Welcome to Week 7

Starting week seven video
Please watch the online video (1 minutes, 18 seconds).

OPTIONAL-Please participate in the online discussion forum.

Chapter 11 - Lead Optimization

Introduction to Chapter 11
Chapter 11 contains six subsections.

- Introduction
- Functional Group Replacements
- Alkyl Group Replacements
- Directed Combinatorial Libraries
- Isosteres
- Peptidomimetics

Upon completing this chapter, you will understand how medicinal chemists decide to make changes to a lead to improve its properties. You should be able to distinguish molecular changes that affect target binding and pharmacodynamics from changes that affect the lead's pharmacokinetics.

OPTIONAL-Please participate in the online discussion forum.

11.1 Introduction

Feedback cycle video
Please watch the online video (6 minutes, 57 seconds).

A condensed summary of this video can be found in the Video summary page.

OPTIONAL-Please participate in the online discussion forum.
Pharmacophores - one last time

**Background:** Breaking down a lead's structure and determining its pharmacophore is a key step toward understanding how new functional groups can be introduced to affect both the binding of the lead as well as its pharmacokinetic properties.

**Instructions:** Read the passage below on a familiar topic - the pharmacophore of morphine.

**Learning Goal:** To appreciate how molecules can be minimized to their core elements that are required for activity.

The idea of a pharmacophore was introduced back in Chapter 1. The classic example of a pharmacophore can be found in morphine. Morphine (1), a natural product isolated from the poppy seed pods, is a very complex structure.

While morphine is indeed a complex compound, the structural elements that are required for analgesic activity are much more modest. By testing pieces of the skeleton of morphine, researchers have found the pharmacophore of morphine to be a relatively simple collection of molecular fragments. Representation 2 shows the pharmacophore in manner to show its directly relationship to morphine. Representation 3 shows the pharmacophore in a more easily viewed form.
By reducing a lead to its pharmacophore, the lead optimization group accomplishes two tasks. First, the group understands what part of the lead is responsible for target binding and what part might be modified to improve pharmacokinetics. Second, the simpler pharmacophore may be easier to prepare synthetically. A more easily made structure will accelerate the rate at which new analogues of the lead can be prepared. For example, two synthetic and approved analogues of morphine are meperidine (4) and ketobemidone (5). These structures are far simpler than morphine and were prepared directly from knowledge of the morphine pharmacophore.

11.2 Functional Group Replacements

Structure-activity relationships video

Please watch the online video (5 minutes, 49 seconds).

A condensed summary of this video can be found in the Video summary page.

Single point modifications

Background: Lead optimization requires the synthesis of analogues of a lead and testing of the new analogues. Through repeated modification and testing, the structure-activity relationships of the lead can be discovered and an optimized structure can be prepared.

Instructions: Read the passage below about an approach that can minimize the number of new analogues required to optimize a lead. Use this information to answer the questions that follow.

Learning Goal: To learn time-saving approaches for lead optimization.

Lead analogues are prepared individually during the lead optimization phase of drug discovery. This synthetic effort can require a considerable amount of time. Shortening the lead optimization process can accelerate the advancement of new leads into the clinic. One method for accelerating the lead optimization process is by breaking a molecule into parts and optimizing each part individually. Once the optimal substituents for each part have been determined, all the optimal parts are combined into a (hopefully) optimized lead. This approach is called single point modification.
An example of the use of single point modifications to optimize a lead is shown below. The lead shown is a compound with two clear halves - the two benzene rings. Let's assume that the plan is to test four different substituents (CH₃, Cl, F, and CN) on each of the two rings. To try all possible combinations would require the synthesis of 16 (4²) compounds. With single point modifications, the task can be accomplished with the synthesis of just 9 compounds.

Four analogues would be made with the left half of the lead being varied. Four analogues would be made with the right half being varied. The best R-group from the left half would be combined with the best R'‐group from the right half to give the final compound with hopefully the highest activity.

