Bioisosterism
A Rational Approach in Drug Design

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Sept. 30th 2005

Why is Bioisosterism?

Majantol 1a

\[
\begin{align*}
\text{Majantol } 1a \\
\text{strong fresh-floral aqueous-aldeydic, lily-of-the-valley flowers odor}
\end{align*}
\]

Sila-majantol 1b

\[
\begin{align*}
\text{Sila-majantol } 1b \\
\text{lily-of-the-valley flowers but more terpineol-like odor}
\end{align*}
\]

Germa-majantol 1c

\[
\begin{align*}
\text{Germa-majantol } 1c \\
\text{weak and not characteristic odor}
\end{align*}
\]

Syntheses, Structures, and Sensory Characteristics of the Perfume Ingredient Majantol and Its Analogs Sila-majantol and Germa-majantol: A Study on C/Si/Ge Bioisosterism

As the world’s population grows older, functional and “chronic” diseases of advanced age have become a greater medical problem.

Also, the increasing strains and stresses of modern life, with concentration of our population in large cities, faster and more dangerous means of locomotion, stiffer competition for professional opportunities, the threat of wars, and the uncertainties of the community in a socially unsettled world have raised the number of psychosomatic and mental disorders and their attendant physiological consequences to higher levels.

1. Introduction

• Brief of drug design process


Lead Compound
The lead compound is the starting point when designing a new drug. The compound should have some desirable property that is likely to be therapeutically useful.

Pharmacodynamics
The pharmacophore of a drug interacting with a molecular target including enzyme, protein, nucleic acid, lipid and carbohydrate in the body.

Pharmacokinetics
The study of what happens to a drug when it is administered to a patient. There are four main factors to be considered – absorption, distribution, metabolism and excretion.
Traditional Drug Discovery Process

Library → *Screening* → Data → *Data analysis* → Further exploration → Start Chemistry → Drug Candidates

**Assay**

- Cellular and molecular biology
- Genomics
- Proteomics
- Genomics
- Bioinformatics
- Knock-out animal models
- Antisense nucleic acids and antibodies
- Proteomics
- Structural biology/structural genomics
- High throughput screening
- Natural Products screening
- NMR-based screening
- Virtual screening
- Combinatorial chemistry
- Compound library design
- Structure-based design
- Medicinal chemistry
- Parallel synthesis
- Design of focused compound libraries
- Molecular modeling, QSAR
- Structure-based design
- In vivo pharmacology
- Pharmacokinetics and toxicology

**Figure 2. Phases of the drug discovery process**

2. Bioisosterism in Drug Design

- Evolvement of Bioisosterism

1919 – Langmuir I.

Compounds having the same number of atoms have also the same total number of electrons, the electrons may arrange themselves in the same manner. In this case the compounds or groups of atoms will be called isosteric compounds or isosteres.

Table 1. Groups of Isosteres as Identified by Langmuir

<table>
<thead>
<tr>
<th>Group</th>
<th>Isosteres</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>N₂O, CO₂, NO, NO₂, SO₂</td>
</tr>
<tr>
<td>2</td>
<td>CH₃, CH₂, CH, H</td>
</tr>
<tr>
<td>3</td>
<td>O₂, O₃, O₂⁺, O₂⁻</td>
</tr>
<tr>
<td>4</td>
<td>Cl₂, Cl⁻, Cl₂⁻</td>
</tr>
<tr>
<td>5</td>
<td>Br₂, Br⁻, Br₂⁻</td>
</tr>
<tr>
<td>6</td>
<td>I₂, I⁻, I₂⁻</td>
</tr>
</tbody>
</table>


- Bioisosterism in Drug Design

1925 – Grimm’s Hydride Displacement Law

Atoms anywhere up to four places in the periodic system before an inert gas change their properties by uniting with one to four hydrogen atoms, in such a manner that the resulting combinations behave like pseudoatoms, which are similar to elements in the groups one to four places respectively, to their right.

