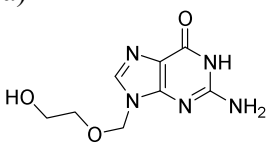
Medicinal Chemistry
Mid Term 1 Answers

1) In the late 1800's, the Bayer company became the first drug company to adopt modern drug discovery practices. What were five key innovations that this company pioneered? (**5 points**)
   - Changed a naturally derived substance to modify the properties to be more "drug-like"
   - Used research to improve the drug (SAR)
   - Used biological assay to measure drug properties (fish gills)
   - Developed a drug to fill a market demand (fever)
   - Sold direct to MD's and pharmacists (not to the public)
   - Invented drug names and trademarked them
   - Used a company sales force
   - Used large scale standardized manufacturing (made the drug from coal tar)
   - Used a non-natural as the active ingredient

   (Any five)
2) Predict whether the following compounds are likely to be orally bioavailable or not, and provide a brief justification for each: (**6 Points**)

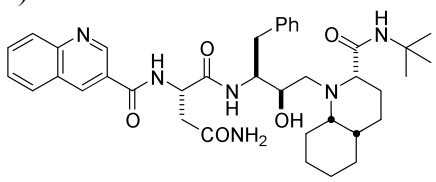
   a)



Mol. Wt.: 225.20
LogP = 3.5

MW < 500
logP < 5
H bond donors = 4 < 5
H bond acceptors = 8 < 10
Does not violate any of Lipinski's rules, likely bioavailable

   b)



Mol. Wt.: 670.84
LogP = 5.4

MW > 500
logP > 5
H bond donors = 6 > 5
H bond acceptors = 11 > 10
Violates all of Lipinski's rules, likely not bioavailable

3) Many drug companies are replacing LogP measurements with assays that determine LogD as a predictor of bioavailability.
   a) What is the definition of LogP? (**2 Points**)

$$\text{LogP} = \text{Log}\frac{[\text{Drug}]_{\text{octanol}}}{[\text{Drug}]_{\text{water}}}$$

   measure at pH in which the drug is in the neutral form

   b) What is the definition of LogD? (**2 Points**)

$$\text{LogD} = \text{Log}\frac{[\text{Drug}]_{\text{octanol}}}{[\text{Drug}]_{\text{water}}}$$

   measure at a defined pH
   the most common pH is 7.4

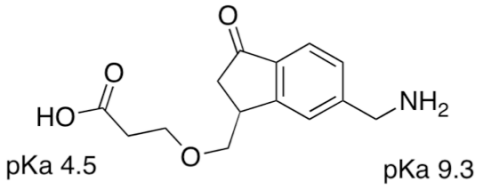
c) What are the advantages of using LogD rather than LogP in drug discovery? (there are 2) (**2 Points**)
LogD is easier to measure (1). When measuring LogP, the pH of the water phase must be adjusted for each molecule. This could require a new buffer for each molecule. LogD measurements are done at a defined pH so the same buffer can be used to make many measurements.
$LogD_{7.4}$ is more physiologically relevant than LogP (1)

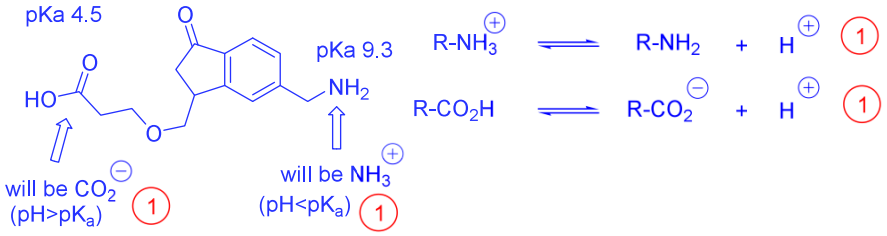
d) What information does LogP and LogD provide to the medicinal chemist? (**2 Points**)
Both measure lipophilicity (1)
Either measurement can be used to predict permeability, and are part of the rule of five (1)

e) How should the rule of five be modified to incorporate LogD? (**2 Points**)
Replace the requirement that CLogP < 5 with the following rule:
$1 < LogD_{7.4} < 3$

4) For each of the following drugs, write the acid-base equation that corresponds to each pKa (use R group notation to simplify your answer). Use your equations to predict whether the original drug will likely be soluble in water at pH 7.4 or not. (**8 Points**)

