Medicinal Chemistry
Mid Term 1 Answers

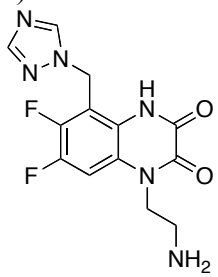
1) During cancer formation, the cell growth signal becomes activated. Explain how this can happen by random mutation. (**3 points**)
   - a random mutation most likely results in attenuated or loss of function. Enzymes become non-functional or protein fold incorrectly
   - most likely way this will "activate" a pathway is if the system looses the ability to "switch off"
   - example is RAS, that looses catalytic function and is unable to hydrolyze GTP to GDP. This keeps it locked in the active form and it continuously stimulates cell growth

   (b) Can this growth signal be de-activated using a drug? Why or why not? (**2 points**)

no
small molecules cannot restore function to a defective enzyme or protein
genetic modification is required

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

a)

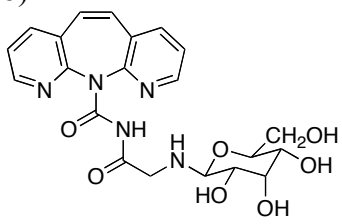


Mol. Wt = 322.10
LogP = 3.5

Mol Wt is less than 500
Log P is less than 5
H bond donors = 3 this is less than 5
H bond acceptors = 8 this is less than 10

Satisfies all Lipinsky rules
likely orally bioavailable

b)



Mol Wt = 457.16
$LogD_{7.4}$ = 2.5

Mol Wt is less than 500
Log $D_{7.4}$ is between 1 and 3
H bond donors = 6 this is more than 5
H bond acceptors = 12 this is more than 10

Breaks 2 Lipinsky rules
likely **Not** orally 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? (**3 Points**) (an equation may be helpful)

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

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

   b) What is the definition of LogD? (**3 Points**) (an equation may be helpful)

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

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) When using LogD with Lipinski's rules a specific range of values is used. What is the range of values for oral bioavailability? (**2 Points**) Explain the significance of this range. (**4 Points**)

Replace the requirement that CLogP < 5 with the following rule:

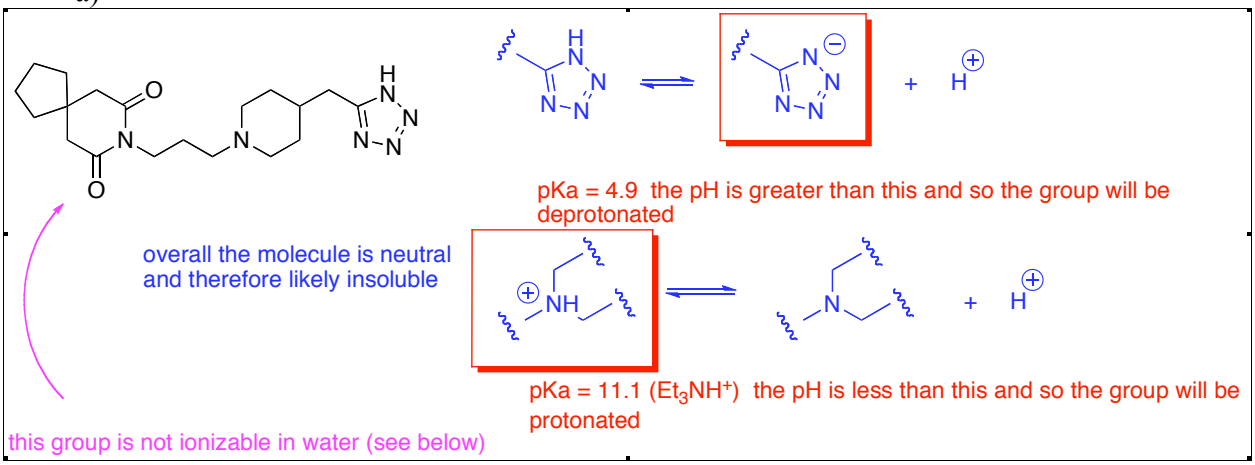
$1 < LogD_{7.4} < 3$ (2)

if LogD7.4 is lower than 1 the drug will be too water soluble and not lipophilic enough to cross membranes (be permeable) (2)