An assumption in single point modification is that changes on one part of a molecule can be made independently of changes on another part of a molecule. This assumption does not always hold true. A seemingly small change on one side of a molecule may alter how the compound fits into the target binding site and therefore affect how all other parts of the molecule interact with the target. Normally, however, the assumptions do hold up with the types of analogues that are prepared in lead optimization studies.

**Please complete the online exercise.**

*OPTIONAL-Please participate in the online discussion forum.*
Compass point nomenclature

**Background:** Leads are often subdivided into parts or positions in the single point modification approach of lead optimization.

**Instructions:** Read the passage below concerning how parts of a molecule or even molecules themselves are sometimes named during lead discovery.

**Learning Goal:** To see how chemists have a little fun in the laboratory.

When leads are divided into parts for individual exploration in lead optimization, the parts and leads normally take on a name of some sort. Titles like "compound 10" or "C3 of the indole" might be functional, but normally the names develop a little more flair.

An example is ezetimibe (1), a drug that decreases the absorption of cholesterol from ingested food. On first glance, ezetimibe has a passing resemblance to the outline of the continental United States.

![Ezetimibe](image)

For this reason, key compounds and functional groups in the development of ezetimibe came to be named by the positioning of groups within the molecule. Two examples are Florida phenol (2) [Florida is a state in the southeast corner of the United States] and Western ketone (3).

![Florida phenol and Western ketone](image)

Naming molecules after compass points or places on a map is a small thing, but it is representative of how chemists, who expend much energy working with series of molecules, bring some levity into the laboratory.

*OPTIONAL-Please participate in the online discussion forum.*
11.3 Alkyl Group Replacements

Homologous series video

Please watch the online video (7 minutes, 8 seconds).

A condensed summary of this video can be found in the Video summary page.

OPTIONAL—Please participate in the online discussion forum.

Ring-chain interconversion

Background: Manipulations of alkyl chains are a common part of lead optimization.

Instructions: Read the passage about converting alkyl chains on leads into rings.

Learning Goal: To learn another use of alkyl chains in lead optimization.

Alkyl chains on leads are not just incrementally extended to generate a homologous series.\(^1\) Alkyl chains are also frequently tied into rings with the same number of carbon atoms. When a chain is restrained into a ring, the lipophilicity of the lead is not greatly changed, but the steric bulk can be reduced. The ring can also affect how the steric bulk of the chain is presented off the lead. Ring-chain analogues allow the medicinal chemistry group to probe different conformations of the alkyl group.

Compound 1 was prepared in a study of anticholinergics. Anticholinergics prevent the binding of acetylcholine, a neurotransmitter, to receptors. Anticholinergics are found in a range of drugs, including those that treat nasal congestion, motion sickness, and muscle spasms. Compound 1, with its hexyl side chain, has no anticholinergic activity. The hexyl chain was replaced with a cyclohexyl group, the new analogue (2) was an anticholinergic. Another valid ring-chain analogue, which was not reported, would be compound 3. The side chain of 3 contains six carbons, just like compounds 1 and 2.

![Image of compounds 1, 2, and 3]

Image credit: Pearson Education


OPTIONAL—Please participate in the online discussion forum.
Case study: oseltamivir

**Background:** Manipulations of alkyl chains are an important part of most drug discovery programs.

**Instructions:** Read the passage below on a chain homologation and ring-chain interconversion study in the development of oseltamivir.

**Learning Goal:** To appreciate the extensive degree to which a single alkyl group modification in a lead can be explored.

Oseltamivir (1) is an inhibitor that blocks neuraminidase, an enzyme that plays a role in the spread of influenza A and B viruses. Inhibition of neuraminidase can shorten the duration and severity of a viral infection.

The five-carbon side chain on oseltamivir was discovered through a long and thorough study of different alkyl groups. The table below shows the different alkyl groups that were studied on the core structure of oseltamivir (2). Entries in the table are sorted by the number of carbons in each chain. The activity of each compound against neuraminidase in both influenza A and B is shown (ND = not determined). An ideal influenza medication should be active (low IC<sub>50</sub>) against both viruses.

