Chimica Farmaceutica
(Insegnamento Integrato di Chimica e Biotecnologie Farmaceutiche)

Drug design (2)
Molecular Variations in Homologous Series: Vinylogues and Benzologues

HOMOLOGOUS SERIES. Definition and classification

The concept of a homologous series was introduced into organic chemistry by Gerhardt. In medicinal chemistry the term has the same meaning, namely molecules differing from one another by only a methylene group.

The most frequently encountered homologous series in medicinal chemistry are monoalkylated derivatives, cyclopolymerethylene compounds, straight chain difunctional systems, polymethylene compounds and substituted cationic heads.
HOMOLOGOUS SERIES

1. Monoalkylated derivatives
   \[ R - X \rightarrow R - CH_2 - X \rightarrow R - CH_2 - CH_2 - X, \text{ etc...} \]

Open, difunctional, polymethylenic series
   \[ X - (CH_2)_n - Y \rightarrow X - (CH_2)_{n+1} - Y \]

4. Substituted cationic heads

Cyclopolymerenic compounds
   \[
   \begin{align*}
   (CH_2)_n & \quad X \quad (CH_2)_{n+1} \quad X \quad \text{etc...} \\
   \end{align*}
   \]
HOMOLOGOUS SERIES

**FIGURE 14.2** Angiotensine-converting enzyme inhibiting potency of enalaprilat analogs.\(^5\)

<table>
<thead>
<tr>
<th>Size</th>
<th>IC(_{50}) (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 2</td>
<td>19,000</td>
</tr>
<tr>
<td>n = 3</td>
<td>1,700</td>
</tr>
<tr>
<td>n = 4</td>
<td>19</td>
</tr>
<tr>
<td>n = 5</td>
<td>4.8</td>
</tr>
<tr>
<td>n = 6</td>
<td>8.1</td>
</tr>
</tbody>
</table>

**FIGURE 14.3** Optimal ring size for a series of cyclanol carbamates.

**FIGURE 14.4** Examples of functional groups encountered in open, difunctional, polymethyleneic compounds and structure of decamethonium.
HOMOLOGOUS SERIES

FIGURE 14.5 Examples of functionalized rings found in straight chain, difunctional, polymethylenic compounds. Structure of pentamidine.

FIGURE 14.6 Thromboxane synthetase inhibiting activity of a series of N-(imidazolyl-alkyl)-thiophene-5-carboxamides.\(^9\)

FIGURE 14.7 Affinity for the thromboxane A\(_2\) receptor.\(^{10}\)

FIGURE 14.8 Anticataleptic activity of substituted dopamines.\(^{11}\)
Shapes of the biological response curves

The most common curves are bell-shaped, the peak activity corresponding to a given value of the number \( n \) of carbon atoms (curve A). However, several other relationships were found among homologous series:

1. The activity can increase, without any particular rule, with the number of carbon atoms (curve B).
2. The biological activity can alternate with the number of carbon atoms, resulting in a zig-zag pattern (curve C).
3. In other series, the activity increases first with the number of carbon atoms and then reaches a plateau (curve D).
4. The activity can also decrease regularly, starting with the first member of the series (curve E). This was found for the toxicity of aliphatic nitriles or for the antiseptic properties of aliphatic aldehydes.
5. A last possibility resides in inversion of the pharmacological activity accompanying the increase in the number of carbon atoms.
Shapes of the biological response curves

FIGURE 14.9  Shapes of the biological response curves in homologous series.
Curves with a maximum activity peak

**Figure 14.10** Antiaggregant activity of structural analogs of PAF-acether.\(^2\)

**Figure 14.11** Non-symmetrical curve with a maximum activity peak.
Curves with a continuous increase of activity

**TABLE 14.1 Local Anesthetic Activity** and Spasmolytic Activity in Homologous Series

![Chemical structures and graphs](image)

