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Good Luck.
**Choose between questions 1 and 2.**

**Question 1.**

A) Answer the following questions related to an experiment that investigated the analgesic effects between codeine and meperidine.

i. Regression analyses of the codeine and meperidine dose-response curves yielded the following information: 1) codeine: slope = 42 and intercept = -6, and 2) meperidine: slope = 46 and intercept = 4. The dose of is expressed as log (mg). Use this information to calculate the ED50 values of both drugs (your answer may be left in log units). Your calculations must be shown for credit. (8 points)

ii. A potency ratio (95% confidence limits) between codeine and meperidine was calculated to be 2.2 (0.8 to 4.4). Based on the potency ratio and ED50 values what conclusions can be made regarding the difference in potency between both opioids? (12 points)

B) Answer the following questions related to the below graph, which depicts the therapeutic and lethal effects of an experimental drug in mice. The following information is needed for your calculations:

- LD1 = 0.01 mg/kg
- ED50 = 0.04 mg/kg
- ED99 = 0.22 mg/kg
- LD50 = 10.9 mg/kg
- LD50 following chronic dosing of a subthreshold dose = 180 mg/kg (not shown in graph)

i. Calculate the therapeutic index of this drug. (5 points)

ii. Calculate the margin of safety of this drug. (5 points)

iii. Calculate the chronicity toxicity of this drug. (5 points)

iv. Based on this information, briefly discuss the pros and cons for further development of this drug. (10 points)
C) The following study was designed to investigate whether the co-administration of opioids and nicotine would be advantageous in treating pain. Subjects were randomly assigned to the following four conditions: 1) Vehicle control (two injections of vehicle); 2) Codeine alone (a subthreshold injection of codeine and a vehicle injection); 3) Nicotine alone (a subthreshold injection of nicotine and a vehicle injection); 4) Drug Combination (a subthreshold injection of codeine and a subthreshold injection of nicotine). The results are graphically illustrated below (***, p < 0.001 compared with the other three groups). State the conclusions that can be made from this study. (20 points)
D) Read the short story below and then answer the question.
A prospective study was conducted in an attempt to investigate the impact of alcohol on serum cholesterol. Subjects were asked to keep track of how much alcohol they consumed on a daily basis over the last 12 months. A strong positive correlation was found between the total amount of saturated fat consumed and LDLs. Based on these findings, the investigators calculated an ED50 dose (95% confidence limits) of 60 mg (38-82) saturated fat is sufficient to cause a significant increase in LDLs. Critique this use of statistics. (15 points)

E) Draw dose-response curves for two different drugs in which one drug is more potent, but less efficacious than the other drug. Hint: the curves should be drawn on the same graph. (5 points)

F) Draw an isobologram depicting a drug interaction study in which the two different analgesic drugs can have the following interactions: a) additive, b) synergistic, and c) antagonistic. In your answer label the ED50 of each drug alone. (15 points)
Question 2.

The compound whose structure is shown below is an analgesic agent. The drug is prescribed to a 75-year-old 165 lb (75 kg) patient with a history of rheumatoid arthritis. Use the following drug information to answer the questions below:

\[
\text{Fractional Oral Bioavailability} \quad 0.70 \\
\text{Fractional urinary excretion (unchanged drug)} \quad 0.5 \\
\text{Clearance (mL/min/kg) (first order)} \quad 8.7 \\
\text{MTC (mg/L)} \quad 20 \\
\text{MEC (mg/L)} \quad 10 \\
\text{Volume of Distribution (L/kg)} \quad 0.1 \\
pKa \quad 7.5
\]

1. Predict whether this drug would be more effectively eliminated in urine when the pH of urine is pH 6.5 or pH 8.5. In a person who is intoxicated with this drug, how might one manipulate the urinary pH to speed the renal excretion of this drug.

2. Assuming that this particular drug is eliminated by a first order mechanism, estimate the elimination half life of the drug. Show your work.

3. Propose a body water compartment that the distribution of the drug might be restricted to.

4. Suggest an appropriate steady state plasma drug concentration (Css) to target to produce a therapeutic effect?

5. Based on your estimated half life of the drug, would administration of a loading dose be useful? Explain why or why not. What would the loading dose be if you wanted to give one. Show your work.