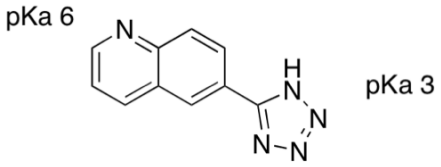
a)



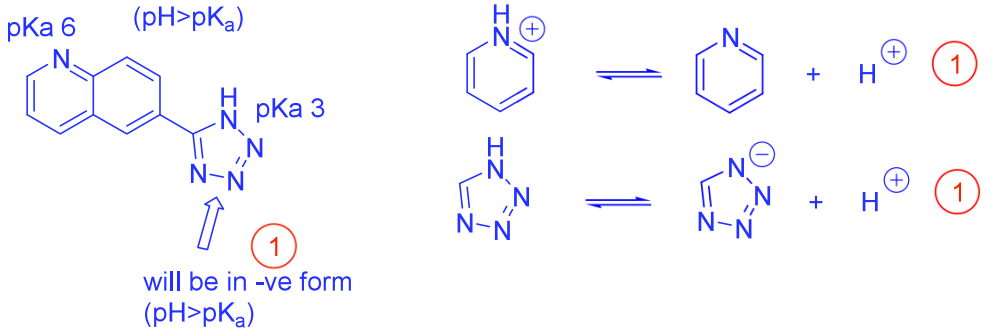


1 molecule is neutral at pH 7.4 therefore low solubility

b)

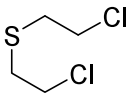


1 will be in neutral form (pH>pKa)

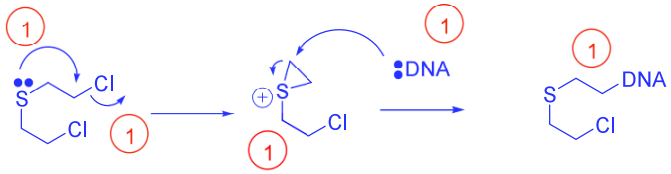


1 molecule is negative at pH 7.4 therefore it will be soluble

5) Many cancer drugs have been developed based on the general reactive principle of mustard gas, a chemical weapon first used in World War I.



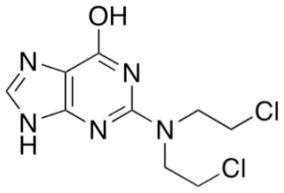
a) What is the <u>mechanism</u> by which mustard gas poisons people? (**6 Points**)



1 produces DNA damage or interferes with DNA replication

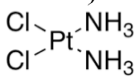
b) What is the name of the chemical principle involved? (**1 Point**)
Anchiomeric assistance or neighboring group participation (1)

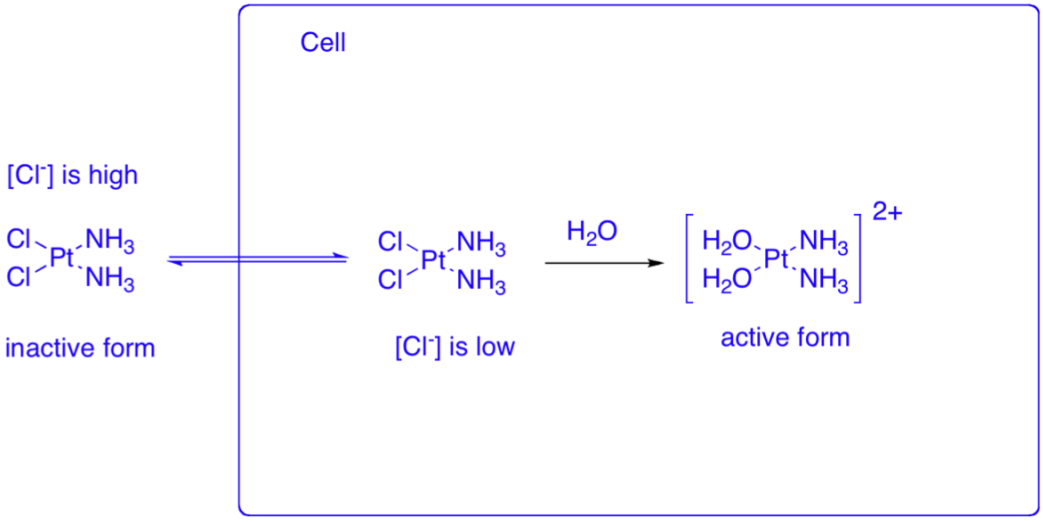
c) Based on this principle, safer drugs such as the one depicted below were developed. What are <u>three</u> key features of this drug that make it safer to use than mustard gas? (use chemical structures as necessary) (**5 Points**)