<table>
<thead>
<tr>
<th>R</th>
<th>Duration of anesthesia in rabbit cornea (min)</th>
<th>R</th>
<th>Spasmolytic activity on guinea-pig isolated gut</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrogen</td>
<td>11</td>
<td>Methyl</td>
<td>8</td>
</tr>
<tr>
<td>Methyl</td>
<td>23</td>
<td>Ethyl</td>
<td>12</td>
</tr>
<tr>
<td>Ethyl</td>
<td>34</td>
<td>Propyl</td>
<td>24</td>
</tr>
<tr>
<td>Propyl</td>
<td>49</td>
<td>Butyl</td>
<td>98</td>
</tr>
<tr>
<td>Butyl</td>
<td>93</td>
<td>Pentyl</td>
<td>240</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hexyl</td>
<td>410</td>
</tr>
</tbody>
</table>
The particular case of polymethylenic bis-ammonium compounds
The particular case of polymethylenic bis-ammonium compounds
Alternating (serrated) variations of activity (zig-zag curves)

**TABLE 14.2** Zig-zag Variations of the Affinity of Hydroxyacetophenone Derivatives for the Human Peripheral Neutrophils. Inhibition of $[^3H]$ LTB4 Binding at 0.1 mM.\(^{20}\)

<table>
<thead>
<tr>
<th>$n$</th>
<th>% Inhibition of $[^3H]$ LTB$_4$ binding at 0.1 M</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>28</td>
</tr>
<tr>
<td>4</td>
<td>17</td>
</tr>
<tr>
<td>5</td>
<td>56</td>
</tr>
<tr>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>7</td>
<td>49</td>
</tr>
</tbody>
</table>

$n$ = Length of the methylene chain

**FIGURE 14.14** Antimalarial activity in a homologous series of bifunctional methoxy-6-amino-8-quinolines. *Source:* After Magidson and Strukov\(^{19}\).
Alternating (serrated) variations of activity (zig-zag curves)

**Figure 14.15** 4,4'-Dimethylamino-diphenoxalkanes\textsuperscript{21} and alkyl-linked bis(amidinobenzimidazoles).\textsuperscript{22}

**Figure 14.16** Inhibition of acetylcholinesterase by donepezil and homologs.\textsuperscript{23}
Alternating (serrated) variations of activity (zig-zag curves)

BOX 14.1  The Origin of the Zig-zag Variations

Zig-zag variations are well known in homologous series for physical properties such as melting points and solubilities. Thus, propane, with an odd number of carbon atoms, melts at \(-189.9^\circ\text{C}\) whereas butane, with an even number, melts at \(51.6^\circ\text{C}\) higher at \(-138.3^\circ\text{C}\). But odd-numbered pentane melts at \(129.7^\circ\text{C}\), only \(8.6^\circ\text{C}\) higher than butane. Boese et al. studying X-ray structures of \(n\)-propane through \(n\)-nonane at \(-90^\circ\text{C}\) say that the methyl groups on chains lying end-to-end are the culprits (Boese, R., Weiss, H.-C., Bläser, D. The melting point alternation in the short claim \(n\)-alkanes: single crystal X-ray analyses of propane at 30K and of \(n\)-butane to \(n\)-nonane at 90K. Angew. Chem. Int. Ed. 1999, 38, 988–992).

In even-numbered chains the methyl groups dovetail nicely and stay out of one another’s way. But in odd-numbered chains methyl groups on one end can only avoid one another by increasing the distance between chain ends. This less-than-tight packing in odd-numbered chains results in their anomalous melting points, the researchers suggest. In the examples above, the alkyl chain represents a spacer group between two binding groups. In some cases, it can be shown that the energy required to fold the molecule to obtain the required separation should change in a zig-zag manner with increasing chain length.
Inversion of Activity

This phenomenon is particularly observed when the bulkiness of cationic heads is progressively increased. In *N-alkylated derivatives of norepinephrine*, progressive alkylation reduces the hypertensive activity according to the sequence: NH2, NHMe, NHEt, NHNPro. Finally, the molecules become hypotensive for the values: NHIsoPro, NHnBu and NHIsoBu.