6. What oral dose of this drug given at 12 hr intervals would maintain the appropriate plasma drug Css?

7. If 10 mg of drug X is administered every 12 hrs, how long would it take to reach 94% of the Css?

8. Make an assessment of the therapeutic safety of this drug from the data given. Is it a relatively safe drug to use, or is its margin of safety narrow? Defend your answer. (Hint: you may want to use an equation).
Choose between questions 3 and 4.

Question 3.

“All mutagens are carcinogens”. Determine whether this statement is true or false.

If true, explain precisely why mutagenesis MUST lead to carcinogenesis.

In addition, describe two assays that are used to determine the mutagenic properties of a compound and two assays that are used to determine the carcinogenic properties of a compound.

Finally, explain how the mutagenesis assays are predictive for carcinogenesis.

If false, indicate what factors come into play to prevent a mutagenic compound from being carcinogenic.

In addition, describe two assays that are used to determine the mutagenic properties of a compound and two assays that are used to determine the carcinogenic properties of a compound.

Finally, explain why mutagenesis assays are not predictive for carcinogenesis.

Question 4.

Human viruses and pathogenic bacteria each have unique characteristics that make them susceptible to particular types of pharmacological agents and strategies, yet each must ultimately accomplish many of the same processes, namely, replication of their respective genomes and production of viral/bacterial proteins. From your extensive knowledge of antiviral agents, select two classes of agents that represent distinctly different strategies and molecular targets. Give 2-3 examples of each class (unless only one such drug exists), and explain the basis of the selectivity of the agents and why they are less toxic to host cells than to the virus. Then for each class, discuss the possibility of using the same strategy or molecular target to develop analogous antibacterial agents. If you think there is no possibility of developing such agents, explain what it is about the life cycle of the virus in question and of bacteria that would make the attempt futile. If you think such agents could be developed, describe any different characteristics that might be required in these agents that would be different from the existing antiviral agents. Choose at least one class of agents for which development of analogous antibacterial agents, however difficult, may be possible.
**Choose between Questions 5 and 6.**

**Question 5.**

Type 2 diabetics have impaired insulin release and are often treated with sulfonylurea drugs such as tolbutamide and glyburide which provoke more insulin release from the islets.

It is known that insulin exocytosis is dependent on a rise in cytosolic free Ca in islet beta cells. Please discuss in detail how sulfonylureas trigger insulin secretion and in the process describe how the main physiologic stimulus, glucose, works to release insulin in normal subjects.

**Question 6.**

Discuss the mechanism of action and therapeutic uses for

1) Forteo (rhPTH 1-34),

2) biphosphonates such as alendronate, and

3) calcitonin.
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Good Luck.
Choose between questions 7 and 8.

Questions 7.
Many alternative medicine proponents advocate for the use of natural plant-derived or herbal products instead of synthetic chemicals found in most prescription drugs. Often the belief is that these “natural” medicines are less dangerous than “drugs.” As a pharmacist, however, you know that several of the effective medicines we have today originally were derived from plants. For example, aspirin is a derivative of a substance that naturally occurs in the bark of some plants such as the willow tree. In many cases, these natural products produce their therapeutic effects through action on existing endogenous systems (e.g., heroin is derived from the opium poppy and is an agonist at μ receptors). Aspirin also acts primarily by affecting one endogenous system.

a. Draw a diagram that illustrates the endogenous system that is the primary substrate for aspirin. The “starting point” of this system should be the membrane-bound ligand that gives the system its name. Be sure to include all steps of the system/cascade, including the name of the enzyme that frees the ligand from its membrane-bound site as well as the names of at three major enzymes that degrade the ligand and their associated end products.

b. List aspirin’s major therapeutic effects and describe how aspirin interacts with this system to produce these effects.

c. Choose two other classes of drugs that produce their therapeutic effects through interaction with this endogenous system, but that do so via a mechanism that is not identical to that of aspirin. Name each class and provide one example of a specific drug from the class. Describe how each of these two classes of drugs affects the endogenous system AND how their actions differ from those of aspirin.

d. Marijuana is another natural product that many argue may have therapeutic effects (i.e., “medicinal marijuana”). How is marijuana’s mechanism of action related to the same endogenous system through which aspirin works?

