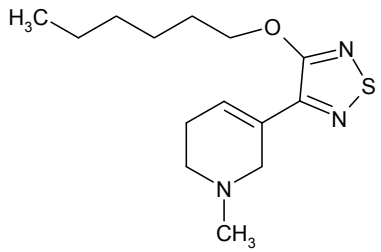
Chem 162/262 (2004) Assignment #2:

Biomolecular Interactions. Pharmacokinetics. Receptors and Enzymes

1. The compound shown below was found to be effective agonist of the M1 subtype of muscarinic acetylcholine receptor and serves as a one of the leads to develop drugs to treat Alzheimer's disease.



   a) Name three roles of the muscarinic acetylcholine receptor in human body.
   b) What are the two main differences between the nicotinic acetylcholine receptor and the muscarinic acetylcholine receptor?
   c) The strength of hydrophobic interaction between a receptor and its ligand generally increases as the hydrophobic surface area of the ligand increases. For example, the analog with methyl ether side-chain binds about 10 times weaker than the hexyl ether analog shown above. Comment of the proposal that in order to further increase the efficacy of orally administered Alzheimer's drug, a significantly longer (e.g. decyl) alkyl ether side-chain analogs should be used.

2. The free energy of interaction between the receptor and its ligand is determined both by the enthalpy and entropy changes that occur in the binding process.
   a) Discuss general strategies how to modify the structure of the lead compound such that the enthalpy of binding becomes more favorable
   b) Discuss general strategies how to modify the structure of the lead compound such that the entropy of binding becomes more favorable
   c) The following compound was synthesized (Tyndall et al, *J. Med. Chem.,* **43**, 3495 -3504, 2000) and showed strong inhibition of HIV protease in vitro (K_i = 0.3 nM).
      i) What are the potential advantages of this compound over existing HIV drugs?
      ii) Discuss the issues that might arise in clinical applications with drugs that are highly conformationally constrained.

3. Consider a drug that has only one mode of clearance (spontaneous pseudo-first order hydrolysis with a rate constant of 0.4 $hours^{-1}$) from the bloodstream.
   a) Calculate the half-life of this drug in the bloodstream.
   b) Calculate the molar concentration of a drug in the bloodstream after 8 hours of injecting 3 mL of 100 mM drug solution into the patient. Assume that the total blood volume is 5.5 L.

Project development.
You will be submitting a drug design proposal at the end of this course. As a first part of this project, you are expected to identify a disease that you want to work on. As part of your second assignment, submit one-page outline where you discuss the nature of the disease, give statistics concerning its prevalence and mortality, and discuss current approaches that are used to tackle this disease.