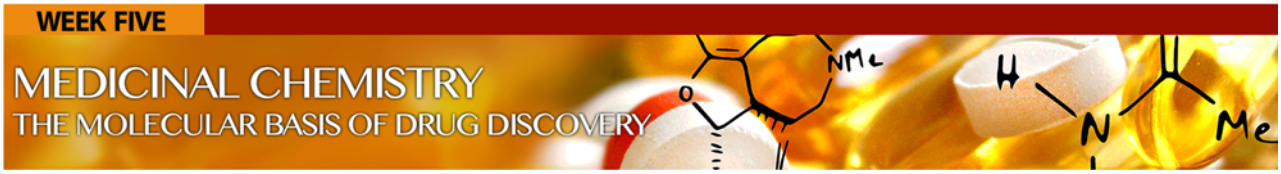


Welcome to Week 5

Starting week five video

Please watch the online video (49 seconds).

OPTIONAL-Please participate in the online discussion forum.

Chapter 9 - Binding, Structure, and Diversity

Introduction to Chapter 9

Chapter 9 contains six subsections.

- Intermolecular Forces
- Case Study - Stromelysin
- Drug-Target Complementarity
- Molecular Diversity
- Molecular Libraries
- Building Libraries

Upon completing this chapter, you should understand how drugs bind a target and how to determine the energy of binding. You should gain a preliminary idea of how to control the shape of a molecule in order to maximize available drug-target interactions. You should realize the challenge of discovering active molecules within the immense number of possible drug molecules and what tools are available to drug companies to explore drug space

OPTIONAL-Please participate in the online discussion forum.

9.1 Intermolecular Forces

Binding energy video

Please watch the online video (10 minutes, 26 seconds).

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

OPTIONAL-Please participate in the online discussion forum.

Henderson-Hasselbalch equation

Background: Hydrogen and ionic bonds are very important for drug-target binding. These bonds can be highly dependent upon pH.

Instructions: Read the passage below concerning the Henderson-Hasselbalch equation and the pK_a of common functional groups. Use the information to answer the questions that follow.

Learning Goals: To review usage of the Henderson-Hasselbalch equation and understand how pH influences the availability of hydrogen and ionic bonds between a target and a drug.

An acid (H-A) can react reversibly with water to form a conjugate base (A^-) and hydronium ion (H_3O^+). The equilibrium constant (K) for this reaction can be expressed in the standard way - the product of the concentrations of the products divided by the product of the concentrations of the reagents. Because the concentration of water is virtually constant at around 55 M, the term $[H_2O]$ is combined with K to define a new constant, K_a.

$$\text{H-A} + H_2O \overset{K}{\rightleftharpoons} A^- + H_3O^+$$

$$K = \frac{[A^-][H_3O^+]}{[\text{H-A}][H_2O]}$$

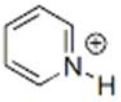
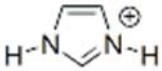
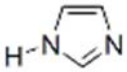
$$K[H_2O] = K_a = \frac{[A^-][H_3O^+]}{[\text{H-A}]}$$

While K_a is a constant, the position of the acid-base equilibrium can be affected by the pH of the medium. A lower pH, with a raised $[H_3O^+]$, shifts the equilibrium to the left to favor H-A. A higher pH, with a lowered $[H_3O^+]$, pulls the equilibrium to the right to favor A^-. The **Henderson-Hasselbalch equation** quantitatively relates how pH affects the equilibrium ratio of A^- and H-A for an acid with a known K_a. Remember that pK_a = −log K_a.

$$\text{pH} = \text{p}K_a + \log\frac{[A^-]}{[\text{H-A}]}$$

Henderson-Hasselbalch equation

To use the Henderson-Hasselbalch equation, one needs to know the pK_a of different functional groups. pK_a values for a handful of common functional groups encountered in drugs are shown in the table below. A much more comprehensive list can be found here.

