \text{H} \quad \text{F} \]
Examples of Bioisosteric Analogues

**Neuroleptics (antipsychotics)**

\[ \text{N} \text{(CH2)3-} X - \text{Ph} \text{R} \]

\[ X = \text{O} \text{ or CHCN} \]

**Anti-inflammation agents**

\[ \text{CH3O} - \text{Ph} - \text{Ph} \text{CO2H} \]

**Antihistamines**

\[ R - X - (\text{CH2})_n - Y \]

\[ X = \text{NH, O, CH2} \]

\[ Y = \text{N(CH3)2 (n = 2)} \]

\[ (n = 1) \]

\[ (n = 1, 2) \]

Diphenhydramine (Benadryl)

Fexofenadine (Allegra)
Changes resulting from bioisosteric replacements:

Effects of bioisosteric replacement:
Rational Drug Discovery
Structure-Activity Relationships (SARs)

1868 - Crum-Brown and Fraser

Examined neuromuscular blocking effects of a variety of simple quaternary ammonium salts to determine if the quaternary amine in curare was the cause for its muscle paralytic properties.

Conclusion: the physiological action is a function of chemical constitution
Structurally specific drugs (most drugs):

Structurally nonspecific drugs:
Example of SAR

\[
\begin{align*}
H_2N & - \text{SO}_2NHR \\
\text{sulfa drugs}
\end{align*}
\]

Lead: sulfanilamide (R = H)

Thousands of analogs synthesized

From clinical trials, various analogs shown to possess three different activities:

- Antimicrobial
- Diuretic
- Antidiabetic
SAR

General Structure of Antimicrobial Agents

\[
\text{NH}_2 - \text{R}
\]

\[ R = \text{SO}_2\text{NHR}' , \text{SO}_3\text{H} \]

- Groups must be *para*
- Must be \( \text{NH}_2 \) (or converted to \( \text{NH}_2 \) in vivo)
- Replacement of benzene ring or added substituents decreases or abolishes activity
- \( R \) can be \( \text{SO}_2\text{NH}_2 , \text{SO}\text{NH}_2 , \text{CONH}_2 , \text{R} \) (but potency is reduced)
- \( R = \text{SO}_2\text{NR}'_2 \) gives inactive compounds
Rational Drug Discovery - Piroxicam

• It took Pfizer ~18 years to develop the anti-inflammatory drug piroxicam, which was launched in 1980 during the “golden age of rational drug discovery”.

• The starting point for the development was chemistry-driven, i.e. to identify acidic, but not carboxylic acid-containing (salicylic acid) structurally novel compounds.

• Measurement of a physical property (pKa) as well as serum half-life in dogs was the guide for the synthesis program.

• Several generations of leads were refined and ultimately led to a successful structure with an acceptable safety and activity profile:
Structure-Based Design of Potent Non-Peptide MDM2 inhibitors

The pharmacological hypothesis:

The p53 tumor suppressor plays a central role in controlling cell cycle progression and apoptosis, and it is an attractive cancer therapeutic target because its stimulation kills tumor cells.

Its low intracellular concentration is maintained by MDM2-mediated ubiquitination and resulting proteolysis.

An approach toward stimulation of p53 activity would be to block its interaction with the MDM2 oncoprotein.

Ding et al. JACS 2005, 127, 10130.
Structure-Based Design: The p53-MDM2 interaction is primarily mediated by three hydrophobic residues of p53 and a small but deep hydrophobic cleft in MDM2. This cleft is ideal for the design of agents that block the p53-MDM2 interaction.

Trp23 appears to be buried most deeply in the hydrophobic cavity, and its NH group forms a hydrogen bond with a backbone carbonyl in MDM2. Indeed, imidazolines were previously reported to inhibit MDM2 ("Nutlins").

What other chemical moieties can mimic the indole ring?
Structure-Based Design of Potent Non-Peptide MDM2 inhibitors

Structure-Based Strategy:
1. The oxindole is a bioisostere of the indole.
2. Identify natural products that contain an oxindole substructure.

3. Although spirotryprostatin and alstonisine fit poorly into the MDM2 cavity, the spiro-oxindole-pyrrolidine core structure fit well.
4. Two additional hydrophobic groups are needed to mimic the side chains of Phe19 and Leu26. Candidates were evaluated by molecular modeling & docking.
Structure-Based Design of Potent Non-Peptide MDM2 inhibitors

Structure-Based Strategy:
1. The initial lead compound was synthesized by an asymmetric 1,3-dipolar cycloaddition.
2. Biological analyses vs a fluorescent-labeled p53-based peptide (K<sub>d</sub> 1 nM) provided a K<sub>d</sub> of 9 uM for the lead compound.
3. How could further optimization be performed?

4. Additional room in the MDM2 cavity could be exploited by larger hydrophobic groups (supported by modeling studies).
5. After several rounds of SAR, where the modeling was tested both by the synthesis of supposedly improved as well as inferior molecules, a new compound with K<sub>d</sub> 86 nM was identified.
Structure-Based Design of Potent Non-Peptide MDM2 inhibitors

**Structure-Based Strategy:**

1. Predicted binding model using computational docking for initial lead compound and for the optimized compound 1d.

   ![Structural images](image)

   - (A) Spiro-oxindole core structure
   - (B) Initial lead compound
   - Structure-based optimization

2. What are the potential issues with MDM2 inhibitors?
Structure-Based Design of Potent Non-Peptide MDM2 inhibitors

Structure-based selection of core structure

Spiro-oxindole core structure

Structure-based design of initial lead

Initial lead compound

Structure-based optimization

Potent inhibitor
Assigned Reading (i.e. your homework!):