Question 8.
Based on their mechanisms of action (MOA) a combination therapy of Mycophenolate Mofetil (Cellcept) and Leflunomide (ARAVA, Brequinar Sodium) would be useful to produce immunosuppression. Describe the MOA of each of these drugs and why they would be useful when administered together. In your answer describe how these drugs have specificity for the lymphocyte cells of the immune system. Include in your answer what uses of these drugs have been approved by the FDA. Describe any adverse effects or contraindications that you know are related to the drugs as well as any drug interactions that can occur with over-the-counter medications.
Choose between questions 9 and 10.

Question 9.

Risk Assessment and Risk Management overlap at one key element common to both. What is this common element? Besides this element what are the other elements which make up the Risk Management paradigm. In addition to naming the elements, give examples of how they play a role in the final Regulatory Decision on a compound. Describe what roles Risk Management can play in dealing with environmental contaminants.

Question 10.

The following questions relate to the pesticides, parathion and carbaryl, whose structures are shown below.

(A) Which one is parathion and which is carbaryl? (10%)

(B) What structural subclasses of pesticides do these chemicals represent? (10%)

(C) One of the compounds requires in vivo metabolism to its active form. Which one is it, what type of reaction does it involve, and what type of enzyme system is required for bioactivation mechanism? (10%)

(D) Both the above mentioned active metabolite and the other compound are rapidly inactivated and eliminated from the body. Based on your general knowledge of drug biotransformation, suggest two possible metabolites that might occur in the body. (There are actually many possibilities). Name the enzyme that could mediate these reactions. (10%)

(E) Describe the biological effects of parathion and carbaryl, noting the biological target and basic similarities or differences in their effects. Describe the underlying basis for the differences. (40%)

(F) Describe how cases of severe poisoning by these two compounds are typically handled in emergency rooms (decontamination and life support measures, therapeutic antidotes), noting similarities and differences if they exist. Describe the underlying mechanisms of the antidotes and the influence of time on their efficacy. (20%)
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Good Luck.
Choose between questions 11 and 12.

**Question 11.**

A. You have begun a collaboration with a colleague in Chemistry to test novel cannabinoid compounds. Your colleague has determined $K_i$ values for several compounds. Describe briefly how this would be done experimentally. What does the $K_i$ value define (include appropriate formulas)?

B. You have identified compound X as a lead compound and are interested in determining the efficacy of compound X. What method would you use? Please explain or illustrate using a graph what the response would be for a full agonist, a partial agonist and an antagonist.

   *Bonus points for naming a known cannabinoid agonist and antagonist!*

C. You have found that compound X is a full agonist and decide to test whether chronic administration of X alters CB1 cannabinoid receptors in brain, using cerebellar homogenates. How would you determine the number and affinity of CB1 receptors in compound X- and vehicle-treated mice? Please include a representative graph for X- and vehicle-treated results and relevant mathematical formulas. What do the results you have mean?
**Question 12.**

You are interested in studying the novel receptor known as XYZ, which is expressed exclusively in the CNS. You read that two subtypes of XYZ have been cloned and both exhibit heptahelical structures. Expression of either XYZ1 or XYZ2 in cell culture leads to inhibition of adenyl cyclase. You further learn that a tritiated compound, [3H]xyz is commercially available, but does not exhibit specificity for XYZ1 vs. XYZ2. Unlabeled agonist and antagonist have recently become available for each receptor subtype.

For each question, please provide a brief experimental rationale, methods including appropriate controls (you can use a diagram), and predicted results with interpretation. Also, note any experimental limitations or confounds that might affect your study.

1. How would you localize XYZ1 and XYZ2 receptors? Please include controls to verify that you are seeing a receptor. How would you localize functional receptor activity?