acid (name)	conjugate base (name)	pK_a
H_3O^+ (hydronium)	H_2O (water)	−1.7
$PhCO_2H$ (benzoic acid)	$PhCO_2^-$ (benzoate)	4.2
$PhNH_3^+$ (anilinium)	$PhNH_2$ (aniline)	4.6
CH_3CO_2H (acetic acid)	$CH_3CO_2^-$ (acetate)	4.8
 (pyridinium)	(pyridine)	5.1
 (imidazolium)	 (imidazole)	7.0
NH_4^+ (ammonium)	NH_3 (ammonia)	9.2
PhOH (phenol)	PhO^- (phenolate)	10.0
H_2O (water)	HO^- (hydroxide)	15.7

For reference, the pH of some different regions in the body are listed below.

- blood - 7.4
- stomach - as low as 1
- small intestine - 7-8
- extracellular fluid - 7.4
- intracellular fluid - 6.8

Please complete the online exercise.

OPTIONAL-Please participate in the online discussion forum.

Calculating binding energies

Background: The binding energy of a drug-target complex can be calculated with the equation below. If 0.00199 kcal*K/mol is used for *R*, then the energy is calculated with units of kcal/mol. Temperature (*T*) is usually 298 K.

$$\Delta G^{\circ}_{bind} = -2.3RT \log \frac{1}{K} = 2.3RT \log K$$

Instructions: Use the equation above to answer the questions that follow.

Learning Goal: To practice calculating binding energies between a drug and target.

Please complete the online exercise.

OPTIONAL-Please participate in the online discussion forum.

9.2 Case Study - Stromelysin

Stromelysin video

Please watch the online video (8 minutes, 30 seconds).

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

OPTIONAL-Please participate in the online discussion forum.

More stromelysin inhibitors

Background: The binding energy of a drug-target complex can be calculated with the equation below. If 0.00199 kcal*K/mol is used for *R*, then the energy is calculated with units of kcal/mol. Temperature (*T*) is usually 298 K.

$$\Delta G^{\circ}_{bind} = -2.3RT \log \frac{1}{K} = 2.3RT \log K$$

Instructions: Use the equation above to answer the questions that follow concerning stromelysin inhibitors.

Learning Goal: To practice calculating binding energies between an enzyme and its inhibitor.

Please complete the online exercise.

OPTIONAL-Please participate in the online discussion forum.

9.3 Drug-Target Complementarity

Pharmacophores revisited video

Please watch the online video (7 minutes, 32 seconds).

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

OPTIONAL-Please participate in the online discussion forum.

Rotatable bonds

Background: Rotatable bonds increase the conformational flexibility of a molecule and minimize the probability that the functional groups in a molecule match the desired pharmacophore.

Instructions: Read the passage below on identifying rotatable bonds. Use the information to answer the questions that follow.

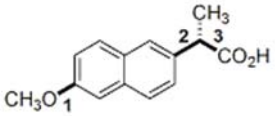
Learning Goal: To learn how to identify which bonds in a molecule qualify as rotatable.

No universally accepted rules exist on defining rotatable bonds. Each set of definitions has its loop holes and problems. Regardless, most methods include the rules shown below.

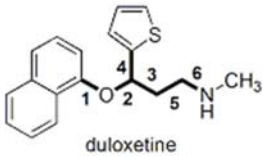
Bonds that are **not** rotatable...

- non single bonds
- bonds to hydrogen and other monovalent atoms (halogens)
- ring bonds
- bonds to terminal atoms, including CH_3, NH_2, and OH
- the C-N bond between a carbonyl and amide nitrogen (also goes for the C-N bond in thioamides and the S-N bond in sulfonamides)
- bonds connecting two aromatic rings with collectively three or more *ortho* substituents
- bonds connected to terminal triple bonds, including bonds to cyano groups

Under these rules, naproxen has only three rotatable bonds (bolded below). Duloxetine has six (bolded below).



naproxen
(Aleve)
analgesic



duloxetine
(Cymbalta)
antidepressant

Please complete the online exercise.

OPTIONAL-Please participate in the online discussion forum.

