Bioisosteres: a Useful Concept in Medicinal Chemistry

Peter Gmeiner, Rio de Janeiro 2009
What is a bioisostere?

A bioisostere is a compound resulting from the exchange of an atom or of a group of atoms with another, broadly similar, atom or groups of atoms. The objective of a bioisosteric replacement is to create a new compound presenting similar biological properties to the parent compound. The bioisosteric replacement may be physicochemically or topologically based (IUPAC, Glossary of terms used in medicinal chemistry).

Classical bioisosteres result from classical isosteres (isoelectronic compounds) = unusual restriction

Why to perform a bioisosteric replacement?

- Pharmacokinetics
- Drug safety
- Target recognition and activity
- Selectivity

- Patent issues
- Availability
- Target – small molecule interactions
Schizophrenia:

abnormal thinking, feeling and perception of surroundings

**positive symptoms:** hallucinations, delusions, hyperactivity, abnormal use of language

**negative symptoms:** apathy, limited speech, affective flattening

(= blunted emotions, loss of interest)
4 portraits of cats of the Londoner painter Louis Wain (early 20th century) = proceeding of the psychosis
Classical antipsychotics show extrapyramidal motoric side effects (similar to Parkinson`s disease) in rats: catalepsy
Dopaminergic synapse

DOPA → DA

A (D_2, D_3)

D_1, D_5

D_2, D_3, D_4

Ca^{2+}

K^+

G_s

G_i

AC
Signal transduction (simplified):

- Equilibrium: high and low affinity
- NT binds to R (step 1)
- GTP binds to R (step 2)
- GTPase activity of the α-unit
  - GTP → GDP (time switch)
- P (second messenger)
- S (second messenger)
- PO₄³⁻
Effector function considering as example the phosphatidylinositol specific phospholipase C (PI-PLC):

- Phosphatidylinositol: phospholipid (part of the membrane)
- PI-PLC
- Phosphatidylinositol diphosphate (PIP$_2$)
- Inositol triphosphate (IP$_3$)
- Diacylglycerol (DAG)
- Protein kinase C $\uparrow$

IP$_3$ + DAG: second messenger
Bioisosterism involving O, N(H), CH₂, S and halogens:

NSAIDs:

aminophenazone (carcinogenic properties, withdrawn 1978)

propyphenazone
Displacement of atoms or pseudo-atoms

Bioisosterism involving O, N(H), CH₂, S and halogens:

Antipsychotics:

\[
\begin{align*}
\text{Haloperidol} & \quad \text{Asp 3.32} \\
\text{carba - Haloperidol} & \quad \text{D2: 1.3 nM, D3: 10 nM, D4: 7.3 nM} \\
& \quad \text{D2: 50 000 nM, D3: 2 500 nM, D4: 47 000 nM}
\end{align*}
\]

= completely conserved Asp 3.32
central position of the binding site crevice
mutation leads to complete loss of ligand binding
Displacement of atoms or pseudo-atoms

Bioisosterism involving O, N(H), CH(2), S and halogens:

D4 Subtype Selectivity

Displacement of atoms or pseudo-atoms

Bioisosterism involving O, N(H), CH(2), S and halogens:

D4 Subtype Selectivity

Displacement of atoms or pseudo-atoms

Bioisosterism involving O, N(H), CH(2), S and halogens:

D4 Subtype Selectivity

Displacement of atoms or pseudo-atoms

Bioisosterism involving O, N(H), CH(2), S and halogens:
Molecular electrostatic isopotential maps (representing a -15 kcal/mol interaction with a point positive charge) for the core fragments based on MO calculations at the RHF level of theory and the 6-31 G* basis set.
<table>
<thead>
<tr>
<th></th>
<th>Pyrrole</th>
<th></th>
<th>Pyrazole</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>D2</td>
<td>14</td>
<td></td>
<td>D2</td>
<td>470</td>
</tr>
<tr>
<td>D3</td>
<td>49</td>
<td></td>
<td>D3</td>
<td>120</td>
</tr>
<tr>
<td>D4</td>
<td>4</td>
<td></td>
<td>D4</td>
<td>0.45</td>
</tr>
</tbody>
</table>
Bioisosterism of carboxylic acids and carboxamides:

Sulfonamides as p-aminobenzoic acid analogs inhibiting dihydropteroate synthesis:

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{CO}_2\text{H} & \quad \text{H}_2\text{N} & \quad \text{SO}_2\text{NH} - \text{R} \\
\end{align*}
\]

HIV protease inhibitors:

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

dipeptide

\[
\begin{align*}
\text{hydroxypropylene bioisostere} & \quad \rightarrow \quad \text{indinavir} \\
\end{align*}
\]
Histamine H2 receptor antagonists:

- Histamine
- Burimamide
- Ranitidine

Displacement of functional groups

Bioisosterism involving arenes:
- Benzene
- Indole
- Imidazole

{ heteroarenes }
2,2-Dicyanovinyl substituted D4 ligands

How academia can help drug discovery?