2. You find that the following regions exhibit the highest receptor density and activity: basal ganglia (caudate-putamen, globus pallidus, substantia nigra), hippocampus, PAG, cerebellum and spinal cord dorsal horn. What functions would you predict for this receptor? Briefly discuss in vivo experiments that could confirm these predictions.

3. A colleague offers you an antibody that recognizes the endogenous peptide ligand for XYZ (peptide xyz). What experiments would you perform?
Choose between questions 13 and 14.

Question 13.
A 56 year old woman over three separate office visits has documented blood pressure of 155/100 mmHg. Upon further examination and many (expensive) tests, no underlying cause of the hypertension can be found and she is given a diagnosis of essential hypertension.

a. The physician wishes to give a single drug treatment to control the hypertension. Assuming there is no other complicating disease present, list the four front-line classes of drugs that would be suitable to treat the hypertension in this individual. Identify the class that is regarded as the first among equals.

b. Assuming the use of a single agent was not sufficient to lower the blood pressure to an acceptable level. What combination therapy would be suitable if the physician wishes to add an additional agent or agents to a vasodilator to treat the hypertension with minimal side-effects and complement each other to lower the blood pressure? Use flow diagrams with arrows to explain your rationale.

Question 14.
Modification of the phenylethylamine “parent compound” can alter sympathomimetic activity on adrenoceptors.

\[
\begin{align*}
\text{Catechol} & \quad \text{Phenylethylamine} \\
\text{OH} & \quad \text{CH}_2-\text{CH}_2-\text{NH}_2 \\
\text{OH} & \quad \\
\end{align*}
\]

Briefly discuss the following points and give an example if possible:

a. How modification of the “parent compound” can alter selectivity to the different receptor subtypes.

b. How modification of the “parent compound” can alter the susceptibility to enzymatic degradation.

c. How modification of the “parent compound” can alter the access to the central nervous system.
Choose between questions 15 and 16.

Question 15.

A pharmaceutical company is interested in developing a novel drug (Compound X) as an analgesic. Extensive *in vitro* studies revealed that Compound X binds to CB1 receptors in the low nM range and binds to µ-opioid receptors in the low µM range. However, the drug did not have any apparent affinity at any other known receptor. Answer the following questions:

a) Based on the above information, describe a series of preclinical (i.e., whole animal) experiments that you would design to determine whether this compound indeed has potential analgesic efficacy. (25 points)

b) Assuming that Compound X reveals positive effects in your first study, describe a single experiment that would elucidate the receptor mechanism(s) of action for its effects? (25 points)

c) Based on the *in vitro* binding profile described above, indicate which is the most likely untoward effect of Compound X, and describe an experiment to assess this effect. (20 points)

d) Explain how the drug discrimination paradigm could be used to determine the relative specificity of Compound X for CB1 and µ-opioid receptors. (15 points)

e) Describe how you would assess whether Compound X has dependence liability. (15 points)

f) Describe how you would assess whether Compound X has dependence liability. (15 points)

Question 16.

Compare and contrast the mechanism of action of the classical tricyclic antidepressant drugs and of the SSRI s. Be sure to name at least one example of each class of drugs. What are the drawbacks to the use of each of these two major classes of antidepressants? (75%) What would be the characteristics of an ideal antidepressant drug? How well do the drugs from the above two classes fulfill these characteristics? (25%)
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Good Luck.
Choose between questions 17 and 18.

Question 17.

Part I (60 points): When certain drugs of abuse are self-administered repeatedly, users often develop physical dependence. Using opiates as an example, describe this phenomenon. Include in your answer a description of dosing conditions favorable for the development of opiate physical dependence, the typical signs and symptoms of withdrawal, the time course of their appearance, how long they typically last if not treated, and methods for treatment of withdrawal. If an opiate abuser becomes physically dependent, what impact does this have on his or her life?

Part II (40 points): For pharmacological research in rodents, how is opiate physical dependence typically produced and measured? What is known and not known about the cellular bases for this phenomenon?

Question 18.