Table 2. Grimm’s Hydride Displacement Law

<table>
<thead>
<tr>
<th>Group</th>
<th>Isosteres</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>N, O, F, (\text{OH}^+), (\text{OH}^-)</td>
</tr>
<tr>
<td>CH</td>
<td>NH, CH⁺, CH₃⁺</td>
</tr>
<tr>
<td>CH₂</td>
<td>NH₂, CH₄⁺</td>
</tr>
<tr>
<td>CH₃</td>
<td>NH₃, CH₄⁻</td>
</tr>
<tr>
<td>CH₄</td>
<td>NH₄⁺, CH₄⁻</td>
</tr>
</tbody>
</table>

3). 1932 – Erlenmeyer H.

Isosteres as atoms, ions, and molecules in which the peripheral layers of electrons can be considered identical.

Table 3. Isosteres Based on the Number of Peripheral Electrons

<table>
<thead>
<tr>
<th>A</th>
<th>S</th>
<th>O</th>
<th>F</th>
<th>N</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>H</td>
<td>N</td>
<td>O</td>
<td>F</td>
<td>S</td>
</tr>
<tr>
<td>Si</td>
<td>P</td>
<td>S</td>
<td>Cl</td>
<td>O</td>
<td>P</td>
</tr>
<tr>
<td>N</td>
<td>Cl</td>
<td>NH</td>
<td>Br</td>
<td>O</td>
<td>F</td>
</tr>
<tr>
<td>F</td>
<td>SiH</td>
<td>ClH</td>
<td>Z</td>
<td>O</td>
<td>P</td>
</tr>
<tr>
<td>As</td>
<td>As</td>
<td>ClS</td>
<td>S</td>
<td>O</td>
<td>P</td>
</tr>
<tr>
<td>V</td>
<td>V</td>
<td>Se</td>
<td>S</td>
<td>O</td>
<td>P</td>
</tr>
</tbody>
</table>


4). 1951 – Friedman H. L.

Bioisosteres were to include all atoms and molecules which fit the broadest definition for isosteres and have a similar type of biological activity, which may even be antagonistic.


5). 1979 – Thornber C. W.

Bioisosteres are groups or molecules which have chemical and physical similarities producing broadly similar biological activity.


6). 1991 – Bürger A.

Compounds or groups that possess near-equal molecular shapes and volumes, approximately the same distribution of electrons, and which exhibit similar physical properties...

Bioisosterism in Molecular Modification

A chemical group can be mimicked by a similar group with similar biological activity – another example of similarity

- Size
- Shape (bond angles, hybridization)
- Electronic distribution (Polarizability, inductive effects, charge, dipoles)
- Lipid solubility
- $pK_a$
- Chemical reactivity (including likelihood of metabolism)
- Hydrogen bonding capacity

Database

Hits

Quantitative Structure-Activity Relationship (QSAR) Models

Extract and Tabulate Descriptors

<table>
<thead>
<tr>
<th>Compound</th>
<th>Molecular Weight</th>
<th>Volume (Å³)</th>
<th>LogP</th>
<th>Dipole Moment (µ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.34</td>
<td>420</td>
<td>2.8</td>
<td>0.97</td>
</tr>
<tr>
<td>2</td>
<td>1.86</td>
<td>332</td>
<td>4.6</td>
<td>2.23</td>
</tr>
<tr>
<td>3</td>
<td>0.23</td>
<td>198</td>
<td>-0.3</td>
<td>3.36</td>
</tr>
<tr>
<td>4</td>
<td>3.67</td>
<td>467</td>
<td>3.7</td>
<td>0.45</td>
</tr>
<tr>
<td>5</td>
<td>2.55</td>
<td>359</td>
<td>-1.5</td>
<td>1.77</td>
</tr>
<tr>
<td>etc.</td>
<td>etc.</td>
<td>etc.</td>
<td>etc.</td>
<td>etc.</td>
</tr>
</tbody>
</table>
Building QSAR Models

\[ \Delta(\text{obs. property or activity}) \propto \Delta(\text{molecular descriptors}) \]

\[ Y = f(X_i) \]

Simple (Univariate) Linear Regression
Hansch, 1969

\[ pKi = a_o + a_1 (\text{Mol Vol}_i) \]

Multiple Linear Regression (MLR)
Hansch, 1969

\[ \text{dep} \ pKi = a_o + a_1 (\text{Mol Vol}_i) + a_2 (\log P) + a_3 (\mu_i) + ... \]

Partial Least-Squares (PLS) Regression
Wold, et al. 1984

\[ pKi = a_o + a_1 (PC1) + a_2 (PC2) + a_3 (PC3) + ... \]

