Reviews
C. G. Wermuth, in The Practice of Medicinal Chemistry,

Definition of Isosterism

Langmuir (1919): Compounds or groups of atoms having the same number of atoms and electrons
Examples: N₂ and CO, N₂O and CO₂, N₃⁻ and NCO⁻

Grimm (1925): “Hydride Displacement Law” addition of hydride to an atom gives to the resulting pseudoatom the properties of the atom with the next highest atomic number.

<table>
<thead>
<tr>
<th>Hydride Displacement Law</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
</tr>
<tr>
<td>CH</td>
</tr>
<tr>
<td>CH₂</td>
</tr>
<tr>
<td>CH₃</td>
</tr>
<tr>
<td>CH₄</td>
</tr>
</tbody>
</table>

Erlenmeyer (1932): atoms, ions or molecules in which the peripheral layers of electrons can be considered identical.

Parameters affected with bioisosteric replacements
Size, conformation, inductive and mesomeric effects, polarizability, H-bond formation capacity, pKₐ, solubility, hydrophobicity, reactivity, stability.

Definition of Bioisosterism

Friedman (1951): Bioisosteres are atoms or molecules that fit the broadest definition for isosteres and have the same type of biological activity.

Thornber (1979): Groups or molecules which have chemical and physical similarities producing broadly similar biological effects.

Bioisosteric replacements: Why?
• Greater selectivity
• Less side effects
• Decreased toxicity
• Improved pharmacokinetics (solubility-hydrophobicity)
• Increased stability
• Simplified synthesis
• Patented lead compounds

Examples: atoms in the same column of the periodic table, Cl and CN and SCN (despite having different number of atoms)
**H to F replacement**

*Fluorine*: similar size with hydrogen  
most electronegative halogen  
C-F bond very stable

<table>
<thead>
<tr>
<th></th>
<th>H</th>
<th>F</th>
<th>Cl</th>
<th>CH₃</th>
<th>CF₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van der Waals radius</td>
<td>1.2</td>
<td>1.35</td>
<td>1.80</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Molecular Refractivity</td>
<td>1.03</td>
<td>0.92</td>
<td>6.03</td>
<td>5.65</td>
<td>5.02</td>
</tr>
<tr>
<td>Inductive effect</td>
<td>-</td>
<td>3.08</td>
<td>2.68</td>
<td>0.00</td>
<td>2.85</td>
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<tr>
<td>Resonance effect</td>
<td>0.00</td>
<td>-0.34</td>
<td>-0.15</td>
<td>-0.13</td>
<td>0.19</td>
</tr>
</tbody>
</table>

Ideal replacement to study the effect of electronegativity change without affecting steric requirements

F (or other halogens) can be placed on easily oxidized positions to increase stability during metabolic processes

Thus, F (or other halogens when size is not critical) are frequently placed on easily oxidized aromatics  
Methyl groups often substituted by CF₃
-OH to -NH₂ or -SH replacement
(also C=O to C=NH or C=S)

O and NH have similar sizes (but not SH)
All three bear H-bonding donor and acceptor capacities

Replacement of OH with NH₂ can stabilize a different tautomer,
especially in the case of heterocyclic systems

Halogen replacements
CN and CF₃ may be used as alternative electron-withdrawing groups instead of halogens.
The two groups have comparable effects on electronics, but CN will increase the overall hydrophilicity.

Ring replacements
Sulfonamide antibacterials: phenyl group may be replaced by many heterocyclic aromatics to give active compounds
**COOH replacements**

- Hydroxamic acid (strong chelating agents)
- Acylcyanamide (similar acidities)
- Sulfonimide
- Phosphonate (more acidic; ionized at physiological pH)
- Sulfonate
- Sulfonamide (less acidic)
- Tetrazole
- Hydroxyisoxazole
- Oxadiazolone

Carboxyl group may be replaced in order to alter acidity, or modify lipophilicity without affecting pKa.

Tetrazoles have comparable pK's with carboxylic acids, but greater lipophilicity.

**Peptide surrogates**

Peptides are characterized by diminished bioavailability when administered orally. Replacement of the sensitive amide bond by various groups can increase their stability.

- Ester
- N-alkylation
- Amide to double bond
- Thioamide
- Dehydroaminoacid
- Azapeptide

Losartan (antihypertensive)
Preparation of tetrazoles

\[ \text{R} = \text{N} \xrightarrow{\text{HN}_3, \text{base}, \Delta} \text{R} = \text{N} \]

\[ \text{Ph} = \text{N} \xrightarrow{\text{HCl}} \text{Ph} = \text{N} \]

\[ \text{Ph} = \text{N} \xrightarrow{\text{NaOH; HCl}} \text{Ph} = \text{N} \]

\[ \text{Ph} = \text{N} \xrightarrow{\text{EtO}} \text{Ph} = \text{N} \]

\[ \text{Ph} = \text{N} \xrightarrow{\text{MeCN, reflux}} \text{Ph} = \text{N} \]

\[ \text{Ph} = \text{N} \xrightarrow{\text{H}_2\text{O}} \text{Ph} = \text{N} \]

Tomudex analogues

Peptide (amide) replacements

Amide to hydroxyethyl

Amide to alpha-difluoroketone


Peptide (amide) replacements

**Amide to alkene**

1. CICO/Ent, NaBH₄
2. Bu₃P, (PhS)₂
3. MCPBA

1. LDA, ICH₂COO-i-Bu
2. LAH
3. DHP
4. O₃, DMS

1. MeLi, MeOAl(i-Bu)
2. Na(Hg), NaH
3. P₄O₆

1. ClCOOEt, NaBH₄
2. Bu₃P, (PhS)₂
3. MCPBA

1. Jones'
2. NaOH, DCC, t-BuOH
3. (Boc)_2O

1. OsO₄, NMO
2. NaIO₄
3. Jones'
4. NaOH

Separate by Flash Chromatography