<table>
<thead>
<tr>
<th>entry</th>
<th>carbons</th>
<th>R-group</th>
<th>neuraminidase IC&lt;sub&gt;50&lt;/sub&gt; (nM)</th>
</tr>
</thead>
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<td></td>
<td>in R-group</td>
<td>R-group</td>
<td>influenza A</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>H</td>
<td>6,300</td>
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<tr>
<td>entry</td>
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<td>R-group</td>
<td>neuraminidase IC\textsubscript{50} (nM)</td>
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<td>-------</td>
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<td>---------</td>
<td>-------------------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>influenza A</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}</td>
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<td>4</td>
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<td>4</td>
<td></td>
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<td></td>
<td>9</td>
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<td>5</td>
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<td>5</td>
<td>CH(CH\textsubscript{3})\textsubscript{2} (oseltamivir)</td>
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<td></td>
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<td>9</td>
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</tr>
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<td>600</td>
</tr>
<tr>
<td>17</td>
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<td></td>
<td>1</td>
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</table>
### WEEK SEVEN

**MEDICINAL CHEMISTRY**

**THE MOLECULAR BASIS OF DRUG DISCOVERY**

<table>
<thead>
<tr>
<th>entry</th>
<th>in R-group</th>
<th>R-group</th>
<th>neuraminidase IC₅₀ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>influenza A</td>
</tr>
<tr>
<td>18</td>
<td>10</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>16</td>
</tr>
<tr>
<td>19</td>
<td>11</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>1</td>
</tr>
</tbody>
</table>

Note that the number of different R-groups allowed the study of not just chain homologation and ring-chain interconversions, but also the stereochemical configuration of side chains off the main alkyl chain. With such an extensive study, the lead optimization group was able to discover the best alkyl chain for binding in the enzyme pocket of both influenza A and B.


**OPTIONAL—Please participate in the online discussion forum.**

### 11.4 Isosteres

**PK-focused changes video**

Please watch the online video (8 minutes, 11 seconds).

A condensed summary of this video can be found in the *Video summary* page.

**OPTIONAL—Please participate in the online discussion forum.**

**Lists of isosteres**

**Background:** Isosteres are groups that can be *frequently* interchanged for one another on a lead without dramatically affecting target binding.

**Instructions:** Read over the list of classical and nonclassical isosteres below. Use the isosteres to answer the questions that follow.

**Learning Goals:** To gain exposure to different isosteres and practice using them to modify leads.
Below are two tables of isosteres. Remember that classical isosteres emphasize maintaining the same steric size between different groups. Nonclassical isosteres emphasize maintaining the same electronic and hydrogen bonding interactions. All the groups listed across a row are potential isosteres of one another. Therefore, replacement of a −CH₂− (a divalent group) with an −O− (another divalent group) is a valid classical isosteric substitution. Replacement of hydrogen atom with a fluorine is a valid nonclassical isosteric substitution. By no means are these tables a complete listing of all isosteres.

**Classical isosteres**

<table>
<thead>
<tr>
<th>Description</th>
<th>Isosters</th>
</tr>
</thead>
<tbody>
<tr>
<td>equivalent univalent groups (by size)</td>
<td>small groups: CH₃, NH₂, Cl</td>
</tr>
<tr>
<td></td>
<td>intermediate groups: Br, CH(CH₃)₂</td>
</tr>
<tr>
<td></td>
<td>large groups: I, C(CH₃)₃</td>
</tr>
<tr>
<td>equivalent divalent groups</td>
<td>−CH₂−, −NH−, −O−</td>
</tr>
<tr>
<td>equivalent aromatic ring groups</td>
<td><img src="image1.png" alt="Diagram 1" /></td>
</tr>
<tr>
<td></td>
<td><img src="image2.png" alt="Diagram 2" /></td>
</tr>
</tbody>
</table>
Nonclassical isosteres (or bioisosteres)

<table>
<thead>
<tr>
<th>Description</th>
<th>Isosters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrogen equivalents</td>
<td>H, D (deuterium), F</td>
</tr>
<tr>
<td>Carboxylic acid equivalent</td>
<td><img src="image" alt="Carboxylic acid" /></td>
</tr>
<tr>
<td>Hydroxy equivalents</td>
<td>OH, CH₂OH, CH(CN)₂, NH(CN)</td>
</tr>
<tr>
<td>Thiourea equivalent</td>
<td><img src="image" alt="Thiourea" /></td>
</tr>
</tbody>
</table>

Please complete the online exercise.