You are in charge of testing two new analgesic opioids (Opioid #1 and Opioid#2) for the development of tolerance and physical dependence. In addition, some evidence suggests that long-term pretreatment with either of the opioids may induce a decrease in the analgesic effects of the other opioid. Define the terms "tolerance", "physical dependence", "cross-tolerance", "cross-physical dependence" and "addiction". Then discuss your experimental design using the two opioids to determine if any of the terms you have defined are applicable to the two new drugs.
Choose between questions 19 and 20.

**Question 19.**

Arrhythmias are a major clinical problem in cardiology and many types of drugs have been identified and are in use as antiarrhythmic agents. Please discuss the way these drugs are classified and include in your discussion major representatives of each antiarrhythmic class, some typical clinical applications and mention at least briefly how the drugs work.

**Question 20.**

For the follow individuals select a suitable agent or agents to treat their medical conditions (cardiovascular) with the least potential for side-effects. Also mention any drug class which may be contraindicated. You have a choice of eleven (11) scenarios; answer any eight (8) scenarios.

1. 55 yr, hypertensive white male with CHF and angina pectoris.
2. 45 yr, hypertensive Afro-American woman with diabetes.
3. 65 yr, hypertensive white woman who is also obese.
4. 50 yr, hypertensive white woman who has asthma and diabetes.
5. 55 yr, hypertensive white male with benign prostate hypertrophy.
6. 35 yr, balding, vain, white male with hypertension.
7. 45 yr, hypertensive white woman who suffers from migraines.
8. 40 yr, hypertensive white woman with glaucoma.
9. 50 yr, hypertensive Afro-American woman with diffuse pheochromocytoma.
10. 25 yr, athletic, hypertensive Afro-American woman who runs marathons.
11. 55 yr, hypertensive white male with angina pectoris and arrhythmias.
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Good Luck.
You are required to answer both of the “advanced” questions 21 and 22.

21.

You are invited by the National Institute of Drug Abuse to attend a scientific meeting to set the course of funding for basic research in neurobiology of drug abuse for the next decade. You have decided to present on the neurobiology of nicotinic receptors, further investigation of which is indeed critical for development of the field. You are asked to write a full report on this area that should include: 1) a background section on what we currently know about the subject; 2) identification of one or two key research topics where more needs to be known; and 3) a justification of why additional knowledge in this area is critical for advancing the neurobiology and treatment of drug abuse (that is, why investigations in this area are especially important). You are not being asked to provide the methods or experiments that might be used to address the problem—only the concept. Hint: You can use the information and examples presented in your Neurochemistry course to help you in your presentation.
Question 22.

The student should answer all four parts to this question.

1) Describe how you could use drug discrimination procedures to make an inference that a drug-produced behavioral effect is receptor-mediated. (This implies you are able to list the criteria that need to be met to infer a drug's effect is receptor-mediated.) Use real or hypothetical graphs to illustrate an effect from which you would infer that a drug discrimination effect is receptor-mediated. 30 pts

For questions 2-4: Imagine you work for a drug company which has been synthesizing compounds which bind to either one of two newly-discovered receptors called Zed1 and Zed2, and bind to no other receptors. Your supervisor has given you two compounds to test and he has asked you to determine whether their discriminative stimulus effects are mediated by the same receptor. He has assured you that each is either an agonist at Zed1 or Zed2 (and not an antagonist at either). He has assigned another laboratory to conduct cross-tests which will determine if each compound generalizes to the discriminative stimulus effects of the other. He wants you to use different approach. He gives you an antagonist, Mork5, which blocks activity at both Zed1 and Zed2 and asks you to use Mork5 to determine whether the discriminative stimulus effects of the two compounds are mediated by the same receptor.

2) What approach would you suggest for using Mork5 to determine if the discriminative stimulus effects of the two compounds are mediated via the same receptor (remember, you can't use the cross-testing being conducted by the other lab). 10 pts

3) Describe procedurally how you would conduct your testing (what would you test and under what conditions and at how many minimal doses). 30 pts

4) Provide hypothetical data using graphs to demonstrate an outcome in which the discriminative stimulus effects of the two agonists were being mediated by separate receptors. Provide hypothetical statistical results if they can be used to illustrate your inference. 30 pts