This anomaly is explained by the fact that norepinephrine can interact with two subclasses of receptors (*α* and *β*-adrenergic receptors). The less hindered derivatives are able to bind to both *α*- and *β*-receptors, hindered ones solely to *β*-receptors. A similar inversion of properties is observed when the cholinergic agonist carbachol is modified by dibutylation at the carbamate function and exchange of one of its methyl groups for an ethyl group. The analog, dibutoline, is a powerful cholinolytic.

**TABLE 14.4 Gradual Inversion of the Activity in a Homologous Series**

<table>
<thead>
<tr>
<th>R</th>
<th>Hypertensive</th>
<th>Hypotensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrogen</td>
<td>++</td>
<td>−</td>
</tr>
<tr>
<td>Methyl</td>
<td>++</td>
<td>−</td>
</tr>
<tr>
<td>Ethyl</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Propyl</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Isopropyl</td>
<td>−</td>
<td>++</td>
</tr>
<tr>
<td>Butyl</td>
<td>−</td>
<td>++</td>
</tr>
<tr>
<td>Isobutyl</td>
<td>−</td>
<td>++</td>
</tr>
</tbody>
</table>

**FIGURE 14.17** Carbachol (left) and dibutoline (right).
Inversion of Activity

In morphine (agonist), the replacement of the $N$-methyl group by a more bulky radical such as $N$-allyl, $N$-cyclopropyl- methyl or $N$- cyclobutyl-methyl leads to powerful antagonists of the opiate receptors.

Introduction of bulkiness in a cationic head does not always cause a change from agonist to antagonist. Thus, the analog $N$-propyl-apomorphine is a more powerful dopaminergic agonist than the apomorphine itself. The creation of bulkiness is obviously not limited to cationic head groups and lipophilic groups can be attached to any other part of the molecule.

![Figure 14.18](image-url)  

**FIGURE 14.18**  Tolerance to bulkiness.$^{26}$
VINILOGUES and BENZOLOGUES

The vinylogy principle was first formulated by Claisen in 1926, who observed for formylacetone acidic properties similar to that of acetic acid. The vinyl group plays the role of an electron-conducting channel between the carbonyl and the hydroxyl group. The same effect explains the acidity of ascorbic acid.

Today the vinylogy principle is explained by the mesomeric effect and it applies to all conjugated systems: imine and ethynyl groups, phenyl rings, and aromatic heterocycles.
Applications of the vinylogy principle

Although numerous applications of the vinylogy concept are found in the medicinal chemistry literature, only a very few of them are of practical interest, mainly because the preparation of vinylogues usually leads to compounds which are more sensitive to metabolic degradation and more toxic (reactivity of the conjugated double bond) than the parent drug, without being more active.

In preparing the vinylogues of acetylcholine, Tenconi and Barzaghi. succeeded in separating the nicotinic from the muscarinic activity.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Nicotinic activity</th>
<th>Muscarinic activity</th>
<th>Sensitivity to ACh-esterase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ach</td>
<td>+</td>
<td>+</td>
<td>Sensitive</td>
</tr>
<tr>
<td>Vinylogue</td>
<td>+</td>
<td>Insensitive</td>
<td>Insensitive</td>
</tr>
</tbody>
</table>
VINILOGUES and BENZOLOGUES
VINILOGUES and BENZOLOGUES

FIGURE 14.21 Vinylogues of phenylbutazone, pethidine and acetylcholine.
VINILOGUES and BENZOLOGUES

FIGURE 14.24 Cinnamic derivatives as vinylogues of benzaldehyde.\textsuperscript{34}
VINILOGUES and BENZOLOGUES

**FIGURE 14.25** Oxotremorine is an ethynologue of the acetylcholine pharmacophore.

**FIGURE 14.26** Oxime ethers as azavinylogues.
TABLE 14.6 Cyclovinyllogues of Procainamide, Relative Activity with Regard to Procainamide\textsuperscript{45}

