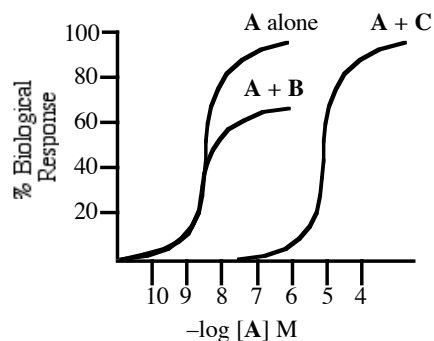


Name: _____ *Intro. To Medicinal Chemistry Chem640*

Student Number: _____ **Exam 2**

April 8th 2004

1) To answer the following questions, consider the dose-response curve shown here for agonist **A** in the presence and absence of compounds **B** and **C**. (6 points)



i) With respect to agonist **A**, what type of activity does compound **B** possess?

ii) With respect to agonist **B**, what type of activity does compound **C** possess?

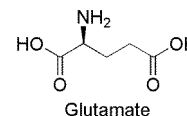
2) In the space provided, draw dose-response curves (on the same plot) for the following three compounds that have the following properties: (6 points)

- 1 $EC_{50} = 10^{-9}$, $a = 1.0$
- 2 $EC_{50} = 10^{-7}$, $a = 0.5$
- 3 an antagonist

3) Assume that the eudismic ratios for a chiral drug are 1 and 1000 at receptors **X** and **Y**, respectively. Provide 2 explanations that could account for the difference in the selectivity for receptors **X** and **Y**. (8 points)

- 6) If a disease state involved decreased concentrations of a neurotransmitter (other than acetylcholine), what pharmacological methods would be potentially effective? **List only 3.** (6 points)

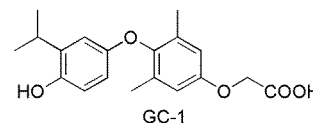
- 7) When glutamate is actively transported back into a cell, via a reuptake mechanism, both glutamate and the transport receptor undergo a conformational change. (10 points)



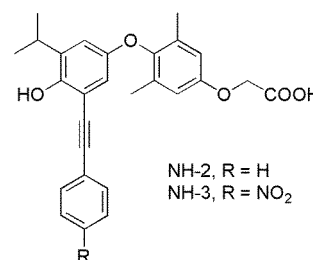
- i) With this in mind, design a conformationally restricted analog of glutamate.

- ii) What effect do you think this compound would have on the reuptake mechanism of glutamate?

- 8) Consider the three compounds shown in the figure provided and answer the following questions. (10 points)

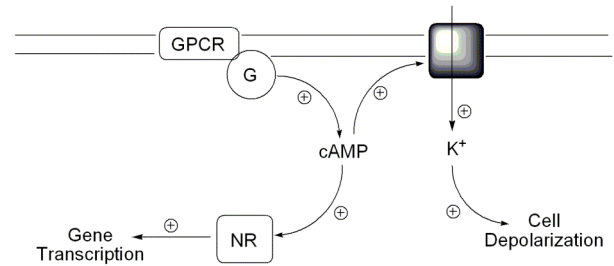


- i) The first compound, GC-1, is a known thyroid hormone nuclear receptor agonist. Based on what you know about other nuclear receptors, what activity do you think NH-2 and NH-3 would have? Explain your answer.



- ii) It turns out that NH-3 is 10 times more potent than NH-2. Give one possible explanation why.

9) Refer to the signaling pathway shown in the figure provided and answer the following questions. (25 points)



i) What G α subunit is this pathway using?

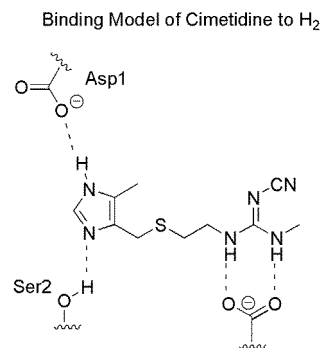
ii) Of the two cellular effects (Gene Transcription and Cell Depolarization) which one constitutes a rapid effect? Which one constitutes a slower effect? Why is there a difference?

iii) Identify **three** places in this pathway that could be targeted by therapeutics. Discuss in terms of agonistic and antagonistic effects on the two cellular effects.

iv) The signal pathway shown is a hypothetical model for cardiac cells responsible for contractile force. If the gene regulated is **AR β 1** and the cell depolarization signals neighboring cells to release **epinephrine**, what effect would an agonist for the GPCR shown in the signaling pathway have on Cardiac Output? Explain your answer.

10) Below is shown a hypothetical binding model for cimetidine to H₂, a known histamine receptor. (10 points)

- i) Recently, a new histamine receptor, H₆, was found. When cimetidine is used as an antagonist for H₆ it was found to be 20-fold **less** potent. Inspection of the amino acid sequence of H₆ revealed that Asp1 had been mutated into a serine and Ser2 had been mutated into an aspartate. Given this information, rationalize this receptor's insensitivity to cimetidine.



- ii) Suggest a new compound based on cimetidine that might restore antagonism against H₆.