→ Riskier approaches: 
  - tackling orphan diseases
  - novel types of assays
  - creating new animal models for disease
  - novel types of compounds
Fancy bioisosteres: fullerene-based HIV inhibitors

(a) \[ C_{60} \]
\[ K_i = \infty \]

(b) Compound 1
\[ K_i = 5 \mu M \]

(c) Compound 2
\[ K_i = 103 \text{nM} \]

(d) Saquinavir (SAQ)
\[ K_i = 0.12 \text{nM} \]

G. Kenyon, JACS 1993, 6506
Fancy bioisosteres: carbocyclic derivatives

\[
\begin{align*}
\text{FAUC 113:} & \quad \text{Ki} = 3.6 \text{ nM (D4)} \\
\text{FAUC 3019:} & \quad \text{Ki} = 0.38 \text{ nM (D4)}
\end{align*}
\]
Fancy bioisosteres: non-aromatic arene surrogates

dopamine

pramipexole
\[ \text{NPr}_2 \quad \overset{\text{Tf}_2\text{O}}{\longrightarrow} \quad \text{NPr}_2 \quad \overset{\text{H} \equiv \equiv \text{X}}{\text{Pd(PPh}_3)_4, \text{Cul}} \quad \text{NPr}_2 \]

\[ \text{CBr}_4, \text{PPh}_3 \quad \overset{\text{Cl}_2\text{Pd(PPh}_3)_2, \text{Cul}}{\longrightarrow} \quad \text{X} = \text{C-Ph, C-Si(Me)}_3, \text{C-H, N} \]
FAUC 73

J. Med. Chem. 2000, 756
Fancy bioisosteres: non-aromatic arene surrogates

Dopamine

FAUC 73

7-HO-DPAT

Pramipexole
EMIL FISCHER CENTRUM

UNIVERSITÄT ERLANGEN
Fancy bioisosteres: non-aromatic arene surrogates

Dopamine

FAUC 73

FAUC 88

FAUC 206
quinpirole (EC<sub>50</sub> = 2.7 nM)

FAUC 88 (EC<sub>50</sub> = 2.5 nM)


log test compound [M]
D3 and D4 Antagonists

Shortening of the distance between N and $\pi_1$ generates D4 selectivity!

Elongation of the distance between N and $\pi_1$ generates D3 selectivity!

for D4: $n = 0$
for D3: $n = 3$

MSD

D2  810 nM  
D3  430 nM  
D4  1.0 nM  

BP 897

D2  210 nM  
D3  1.4 nM  
D4  39 nM  

FAUC 113

D2  4700 nM  
D3  5000 nM  
D4  2.0 nM  

FAUC 365

D2  3600 nM  
D3  0.50 nM  
D4  340 nM  

Haloperidol
Fancy bioisosteres: bilayered arene surrogates

1. Paracyclophanes
Fancy bioisosteres: paracyclophanes as bilayered arene surrogates
CHO

\[
\text{Ki} = 75 \text{ nM (D4)}
\]

\[
\text{Ki} = 250 \text{ nM (D4)}
\]

\[
\text{Ki} = 120 \text{ nM (D4)}
\]

\[
\text{Ki} = 5400 \text{ nM (D4)}
\]

1. ClCOOEt
2. HCl

\[
\text{Ki} = 120 \text{ nM (D4)}
\]

\[
\text{Ki} = 250 \text{ nM (D4)}
\]

\[
\text{Ki} = 75 \text{ nM (D4)}
\]
Bilayered heterocyclic systems

\[
\text{X} = \text{Br} \quad [\text{Pd}_2(\text{dba})_3] \quad \text{P(t Bu)}_3 \\
\text{NaOt Bu} \quad \text{Toluol} \quad (87 \%) \\
\text{X} = \text{OTf} \quad \text{pure enantiomers} \\
\text{TosOH} \quad \text{EtOH} / \text{H}_2\text{O} \\
\text{HCl} \quad \text{POCl}_3 / \text{DMF}
\]
D3 Selective Ligands

BP 897

FAUC 365

D2 210 nM
D3 1.4 nM
D4 39 nM

D2 3600 nM
D3 0.50 nM
D4 340 nM

D2 18 (34) nM
D3 0.20 (4.1) nM
D4 5.4 (9.5) nM
Fancy bioisosteres: metalloccenes as bilayered arene surrogates

Me = Fe; R1, R2 = Cl

D2: 31 nM  
D3: 0.64 nM  
D4: 0.63 nM

Me = Fe; R = 2-OMe

D2: 290 nM  
D3: 6.0 nM  
D4: 23 nM
Fancy bioisosteres

GPCR PLASTICITY