<table>
<thead>
<tr>
<th>Compound</th>
<th>Local anesthetic power</th>
<th>Antiarrhythmic activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procainamide</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Ortho-cyclovinyllogue</td>
<td>\sim 0</td>
<td>0.17</td>
</tr>
<tr>
<td>Meta-cyclovinyllogue</td>
<td>47</td>
<td>0</td>
</tr>
<tr>
<td>Para-cyclovinyllogue</td>
<td>35</td>
<td>0</td>
</tr>
</tbody>
</table>

FIGURE 14.27 TA-1801, an arenologue of clofibrate\textsuperscript{48}

FIGURE 14.28 The vinylogous relationship between the carbonyl and the amino group in pyrroline-3-ones gives them the reactivity of secondary amides\textsuperscript{49}
VINILOGUES and BENZOLOGUES

**FIGURE 14.30** Linear benzologues derived from zaprinast.\(^{57}\)

**FIGURE 14.31** Application of the vinylogy principle to the design of a fenbendazole bioisostere.\(^ {59}\)
VINILOGUES and BENZOLOGUES

FIGURE 14.32  Unexpected chemical reactivities attributable to vinylogy.
Conclusion

Due to important changes in the geometry, vinylogues often have unpredictable activity. For this reason, vinylogues play a minor role in medicinal chemistry. In addition, their metabolic vulnerability or their increased toxicity may represent a significant drawback.

However, the vinylogy principle is sometimes applied to the design of bioisosteres. Thus, the guanidinic group of the benzimidazole fenbendazole can be compared to its vinylogue in the corresponding imidazo[1,2-a]pyridine. Both compounds are anthelmintics of similar potency.

The vinylogy principle can account for unexpected chemical reactivity that is not always recognized at a first glance. So, for example, the basicity of the N1 nitrogen is strengthened in compound CGS 8216 thanks to the vinylogous influence of the quinoline nitrogen.

For a similar reason the carbonyl group of benzopiperidones or of 3-acylindoles behaves chemically more like an amidic carbonyl then like a ketonic one. In 2-methoxy-para-benzoquinone the reactivity of the methoxy group is that of a carboxylic ester, rendering it susceptible to attack by secondary amines.
Homo and Heterodimer Ligands: the Twin Drug Approach

During the study of the structure-activity relationships (SARs) of a lead compound, the combination of two pharmacological entities in a single compound could be considered as a promising drug design strategy. Drugs containing two pharmacophoric groups covalently bounded are called twin drugs. Numerous terms have appeared recently in the literature such as "dual, dimeric, bivalent, hybrid, mixed or multiple" associated with the terms "ligands, inhibitors, activators, modulators or antagonists." Reviews discussing the interest of designing multiple ligands have been published during the last years.

The association of two identical pharmacophoric entities will generate an "identical twin drug" which is equivalent to a homodimer derivative. A compound, where two different pharmacological entities are bounded, is called a "non-identical twin drug" or heterodimer. The first design strategy is equivalent to a duplication/dimerization process of an active compound or lead. The aim of this approach is the production of a more potent and/or more selective drug compared to the single entity.
Homo and Heterodimer Ligands: the Twin Drug Approach

**FIGURE 18.1** Identical and non-identical twin drugs.
The second strategy consists of an association of two different pharmacophores. In this case, the new compound will possess both initial pharmacological activities. This approach could be an advantage when the two targeted enzymes or receptors are involved in the same disease or disorder. The heterodimer drug will produce a synergic effect by modulating simultaneously the two biological targets.

