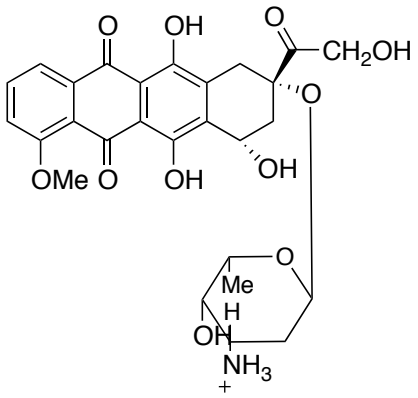
Essentials of Medicinal Chemistry

CHM 310

Worksheet 1

Name: _____ Date: November 9, 2015

1. The following antibiotic structure is an intercalating agent. What role does the ionic group serve in making this molecule an effective intercalating agent?



a) It increases water solubility allowing high dose levels to be used.
b) It interacts with charged phosphate groups in DNA to stabilize intercalation.
c) It acts as a strong hydrogen bond donor with nucleic acid bases to stabilize intercalation.
d) It only becomes protonated when it enters cells and so becomes trapped within the cell leading to high concentrations of drug.

2. Which of the following statements is false regarding the blood-brain barrier?

a) The walls of the capillaries supplying the brain have tight fitting cells making it difficult for polar drugs to leave the capillaries.
b) The capillaries in the brain have a fatty coating making it more difficult for drugs to enter the brain.
c) The walls of the capillaries supplying the brain are made up of several layers of cells, which act as a barrier to the release of drugs.
d) Hydrophobic drugs pass through the blood brain barrier more easily than hydrophilic drugs.

3. Which of the following statements is the closest description of Phase I metabolism?

a) Reactions which add a polar molecule to a functional group already present on a drug or one of its metabolites.
b) Reactions which occur in the blood supply.
c) Reactions which add a polar functional group to a drug.
d) Reactions which occur in the gut wall.

4. Which of the following statements is not true about cytochrome P450 enzymes?

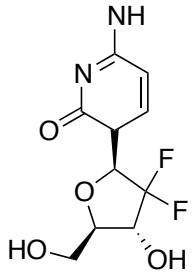
a) They contain haem and magnesium.
b) They belong to a general class of enzymes called monooxygenases.
c) There are over 30 different cytochrome P450 enzymes.
d) Variation in cytochrome P450 enzyme profile between individuals can explain individual variation in drug susceptibility.

5. Which of the following groups is least susceptible to cytochrome P450 enzymes?

a) terminal methyl groups
b) allylic carbons
c) benzylic carbon atoms
d) quaternary carbon atoms

Read and answer questions 6 through 8.

Gemcitabine is an anti-cancer and anti-viral drug developed by Eli Lilly Pharmaceutical Company.



Gemcitabine (GEM)

Glioblastoma Multiforma (GBM) has a poor prognosis and is poorly sensitive to cytotoxic drugs. Gemcitabine (GEM) is a very potent radio-sensitizer. However, in order to apply GEM in combination with radiation in the treatment of GBM, the drug needs to be taken up by the brain into the tumor and metabolized to its active nucleotides. The aim of our study was to investigate whether GEM would pass the blood-tumor barrier and would be taken up at sufficiently high concentrations in the tumor to enable radio-sensitization. In addition, we investigated whether critical enzymes in GEM metabolism would be expressed in GBM: deoxycytidine kinase (dCK), responsible for GEM activation, and deoxycytidine deaminase (CDA), converting GEM to difluorodeoxyuridine (dFdU), which is supposed to be an inactive metabolite. GEM was administered just before surgery or during anesthesia to 10 patients with recurrent GBM, at two doses of 500 and 1000 mg/m2 , each group consisting of 5 patients. Tumor samples were obtained between 2-4 hr after administration. GEM levels in plasma at the time of the biopsy varied from 0.9-9.2