Predicting Activities of Untested Compounds
Using QSAR models as a predictive tool

New Lead:

Validated QSAR model:

\[ pK_i = 0.52 (V_i) + 0.27 (\log P_i) - 0.38 (\mu_i) \]

Predicted activity of new lead
Bioisosteres

Classical Bioisosteres

1. Monovalent Atoms or Groups
   \[
   \text{CH}_3, \text{NH}_2, \text{OH}, \text{F}, \text{Cl}
   \]
   \[
   \text{Cl}, \text{PH}_2, \text{SH}
   \]
   \[
   \text{Br}, i-\text{Pr}
   \]
   \[
   \text{I}, t-\text{Bu}
   \]

2. Divalent Isosteres
   \[
   \text{CH}_2, \text{NH}, -\text{O}, -\text{S}, -\text{Se}
   \]
   \[
   -\text{COCH}_3, -\text{CONHR}, -\text{COOR}, -\text{COSR}
   \]

Nonclassical Bioisosteres

3. Trivalent Atoms or Groups
   \[
   \text{H}, \text{C}, \text{N}
   \]
   \[
   -\text{P}, -\text{As}
   \]

4. Tetrasubstituted Atoms
   \[
   \text{C}, \text{Si}
   \]
   \[
   -\text{O}, -\text{S}, -\text{N}
   \]

5. Ring Equivalents

\[
\text{Cycle Structures}
\]
Antineoplastic

<table>
<thead>
<tr>
<th>X</th>
<th>H</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>van der Waal’s radius (Å)</td>
<td>1.2</td>
<td>1.35</td>
</tr>
</tbody>
</table>

**DNA**

Anti-inflammatory corticosteroid

Table 5. Biological Activities of Halomethyl Androstane-17β-carboxithionates

<table>
<thead>
<tr>
<th>compound</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>topical anti-inflammatory activity*</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>H</td>
<td>F</td>
<td>=CH$_2$</td>
<td>42</td>
</tr>
<tr>
<td>3b</td>
<td>F</td>
<td>F</td>
<td>=CH$_3$</td>
<td>108</td>
</tr>
<tr>
<td>3c</td>
<td>H</td>
<td>H</td>
<td>$\beta$-CH$_3$</td>
<td>27</td>
</tr>
<tr>
<td>3d</td>
<td>H</td>
<td>F</td>
<td>$\beta$-CH$_3$</td>
<td>41</td>
</tr>
</tbody>
</table>

*Topical anti-inflammatory activity was measured in mice by modifications of the croton oil ear assay. Fluocinolone acetonide served as a positive control and is assigned a relative potency index of 100.

b. NH₂, OH, SH interchange

\[
\begin{align*}
\text{N}_2\text{C}-\text{CH}_2 &\quad \rightarrow \quad \text{N}_2\text{C}-\text{CH}_2 \\
\text{H} &\quad \text{H} \\
\text{H} &\quad \text{O} \\
\text{N}_2\text{C}-\text{CH}_2 &\quad \rightarrow \quad \text{N}_2\text{C}-\text{CH}_2 \\
\text{H} &\quad \text{H} \\
\text{H} &\quad \text{S} \\
\text{N}_2\text{C}-\text{CH}_2 &\quad \rightarrow \quad \text{N}_2\text{C}-\text{CH}_2 \\
\text{H} &\quad \text{H} \\
\text{H} &\quad \text{S} \\
\end{align*}
\]


c. Trivalent Atoms or Groups

\[
\begin{align*}
\text{CH}_3 \text{OCOC} &\quad \text{N} \quad \text{COOEt} \\
\end{align*}
\]


d. Tetrasubstituted Atoms

Table 7. Calcium Channel Blocking Activity of 1,4-Dihydropyrimidines

<table>
<thead>
<tr>
<th>compound</th>
<th>X</th>
<th>van der Waal's radius [Å]</th>
<th>IC₅₀ (mM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15a</td>
<td>=O</td>
<td>1.40</td>
<td>140</td>
</tr>
<tr>
<td>15b</td>
<td>=NH</td>
<td>1.50</td>
<td>160</td>
</tr>
<tr>
<td>15c</td>
<td>=S</td>
<td>1.35</td>
<td>17</td>
</tr>
</tbody>
</table>

* Concentration that produced 50% inhibition and determined for the vasorelaxant activity with potassium depolarized rabbit thoracic aorta.