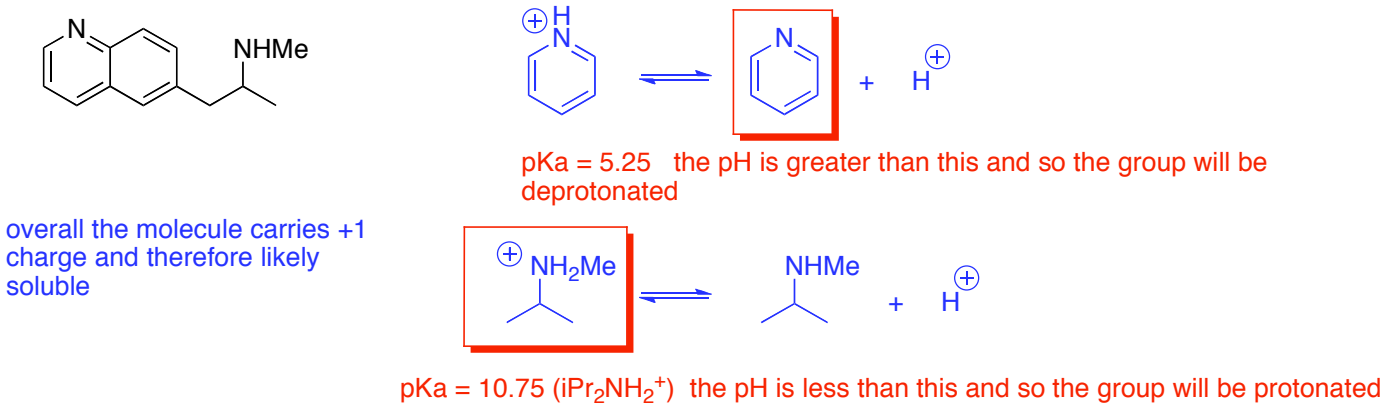
if LogD7.4 is higher than 3 the drug will be too lipophilic. Can cross membranes (be permeable) but will not be soluble enough in water to reach the membranes (2)

4) For each of the following drugs, identify the functional groups that are ionizable. Write the applicable acid-base equation for each (use R group notation to simplify your answer). Use your equations and the appropriate pKa value (table at the back) to predict whether the original drug will likely be soluble in water at pH 7.4 or not. (**10 Points**)

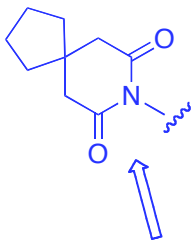
a)



b)



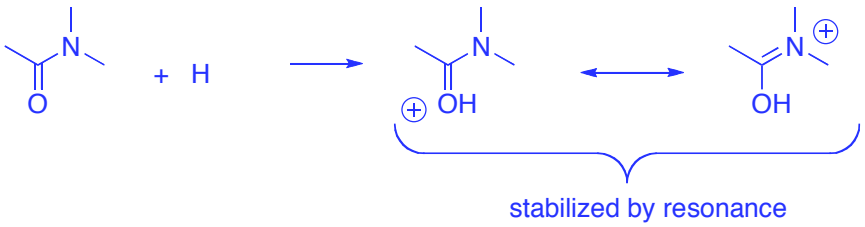
Note for part a:



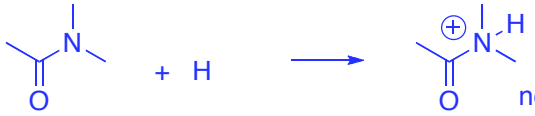
This group has no hydrogens and cannot be an acid

to find it's pKa as a base, add an H^+ and look for the closest structure on the table

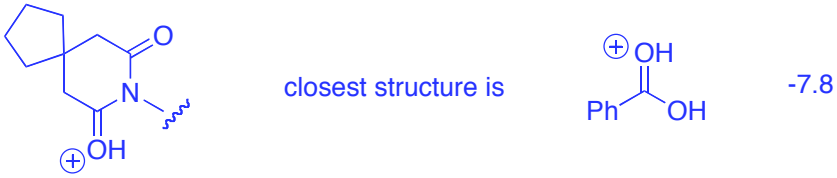
functional groups containing carbonyls are always protonated on the carbonyl. this location is the most basic because it provides resonance stabilization



stabilized by resonance

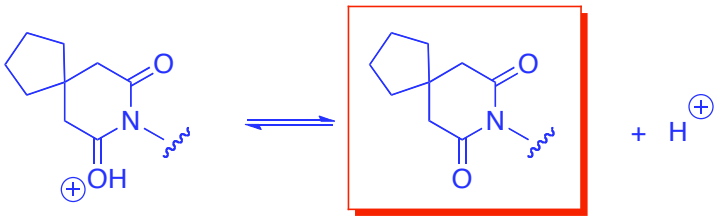


no resonance possible



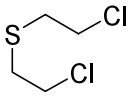
closest structure is

-7.8

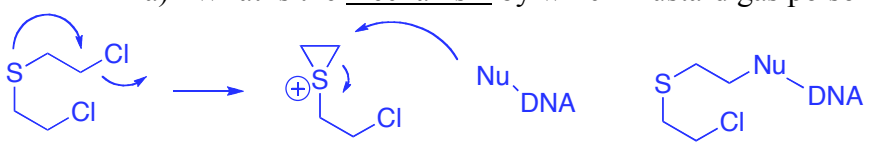


pKa = -7.8 the pH is greater than this and so thr group will be deprotonated

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? (**5 Points**)

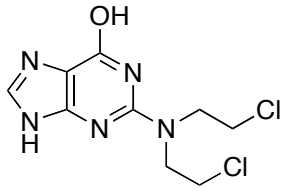


alkylation of DNA is fatal to fast growing cells

b) What is the name of the chemical principle involved? (**1 Point**)