OPTIONAL—Please participate in the online discussion forum.

Case study: venlafaxine

**Background**: Isosteres are groups that can be frequently interchanged for one another on a lead without dramatically affecting target binding.

**Instructions**: Read the following passage about the development of improved forms of venlafaxine.

**Learning Goals**: To see an application of isosteres in compounds that are currently in clinical trials.

In the drawing on the following page, Venlafaxine (1) is an approved and marketed antidepressant. Venlafaxine is metabolized primarily by phase I oxidation of the O-methyl group off the benzene ring. This demethylation is performed by CYP2D6. The activity of CYP2D6 can vary significantly across different patient populations. Because of this metabolic variability, the $C_p$-time profile for venlafaxine can also vary from one patient to another. Inconsistent $C_p$ values have been implied to be associated with some of the side effects of venlafaxine.¹
In order to make venlafaxine more predictable, researchers made numerous bioisosteric replacements to the drug. All the hydrogens on the methyl groups - nine hydrogens in all - were replaced with deuterium atoms (²H). The resulting compound (3) is shown below.

Deuterium, because it is identical in size and electronic character to hydrogen, should have no effect on the reversible binding of the molecule to its protein target. Deuterium, because it has a higher mass than hydrogen, can differ in how it participates in chemical reactions. The deuterium-carbon bond vibrates at a lower frequency than the hydrogen-carbon bond. With the lower frequency comes lower reactivity - potentially a slower rate of metabolism by the population-dependent CYP2D6. Compound 3 has completed phase I trials and reportedly shows a more consistent Cp-time profile than venlafaxine.


OPTIONAL-Please participate in the online discussion forum.

11.5 Directed Combinatorial Libraries

Covering all possibilities video

Please watch the online video (5 minutes, 51 seconds).

A condensed summary of this video can be found in the Video summary page.

OPTIONAL-Please participate in the online discussion forum.
Case study: sorafenib

**Background:** Directed combinatorial libraries are useful for quickly searching for optimized leads and can help discover compounds that might be missed by traditional SAR techniques.

**Instructions:** Read the passage below about sorafenib, a drug that was discovered in part through use of a directed combinatorial library.

**Learning Goal:** To see a specific example of how directed combinatorial libraries can play an important role in drug discovery.

Many kinases (enzymes that phosphorylate other molecules) are very important targets in cellular pathways that are associated with cancer. One such kinase is called raf kinase.

Compound 1 was found in a lead discovery program that was focused upon raf kinase inhibitors.\(^1\) As part of the lead optimization process, researchers generated a directed combinatorial library around the scaffold of lead 1.

The library initially included around 1,500 analogues of 1, but only about 1,000 were determined to be adequately pure for reliable testing. The best molecule in the library was found to be structure 2.\(^2\)

The discovery of 2 was a surprise to the lead optimization team. As with all leads, the structure of 1 had been explored somewhat before 1 had been elevated to lead status. In that early SAR work, the replacement of the thiophene ring with an isoxazole ring was found to decrease the activity of the molecule. The inclusion of groups larger than a CH\(_3\) group C4 of the benzene ring also caused activity to decrease. For these two reasons, the activity of compound 2 was unexpected. In a traditional, single-point modification SAR study, it is very unlikely that these two non-promising functional groups would be pursued for further study. An advantage to a directed combinatorial library is that activity assumptions are ignored and all feasible analogues are prepared and tested.
Lead 2 was further optimized and sorafenib (3), a potent inhibitor of raf kinase and an effective treatment for certain forms of cancer. Without the preparation of a combinatorial library, sorafenib may not have been discovered.


OPTIONAL—Please participate in the online discussion forum.

Back to bioisosteres

Background: Bioisosteres were introduced in the previous section, Chapter 11 Section 4.

Instructions: Read the following passage about the bioisosteres of a specific, common organic function group - the carboxylic acid. Use the JSDraw application to draw valid bioisosteric analogues of ibuprofen.