Table 23. In Vitro and ex Vivo Inhibition of Lipid Autoxidation in Mouse Heart Homogenate

<table>
<thead>
<tr>
<th>compound</th>
<th>X</th>
<th>IC₅₀ (μM)</th>
<th>ID₅₀ (μM/kg)</th>
<th>IC₅₀/ID₅₀</th>
</tr>
</thead>
<tbody>
<tr>
<td>45a</td>
<td>N(CH₃)₂</td>
<td>19</td>
<td>11</td>
<td>1.7</td>
</tr>
<tr>
<td>45b</td>
<td>P(CH₃)₃</td>
<td>10</td>
<td>8</td>
<td>1.3</td>
</tr>
<tr>
<td>45c</td>
<td>S(CH₃)₂</td>
<td>7</td>
<td>6</td>
<td>1.3</td>
</tr>
</tbody>
</table>

* Concentration that inhibits thiobarbituric acid reactive substances (TBARS) formation by 50%. a Dose that inhibits TBARS formation by 50% 1 h after sc administration.

A Study on C/Si/Ge Bioisosterism

Reinhold Tacke

Majantol 1a
strong fresh-floral aqueous-aldehydic, lily-of-the-valley flowers odor

Sila-majantol 1b
lily-of-the-valley flowers but more terpineol-like odor

Germa-majantol 1c
weak and not characteristic odor


J. Ring Equivalents

![Chemical Structures]

Table 25. In Vitro cAMP PDE III Activity of Ring-Equivalent Bioisosteres of 5-(4-Pyridinyl)benzoxazol-2(3H)-one

<table>
<thead>
<tr>
<th>Compound</th>
<th>X</th>
<th>IC₅₀ (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td></td>
<td>28</td>
</tr>
<tr>
<td>51</td>
<td></td>
<td>0.36</td>
</tr>
<tr>
<td>52a</td>
<td>−O−</td>
<td>9.8</td>
</tr>
<tr>
<td>52b</td>
<td>−CH₁−</td>
<td>5.3</td>
</tr>
<tr>
<td>52c</td>
<td>−NH−</td>
<td>1.3</td>
</tr>
<tr>
<td>52d</td>
<td>−S−</td>
<td>0.54</td>
</tr>
</tbody>
</table>

* Concentration required to cause 50% inhibition of cAMP PDE III in vitro.

Nonclassical Bioisosteres

a. Cyclic vs Noncyclic Replacement

Table 33. Minimum Inhibitory Concentration (MIC) of β-Aminooxypropionyl Penicillins

<table>
<thead>
<tr>
<th>compound</th>
<th>MIC (µg/mL)</th>
<th>Gram-positive bacteria</th>
<th>Gram-negative bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>0.05</td>
<td>71</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>0.10</td>
<td>136</td>
<td></td>
</tr>
</tbody>
</table>


b. Replacements of Functional Groups

Hammett constant: σp
Lipophilic value: π
Relative size index: MR

Table 36. Aromatic Substituent Constants for Hydroxyl Group Bioisosteres

<table>
<thead>
<tr>
<th>Bioisosteres</th>
<th>σp</th>
<th>π</th>
<th>MR</th>
</tr>
</thead>
<tbody>
<tr>
<td>OH</td>
<td>-0.67</td>
<td>2.85</td>
<td></td>
</tr>
<tr>
<td>CH₃OH</td>
<td>-1.93</td>
<td>7.19</td>
<td></td>
</tr>
<tr>
<td>NHCONH₂</td>
<td>-1.30</td>
<td>13.72</td>
<td></td>
</tr>
<tr>
<td>NHCOCH₃</td>
<td>-0.97</td>
<td>14.93</td>
<td></td>
</tr>
<tr>
<td>NH₂SOCH₃</td>
<td>-1.18</td>
<td>18.17</td>
<td></td>
</tr>
<tr>
<td>NH-CN</td>
<td>-9.26</td>
<td>10.14</td>
<td></td>
</tr>
</tbody>
</table>