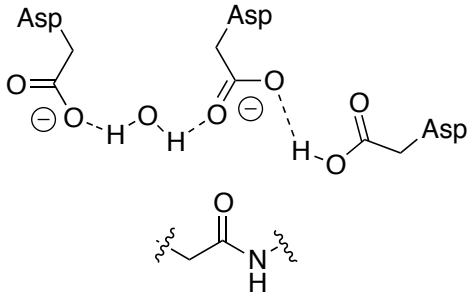
uM, dFdU from 25-72 uM and that of the active metabolite, gemcitabine triphosphate, dFdCTP in white blood cells from 2-108 pmol/10^6 cells. GEM levels could be measured in tumor samples of 5 patients by LC-MS-MS and varied between 2.5-47 pmol/g tissue; no difference was observed between the 500 and 1000 mg/m2 group. In 7 patients dFdU was measured by HPLC and varied from 29-60 nmol/g tissue in the 500 and from 49-72 in the 1000 mg/m2 group (t-test, not significant). From the other patients insufficient material was available to evaluate GEM and dFdU. The relative gene expression of dCK compared to ß-actin as measured with real-time light cycler PCR varied from 0.44-2.56. The dCK activities were in a relatively small range of 1.1-2.32, while that of CDA were between 1.5-5.5 nmol/hr/mg protein. Since the CDA levels are very low compared to e.g. liver (100-fold lower) and dCK close to that of intermediately sensitive xenografts, GEM is likely to be phosphorylated under these conditions, although we were not able to measure the active nucleotide, since this is rapidly degraded during tissue preparation. These data demonstrate for the first time that GEM passes the blood-tumor barrier in GBM-patients. In tumor samples both the levels of GEM and even of dFdU are high enough to enable radiosensitization and warrant clinical studies using GEM in combination with radiation.

6. Gemcitabine is another example of a pro-drug. based on the abstract above, what must happen to GEM to make it an active drug?

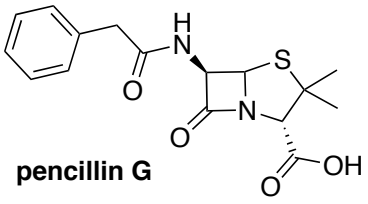
7. According to PubChem, GEM has a log P value of -1.318. Why might the researchers at think it necessary to study the viability of GEM in the treatment of glioblastomas, a common form of brain cancer?

8. The fluorine atoms on GEM are very important for its activity. Though you might not guess it, fluorine atoms are nearly the same size as a hydrogen. How does the introduction of fluorine, in part, explain the basis of GEM's bioactivity.

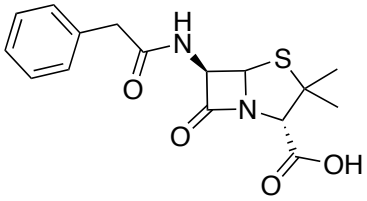
9. Provide a reasonable curved electron flow arrow mechanism and intermediate structures for the mechanism of HIV protease.

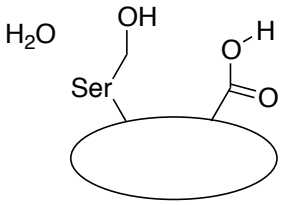


10. The structure of penicillin G is shown. Show the curved electron flow arrow mechanism for the reaction of penicillin with transpeptidase, a serine protease.

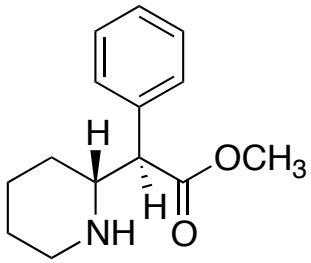


pencillin G





11. Predict as many phase I metabolites (there are four or five that I can think of) as you can for methylphenidate (Ritalin), the most commonly prescribed treatment for attention deficit hyperactivity disorder. Can you suggest any Phase II metabolites?



methylphenidate