The administration of twin drugs can be favorable compared to the two separated drugs. The new entity will have its own pharmacokinetic property (absorption, distribution and metabolism) and pharmacodynamic property. These properties will be more predictable compared to the administration of two separated drugs. This aspect represents the main advantage of designing dual acting drugs in addition to the beneficial therapeutic combination of the two active principles. The twin drug must express both activities in an appropriate balance: a stoichiometric association of diazepam (2-20 mg per day) with aspirin (200-2,000 mg per day) would be nonsense.
Homo and Heterodimer Ligands: the Twin Drug Approach

A twin drug where the two different pharmacophores are released after its administration will be considered as a prodrug of the two different entities. The linker (e.g. polymethylene, polyamine) or the covalent bond present in the twin drug should resist to the metabolic process.

Combination of identical or non-identical pharmacophores can be classified according to the connection modes used between the two entities. The combination could be achieved by the means a linker or not (single bond) or according to an overlap mode. The linker group can be a polymeric chain (usually a methylenic chain), an aromatic or an heteroaromatic ring and in some cases an non-aromatic cycle. Pharmacophores can be overlapped when a common structural motif (i.e. a ring or a chemical function) is identified in the two different drugs. Duplication of aspirin led to the identical twin drug diaspirin where the connection mode is a non-linker mode. Tacrine, an acetylcholinesterase (AChE) inhibitor, was dimerized by the mean of a linker (polymethylenic chain) leading to bis-tacrine derivatives. Salicylic acid and paracetamol structure can be merged (overlap mode) to give the non-identical twin drug acetaminosalol.
Homo and Heterodimer Ligands: the Twin Drug Approach

**FIGURE 18.2** Combination modes for twin drugs.

- **Linker mode**
  - A – A

- **No linker mode**
  - A – A

- **Overlap mode**
  - A – B

**Examples:**
- **Tacrine**
- **Bis-tacrine**
- **Diaspirin**
- **Acetylsalicylic acid**
- **Paracetamol**
- **Acetaminosalol**
- **Salicylic acid**
Homo and Heterodimer Ligands: the Twin Drug Approach

Non-identical twin drugs are also named dual acting drugs or hybrids because of the different pharmacological responses targeted by the two pharmacophoric moieties. The design of dual acting drugs, called the symbiotic approach, can be realized accordingly to two strategies. The first strategy combines two non-identical selective pharmacophores into a hybrid molecule as illustrated by the sulfonamidic derivative. The associative synthesis of a chlorobenzenesulfonamide with an indole derivative through a methylenic linker generates a dual (β-blocker and diuretic agent. The two pharmacological entities could be easily identified in the conjugated derivative. A biphenyl motif was used to merge an angiotensin II receptor (AT\textsubscript{1}) antagonist and an endothelin-1 receptor (ET\textsubscript{a}) antagonist. Structural elements of initial selective ligands are still recognizable in the hybrid molecule. The second strategy starts with a lead compound found to exhibit already both activities. A rational optimization will lead to an intrinsically dual acting drug such as the histamine (H\textsubscript{1}) and platelet activating factor (PAF) antagonist benzocycloheptapyridinylene piperidine.
Homo and Heterodimer Ligands: the Twin Drug Approach

In this case, it is impossible to attribute the structural features of the molecule responsible of each biological activity. The degree of pharmacophore overlap is correlated with the molecular size of the twin drug and the structure complexity. With a low molecular weight, it would be difficult to clearly identify the structural elements necessary for both activities.

For the last 20 years drug design strategies were driven by the traditional concept: one disease-one target-one ligand approach. Identification of a biological target responsible of a disease has led to the design of potent and selective ligands or inhibitors. But in most cases, diseases involve multiple and complex systems where more than one biological target must be modulated. Some studies have shown that simultaneous and moderate inhibition or activation of several targets is more efficient than the use of selective and potent drug. During the last years, combinatorial therapy (cocktail of several drugs) has been used intensively to treat diseases, such as cancer and AIDS. Thus, the development and the use of ligands that could modulate simultaneously multiple biological targets represent a promising approach for the treatment of complex disorders.
Homo and Heterodimer Ligands: the Twin Drug Approach

