1. The following multi-part question provides you with an opportunity to analyze, interpret, and summarize a research paper that deals with the 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(s) is/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.

Using any source(s) 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. Read the paper “Glyco- and Peptidomimetics from Three-Component Joullié–Ugi Coupling Show Selective Antiviral Activity“ by Tim Chapman and colleagues (J. Am. Chem. Soc., 2005, 127, pp 506–507) and answer the following questions:

a) Explain in your own words what is the Ugi reaction and why is it relevant in medicinal chemistry.

b) Draw a plausible reaction mechanism, and show any auxiliary reagents needed, for the step in the Ugi reaction shown below:

\[ \text{O} \quad \text{C} = \text{N} \rightarrow \text{H} \quad \text{N} \quad \text{O} \]

\[ \text{H} \quad \text{O} \quad \text{H} \quad \text{O} \]

\[ \text{N} \quad \text{H} \quad \text{O} \quad \text{N} \]

\[ \text{N} \quad \text{H} \quad \text{O} \quad \text{N} \]

c) Which specific starting compounds are needed for the preparation of a combinatorial library of polyhydroxylated pyrrolidines shown below?

\[ \text{O} \quad \text{N} \quad \text{O} \quad \text{O} \]

\[ \text{H} \quad \text{O} \quad \text{H} \quad \text{O} \]

\[ \text{N} \quad \text{H} \quad \text{O} \quad \text{N} \]

\[ \text{N} \quad \text{H} \quad \text{O} \quad \text{N} \]

\[ \text{N} \quad \text{H} \quad \text{O} \quad \text{N} \]

d) What disease(s) could possibly be cured if a more potent drug from lead candidates present in this library could be developed?

e) The library members are neutral at physiological pH (amides require pH < 0 for protonation; N,N-dimethylaniline has pKₐ of 5.15). Propose a modification or extension to this procedure that allows synthesizing molecules that carry a positive charge at the N1 nitrogen (blue) but not at other nitrogen atoms.