9.4 Molecular Diversity

Numbers game video

Please watch the online video (7 minutes, 55 seconds).

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

OPTIONAL-Please participate in the online discussion forum.

Behind the numbers

Background: *Molecular space for molecules with the proper size for oral drugs has been estimated to contain 10^{63} molecules*.

Instructions: Answer the questions below concerning probabilities in potential drug space.

Learning Goal: To appreciate the vast numbers of different molecules that could possibly be candidates as oral drugs.

Please complete the online exercise.

OPTIONAL-Please participate in the online discussion forum.

Privileged structures

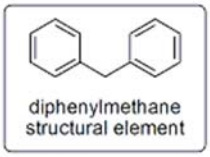
Background: Molecular space for potential drug molecules is indescribably diverse.

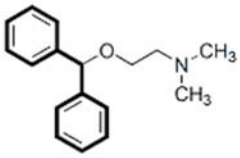
Instructions: Read the passage below about certain types of structures and substructures that repeatedly appear in many different types of drug.

Learning Goal: To understand the concept of privileged structures.

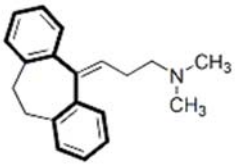
While drug space is incredibly diverse, a handful of common structures and molecular fragments can be found regularly among active sets of molecules. These compounds and fragments have become known as **privileged structures** because of their seemingly universal ability to bind protein targets.

One such privileged structure is the diphenylmethane subunit. The subunit can be seen in numerous compounds that bind a variety of different targets.

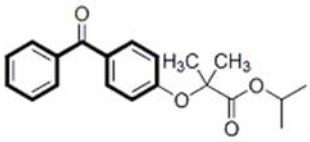




diphenylhydramine
(Benadryl)
antihistamine



amitriptyline
antidepressant



fenofibrate
(Tricor)
antihyperlipidemic

Privileged structures are both good and bad for drug discovery. On the good side, privileged structures help researchers focus on molecular scaffolds that are more likely to show activity. The drug discovery team can focus on promising compounds and hopefully avoid the less interesting structures. On the bad side, single compounds that contain privileged structures may show activity against multiple targets. Compounds that bind multiple targets often cause side effects. Such compounds are sometimes labeled as **promiscuous**. Another issue with privileged structures is that they have received considerable research attention. Patenting a compound with a privileged structure can be a challenge because so many similar structures have already been patented

OPTIONAL-Please participate in the online discussion forum.

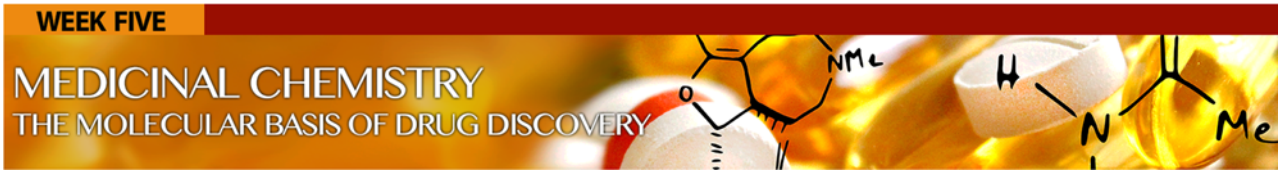
9.5 Molecular Libraries

Molecule collections video

Please watch the online video (6 minutes 56 seconds).

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

OPTIONAL-Please participate in the online discussion forum.



High-throughput screening

Background: Potential drug space is immense with an estimated number of molecules of 10^{63}. Compound libraries, although nowhere near the same size as drug space, are regardless very large and may include 1,000,000 or more compounds.

Instructions: Read the text below and the accompanying Wikipedia entry concerning the rapid testing of molecular libraries.

Learning Goal: To understand how the large number of molecules in compound libraries can be quickly and inexpensively tested for biological activity.

For molecular libraries to be useful to a drug company, there must exist a method for quickly and inexpensively testing the activity of each compound in the library. Fortunately there is. That method is called **high-throughput screening** or **HTS**.