The design of twin drugs will be classified into two different parts. Homodimer and symmetrical ligands will be discussed in the first time. Homodimer ligands result from the dimerization of a single pharmacophoric unit whereas symmetrical drug could be obtained after an optimization process starting from an initial symmetrical active compound. The second part will focus on heterodimer ligands and dual acting drugs. Heterodimer ligands are prepared by association of two biologically active moieties for different biological targets. Dual acting drugs possess intrinsically two biological activities that could not be correlated with structural features. Such derivatives are obtained after optimization of a lead compound that possess initially both activities. The binding mode of identical and non-identical twin drugs with macromolecular structures will also be discussed in the last part. Several examples will be presented where design of twin drugs has been guided by crystallographic and molecular modeling studies.
Homo and Heterodimer Ligands: the Twin Drug Approach

**FIGURE 18.5**  Natural compounds presenting a $C_2$ symmetry axis.
Homo and Heterodimer Ligands: the Twin Drug Approach

*Trans*-piperidine derivative
DAT: $K_i = 228 \text{ nM}$
SERT: $K_i = 5880 \text{ nM}$

Homodimer ligand
DAT: $K_i = 39 \text{ nM}$
SERT: $K_i = 7 \text{ nM}$

Oxprenolol

Bis-oxprenolol

**FIGURE 18.6** Duplication of monoamine receptors ligands.
Homo and Heterodimer Ligands: the Twin Drug Approach

![Chemical structures of homodimer and heterodimer ligands.](image)

**FIGURE 18.7** Ligands of acetylcholine receptor.
Homo and Heterodimer Ligands: the Twin Drug Approach

FIGURE 18.9 Twin drugs for opioid receptors.
Homo and Heterodimer Ligands: the Twin Drug Approach

**FIGURE 18.10** Other symmetrical receptor ligands.

**FIGURE 18.11** Melatonin receptor ligands.
FIGURE 18.12  PPARs ligands.
Homo and Heterodimer Ligands: the Twin Drug Approach

![Chemical structures of ligands](image)

**FIGURE 18.18** DNA ligands.
Homo and Heterodimer Ligands: the Twin Drug Approach

\[ \text{Ritanserin (} 5\text{-HT}_2 \text{ antagonist)} \]

\[ 5\text{-HT}_2: K_i = 0.82 \text{nM} \]
\[ D_2: K_i = 93 \text{nM} \]

\[ \text{γ-Carboline derivative} \]

\[ 5\text{-HT}_2: K_i = 2.98 \text{nM} \]
\[ D_2: K_i = 2.77 \text{nM} \]

\[ \text{Naphthylpiperazine derivative} \]

\[ 5\text{-HT}_2: K_i = 20 \text{nM} \]
\[ D_2: K_i = 38 \text{nM} \]

\[ \text{Optimization} \]

\[ \text{Optimization} \]

\[ \text{Ziprasidone} \]

\[ 5\text{-HT}_{2A}: K_i = 0.42 \text{nM} \]
\[ D_2: K_i = 4.8 \text{nM} \]

**FIGURE 18.21** Dopaminergic and serotonergic dual acting drug.
Homo and Heterodimer Ligands: the Twin Drug Approach

FIGURE 18.25 Substance P and adenosine hybrid ligand.
Homo and Heterodimer Ligands: the Twin Drug Approach

**KME-4**
- COX: $IC_{50} = 2.5 \mu M$
- 5-LO: $IC_{50} = 0.15 \mu M$

**Cl-1004**
- COX: $IC_{50} = 0.77 \mu M$
- 5-LO: $IC_{50} = 0.39 \mu M$

**Celecoxib (COX-2 inhibitor)**

**ZD-2138 (5-LO inhibitor)**

**Conjugate**
- COX-2: $IC_{50} = 50 nM$
- 5-LO: $IC_{50} = 3 nM$

**FIGURE 18.27 Dual COX/5-LO inhibitors.**