1) Change the Sulfur to a nitrogen. Because Nitrogen is less nucleophilic than sulfur, the compound will be less reactive (less anchiomeric assistance), making the compound more selective (1)
2) Adding an aromatic group next to the nitrogen reduces the electron density on the nitrogen through resonance (1). This reduces the nucleophilicity of the nitrogen and hence improves the selectivity of the compound (1)
3) Attaching the purine-type structure to the molecule increases bioavailability (1). The compound is able to penetrate into the cell because the structure resembles a normal metabolite (1)

d) The following anti-cancer drug produces a relatively low incidence of side effects by selectively targeting cancer cells. Describe in detail how this happens. It may be helpful to use a diagram for part of your answer. (**7 Points**).

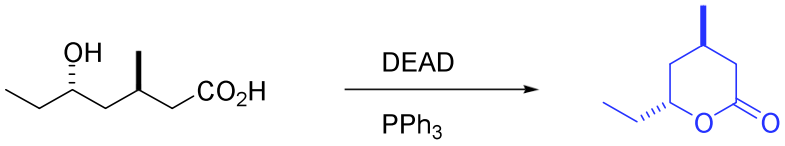




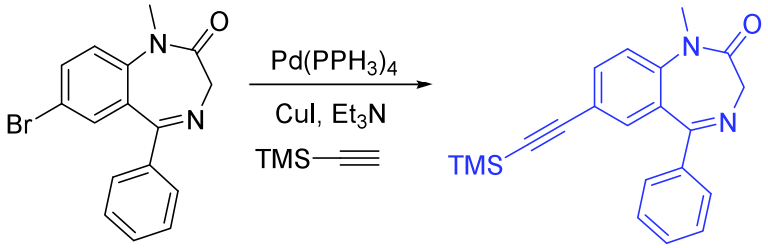
- the drug is a neutral molecule and is able to diffuse into, and out of, normal cells
- in cancer cells the [Cl]- is low, and so the chlorides exchange with water. This creates a charged species that cannot cross membranes well and so the drug is trapped inside the cancer cell
- the drug is only "active" after the chlorides have been replaced. This happens in cancer cells but is less likely in a normal cell

6) Provide the missing product, starting material or reagent as necessary. (**6 Points**)

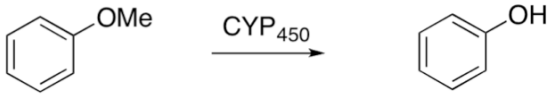
a)

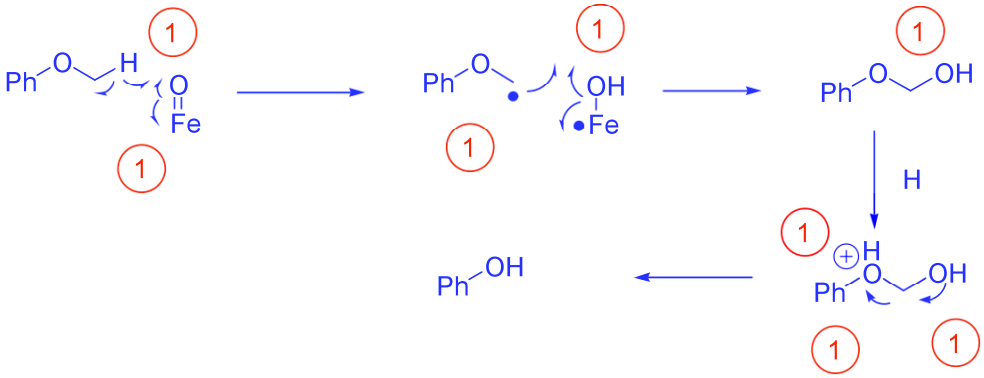


b)



7) Give a mechanism to explain the following result. For clarity, you may assume the enzyme active component is in the Fe=O state. (**8 Points**)

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