Table 37. Ligand Binding Data for N,N-Di α-propyl dopamine (DPDA) Cogeners

<table>
<thead>
<tr>
<th>compound</th>
<th>X</th>
<th>Y</th>
<th>pKᵦₐᵦ*</th>
</tr>
</thead>
<tbody>
<tr>
<td>66a</td>
<td>NHCHO</td>
<td>OH</td>
<td>6.94</td>
</tr>
<tr>
<td>66c</td>
<td>NHCOCH₃</td>
<td>OH</td>
<td>5.10</td>
</tr>
<tr>
<td>66d</td>
<td>NHCONH₂</td>
<td>OH</td>
<td>5.15</td>
</tr>
<tr>
<td>66f</td>
<td>NHCOCH₃</td>
<td>H</td>
<td>4.69</td>
</tr>
<tr>
<td>66g</td>
<td>NHCONH₂</td>
<td>H</td>
<td>4.87</td>
</tr>
<tr>
<td>66h</td>
<td>NH₂SOCH₃</td>
<td>H</td>
<td>5.45</td>
</tr>
</tbody>
</table>

*Negative log of the concentration required to produce 50% inhibition in EDTA-washed rat striatal membranes using [3H]piperone

3. Case Study

From lead compound to dianilino-phthalimides

1. The lead compound

2. Dianilino-phthalimides

PKC selective

Steric clash

Planar

Propellor shape

1. Synthesis of dianilino-phthalimides

```
TMSCl, NEt3
DMF, 100 °C

O
O

Si(CH3)3

H2C
H2C

O

Si(CH3)3

H2C

CO2Me

CO2Me

Toluene

H3C

OSi(CH3)3

O

anilines

Acetic acid, 120 °C

O

O

(H3C)3SiO

O

O

CH3H3C

a) LiOH, MeOH

b) (Ac)2O, toluene

NH3 or formamides

140-150 °C
```

4. Drug metabolism of CGP52411.

- CGP 52411 (IC50 0.7µM)
- Metabolism in man, mouse, rat and dog
- Metabolism in monkey

5. Use of metabolic of blockers.
7. Ring expansion

Ring expansion

Remove polar group

CGP 52411 (IC\textsubscript{50} 0.7\,µM)

CGP 54690 (IC\textsubscript{50} 0.12\,µM)

CGP 57198 (IC\textsubscript{50} 0.18\,µM)

6. Chain extension

Chain extension

Chain contraction

X= OH, Y= H  \text{EC}_{50} 0.026\,\mu M
X= OH, Y= H  \text{EC}_{50} 0.006\,\mu M
X= OH, Y= H  \text{EC}_{50} 0.006\,\mu M
X= OH, Y= H  \text{EC}_{50} 0.008\,\mu M

Modeling Studies

X= OH  \text{EC}_{50} 0.22\,\mu M
X= OH  \text{EC}_{50} 0.001\,\mu M
X= Cl  \text{EC}_{50} 0.033\,\mu M
X= OMe  \text{EC}_{50} 0.008\,\mu M
4. Summary

(i). The marketing of a drug has to be approved by regulatory authorities to ensure that the claims made for the product are accurate.

(ii). Health authorities across the world have attempted to cut the costs of medical health care by focusing on cheap generic drugs.

There has been a steady decline in the number of drugs introduced each year into human therapy, from 70-100 in the 1960s, 60-70 in the 1970s, to about 50 in the 1980s and below 40 in the 1990s.

Thanks for your attention!

“We are aggressively implementing a cutting-edge technology for a treatment that could extend millions of lives.”

(i) Drug-like Behavior

**The Lipinski “Rule of Five”** (1)

- Molecular Weight $\leq 500$ (opt = $\sim 350$)
- Hydrogen Bond Acceptors $\leq 10$ (opt = $\sim 5$)
- Hydrogen Bond Donors $\leq 5$ (opt = $\sim 2$)
- $-2 < \text{cLog P} < 5$ (opt = $\sim 3.0$)
- Rotatable Bonds $\leq 5$


Clinical: of or relating to the examination and treatment of patients and their illnesses.

Clinical trials are carried out to test the therapeutic effects of new drugs and to ensure that they have no unacceptable side effects. There are four phases.
Types of Molecular Descriptors

- Constitutional, Topological
  - 2-D structural formula
- Geometrical
  - 3-D shape and structure
- Quantum Chemical
- Electrostatic
- Thermodynamic