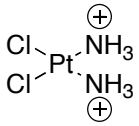
Anchiomeric assistance or neighboring group participation (1)

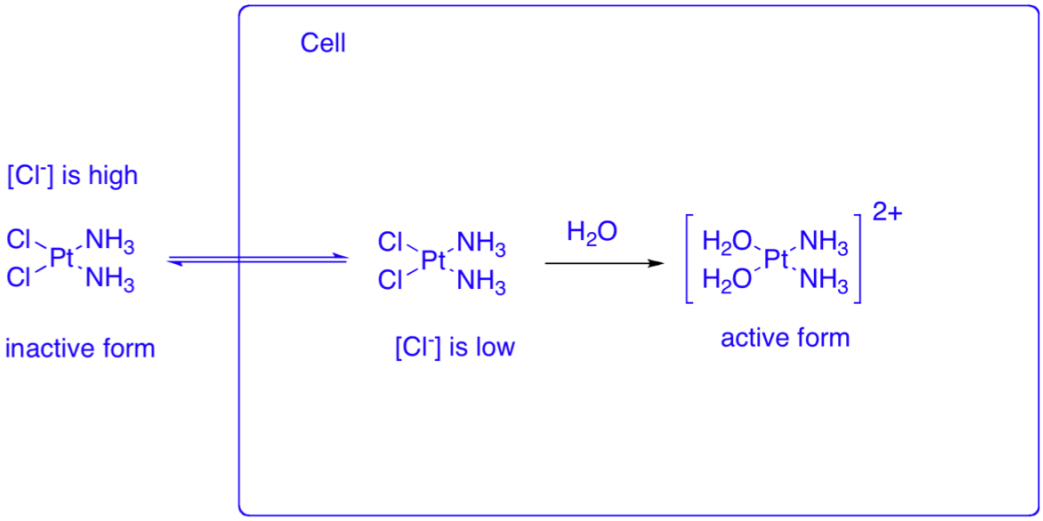
c) Based on this principle, safer drugs such as the one depicted below were developed. What are three key features of this drug that make it safer to use than mustard gas? (use chemical structures as necessary) (**4 Points**)



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. The compound is able to penetrate into the cell because the structure resembles a normal metabolite (1)

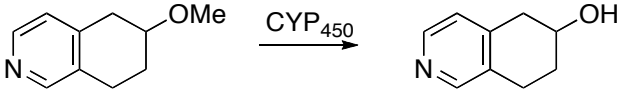
d) The following anti-cancer drug produces a relatively low incidence of side effects by selectively targeting cancer cells. Describe in detail how this happens. It may be helpful to use a diagram for part of your answer. (**7 Points**).

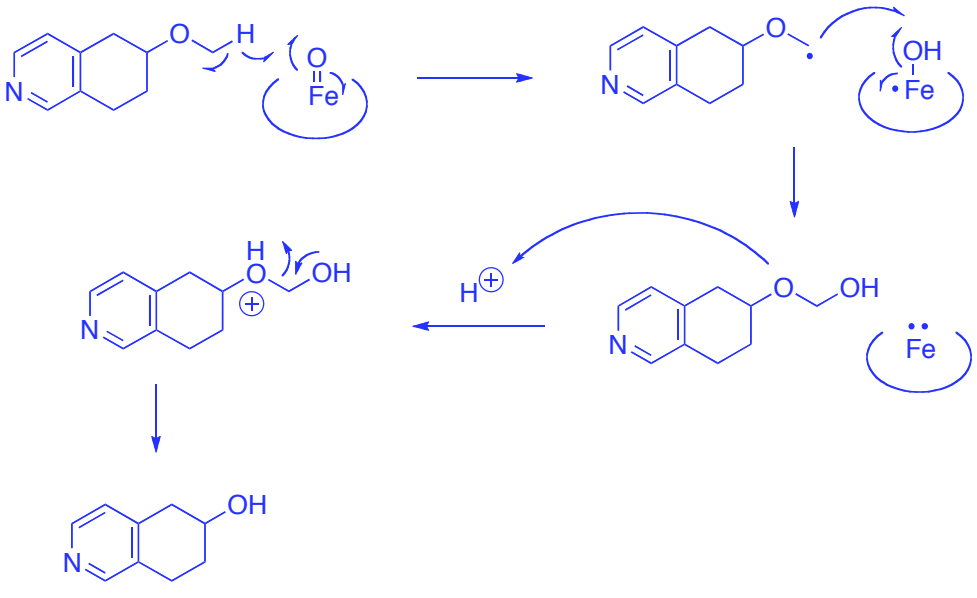




- the drug is a neutral molecule and is able to diffuse into, and out of, normal cells
- in cancer cells the [Cl]- is low, and so the chlorides exchange with water. This creates a charged species that cannot cross membranes well and so the drug is trapped inside the cancer cell
- the drug is only "active"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

6) Give a mechanism to explain the following result. For clarity, you may assume the enzyme active component is in the Fe=O state. (**6 Points**)

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