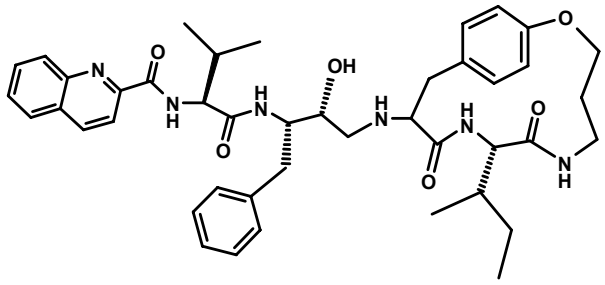
Chem 162/262 (Kahn, 2005) Assignment #5 Due Wed, Nov 16

## Biomolecular Interactions and Assay Development

1. The following multi-part question provides you with opportunity to analyze, interpret, and summarize a research paper that deals with development of a novel cell-based assay. The paper in question, "*A cell-based radioligand binding assay for farnesyl:protein transferase inhibitors*" by Robert Lobell and colleagues was published in the *Journal of biomolecular screening*, vol. 8, pg. 430 in 2003. After carefully reading the paper, answer the following questions:

    a) What was the purpose of drug verapimil in this study?
    b) Rank the inhibitors FTI-3, FTI-4, FTI-5, FTI-7, FTI-8 and FTI-9 according to their potency starting with the least potent and ending with the most potent.
    c) Describe the principle of the *in vitro* assay that was commonly used to assay for farnesyl:protein transerase inhibitors before the development of the CRAFTI assay.
    d) Explain why some of the inhibitors showed low potency in the cell-based CRAFTI assay even though they were among the most potent inhibitors according to the older *in vitro* assay.
    e) What disease are the authors trying to cure with their inhibitors?
    f) Why did the authors prefer to use radiolabeled FTI-2 over radiolabeled FTI-1 in most of their assays?
    g) Describe in your own words the principle behind the CRAFTI assay.
    h) Using any source available to you, find out if any of the inhibitors studied in this paper turned out to be potentially useful human medicines. Provide specific details to justify your answer.

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 (Joel Tyndall and co-workers, *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.