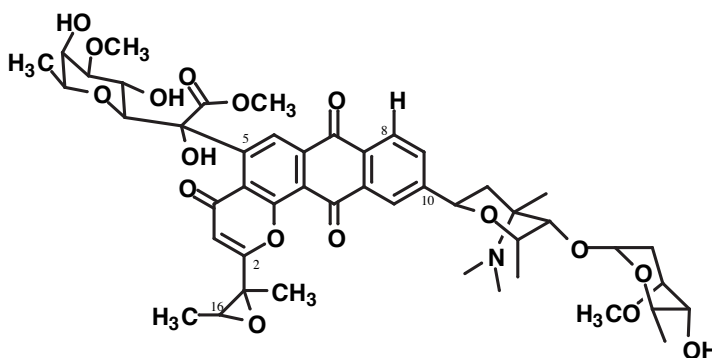


CHEM 4170
Homework 4

1. (a) Why are DNA-targeted drugs largely used as anticancer agents and not as, say, antibacterial or antifungal agents?

(b) Provide an explanation for how anticancer drugs can selectively kill cancer cells over normal human cells.

2. Suggest how the compound shown below binds to DNA. Suggest a general binding "mode" and the specific type of weak force interactions that are like to occur.



Altromycin B

3. Altromycin B alkylates DNA at the N7-position of 2'-deoxyguanosine in double-stranded DNA. Show this reaction and how it ultimately leads to a DNA strand break.

4. Altromycin does *not* alkylate single-stranded DNA. Why?

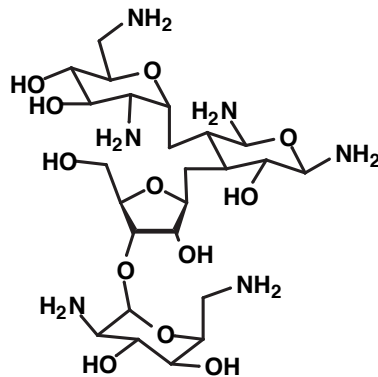
5. Ene-diyne reactions are able to abstract hydrogen atoms from DNA. Do a quick calculation involving bond enthalpies to help rationalize this observation. Data: C-H bond in deoxyribose is ~ 85 kcal/mol and a typical Ph-H bond is about 103 kcal/mol.

6. Show how abstraction of a hydrogen atom from the 2'-deoxyribose sugar residue of DNA lead to a strand break.

7. I gave you a paper in class that described the sequence-specific DNA-binding molecules developed by Dervan and coworkers. I have also posted a couple of papers on the website that describe this work. (a) Describe why it is possible, in principle, that these compounds could be used to treat any disease that can be treated by an enzyme inhibitor? (Unlike the typical DNA-damaging drugs mentioned in Question 1). (b) However, some medicinal chemists believe that these compounds will *never* be useful drugs. This view is based upon a simple rule that is known to all CHEM 317 students. Look closely at the structure of these compounds and explain why some experts in the field believe that they will never become clinically used drugs.

8. Draw a diagram that depicts the flow of information in the cell. Show the point in this flow of cellular information at which "antigene", "antisense" and "traditional" therapeutics elicit their activity. Briefly describe the antisense approach. What is the major drawback to current antisense drugs?

9. I posted two articles about RNA-small molecule interactions on the course website. Read them. The drug neomycin binds to the 16S subunit of the procaryotic ribosome and blocks bacterial protein synthesis. Electrostatic interactions are probably very important in the binding of neomycin to its target. (a) What are the specific functional group interactions that are involved here? (b) Take a look at the research paper I gave you by Tor and coworkers. I handed a copy out in class and also posted it on the course website. Neomycin contains multiple amine residues that can be protonated at pH 7. Following protonation of one amino group, it becomes more and more difficult to protonate each subsequent amine residue. Explain why.



10. How do the magainins punch holes in cell membranes? How do gramicidins punch holes in cell membranes? Draw a schematic diagram of the cell membrane and these agents as part of your answer.

11. Provide clear definitions for the following terms:

Pharmacophore
Receptor
Autocoid
Competitive Antagonist
Enzyme
Substrate
Competitive Inhibitor

Drug Metabolism: Chapter 7. Problems 1 & 11.

Prodrugs: Chapter 8. Problems 1, 2, 3, 4, & 7.