HTS involves the automated testing of molecules in a quick, inexpensive, in vitro assay. The process relies upon robotic equipment to perform the screen reproducibly. With such a method, a pharmaceutical company can screen an entire large library, which may include a million or more compounds, in around a week in a particular screen. Therefore, in a fairly short period of time, hits for a specific target can be identified.

The entry for high-throughput screening in Wikipedia provides some more details on precisely how the process is automated. The statistical and emerging technology discussions in the article are beyond the scope of this course, but they do reveal interesting facets of HTS.

OPTIONAL-Please participate in the online discussion forum.

HTS and academia

Background: High-throughput screening (HTS) is an automated, quick method for gaining preliminary activity information on molecules in a compound library. HTS has traditionally been a technique only available to pharmaceutical companies.

Instructions: Read the linked article from the journal *Nature Methods* concerning a growing movement of academic laboratories screening their own molecular libraries. Use the information in the article to answer the questions that follow.

Learning Goal: To understand how the drug discovery process is becoming increasingly available to groups outside the pharmaceutical industry.

Please return to the online course and read the article to which the above instructions refer.

Please complete the online exercise.

OPTIONAL-Please participate in the online discussion forum.

9.6 Building Libraries

Combinatorial chemistry video

Please watch the online video (7 minutes 10 seconds).

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

OPTIONAL-Please participate in the online discussion forum.

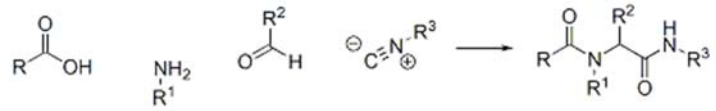
Ugi reaction

Background: Reactions that can quickly and easily assemble large numbers of diverse molecules are highly sought after in combinatorial chemistry.

Instructions: Read passage below on the Ugi reaction and answer the question that follows.

Learning Goal: To learn about a reaction that is commonly exploited in combinatorial chemistry.

The Ugi reaction involves the reaction of four different starting materials in a single reaction vessel. The starting materials are a carboxylic acid (**1**), primary amine (**2**), aldehyde (**3**), and isocyanide (**4**).



The simplicity of the Ugi reaction and the widespread availability of the starting materials make the reaction very popular starting point in preparing molecular scaffolds in combinatorial chemistry.

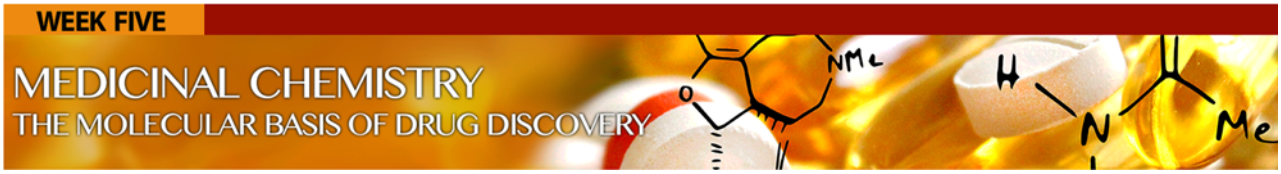
Please complete the online exercise.

OPTIONAL-Please participate in the online discussion forum.

Combichem challenges

Background: In the early 1990s combinatorial chemistry was hoped to accelerate greatly the rate at which new drugs could be discovered. The benefits of combinatorial chemistry did not however materialize as expected.

Instructions: Read the *Chemistry and Engineering News* article linked below. Use the information to answer the questions that follow.



Learning Goal: To learn about a reaction that is commonly exploited in combinatorial chemistry.

Although over 15 years old, an article from *Chemistry and Engineering News*, a trade magazine published by the American Chemical Society, captures the early sentiments of a booming field called combinatorial chemistry. Even in 1998 in the face of great enthusiasm, the promises of combinatorial chemistry were already being questioned. The article nicely captures both sides of the story.

Please return to the online course and read the article to which the above paragraph refers.

Please complete the online exercise.

OPTIONAL-Please participate in the online discussion forum.