

1. Based on the lectures, posted required readings, or any other materials available to you, discuss the validity of each of the following statements or hypothesis. Provide appropriate supporting or countering evidence from literature when appropriate.

- a) “As the evolution has optimized the structure of the receptor to be nearly ideally complementary to its natural ligand, nearly every chemical compound that resembles the natural ligand is expected to behave as a strong agonist. For the same reason, structures that differ significantly from the native ligand are not expected to bind with practically useful affinity to the receptor. Thus, to identify strong agonists with the best pharmacokinetics properties, one should exclusively focus on screening molecules that are close structural analogs of the natural ligand.” (3 pts)
- b) “Analysis of the structure of epibatidine immediately suggests that the replacement of chlorine with groups that are electron-withdrawing via inductive effect but electron donating through resonance (e.g. hydroxyl or amino group) are expected to give strong nicotinic acetylcholine receptor agonists with reduced toxicity.” (3 pts)

2. Imagine that you are the head of the pharmacodynamics department at *Better Minds, Inc.* and need to decide on the most promising memory enhancer for young adults. Your department has identified three novel structurally different nicotinic acetylcholine receptor agonists and characterized their binding to two important subtypes of receptors that are present in the brain. The binding was studied by competitively displacing radioactive acetylcholine by each of the novel agonists. In each experiment, the concentration of labeled acetylcholine was the same and the concentration of the agonists was varied. Independent studies showed that acetylcholine has a nearly similar affinity toward these two receptor subtypes. Analyze this data and suggest which of the three compounds is the most promising lead for further development of cognitive enhancers that FDA is most likely to accept? Justify your answer. (4 pts)