Learning Goals: To gain more exposure to bioisosteres and become more comfortable with the new JSDraw interface.

The carboxylic acid is a functional group that has been explored extensively in terms of bioisosteric substitutions. On the following page is a small listing of the number of different groups that have demonstrated potential as replacements for a carboxylic acid in a drug candidate. To some degree, each group preserves the electronic and hydrogen bonding ability of a carboxylic acid.
Please complete the online exercise.

OPTIONAL-Please participate in the online discussion forum.

11.6 Peptidomimetics

Peptides as hits and leads video

Please watch the online video (8 minutes, 9 seconds).

A condensed summary of this video can be found in the Video summary page.

OPTIONAL-Please participate in the online discussion forum.
Case study: HIV-1 protease inhibitors

**Background:** Peptidomimetics describes the design of a compound that imitates the activity and appearance of a peptide while improving its bioavailability for oral delivery.

**Instructions:** Read the passage below about the development of HIV-1 protease inhibitors.

**Learning Goal:** To see the challenges of developing an oral drug based on a peptide lead.

HIV-1 protease cleaves peptide chains, so its natural substrate is a peptide. Early x-ray crystallographic data on HIV-1 protease showed a handful of important hydrophobic and hydrogen bonding interactions between the substrate and enzyme. Based off this information, researchers at Abbott reported in 1994 a pseudopeptide, compound A74704 (1), with low nanomolar inhibitory activity. Compound 1 preserved the key interactions of the native substrate in part by allowing the inclusion of a water molecule in the binding pocket.1,2

![Chemical structure of A74704 (1)](image)

Within five years three HIV-1 protease inhibitors were approved by the US FDA. Ritonavir (2) from Abbott and saquinavir (3) from Roche were approved first, and amprenavir (4) from GlaxoSmithKline appeared a few years later. Both ritonavir and saquinavir retain some peptide character and even contain an amino acid residue. Amprenavir, on the other hand, is a true peptidomimetic with no amide linkages or amino acid residues. All three compounds have visual similarities, especially their common reliance upon CH₂Ph and isopropyl side chains.

![Chemical structures of ritonavir (2), saquinavir (3), and amprenavir (4)](image)
Not all research efforts into HIV-1 protease inhibitors took the peptidomimetic route. A group at DuPont Merck use computer-based screening techniques and brought forward a non-peptide lead (5) which evolved into DMP323 (6). Similarly, a group at Abbott developed a nearly identical compound (7), A98881. Abbott's inclusion of an extra nitrogen in the ring was to avoid patents that DuPont Merck held around their own related compounds. Although it may not be obvious, both 6 and 7 contain the required number of hydrophobic and hydrogen bonding groups to interact the exact same binding positions as were revealed with Abbott original pseudopeptide lead (1), A74704.

Compounds 6 and 7 both failed in clinical trials. Compound 6 showed poorly reproducible bioavailability. Compound 7 was poorly bioavailable. The poor bioavailability was linked to the third nitrogen in the ring.

In this example of HIV-1 protease inhibitors, the peptidomimetic route won out over the small molecule, traditional lead discovery route. Sometimes, when a peptide is the primary lead, the small molecule approach ends up being the better path to a drug. Regardless, designing a drug from a peptide lead is a challenging problem.


**OPTIONAL-Please participate in the online discussion forum.**

**Identifying peptide isosteres**

**Background:** Peptide isosteres are often used to improve the bioavailability of peptide leads.

**Instructions:** Examine the compounds below and answer the questions that follow.

**Learning Goal:** To practice identifying peptide isosteres.

**Please complete the online exercise.**

**OPTIONAL-Please participate in the online discussion forum.**
Examination 3

Third Examination
The exam is open book and open notes. All questions may be attempted once, so be certain of your answer before submitting it. There are ten questions. Each is its own unit within the Examination 3 subsection.

Remember that you are bound by the honor code. No postings to the forum concerning the exam are allowed. Furthermore, you must work on the examination independently.

Problems
Please complete the online problems in Examination 3.