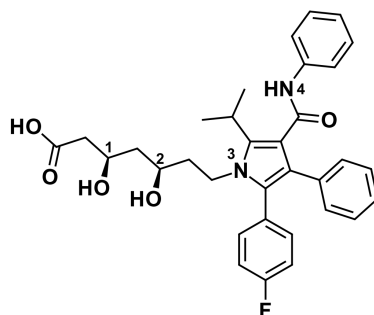


MDCM 601 2024 Exam 1 Key

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Problem 1. Lipitor (atorvastatin; structure shown) is a cholesterol-lowering drug. Answer the following questions about it:



1. What is the configuration of carbon 1? **R**
2. What is the configuration of carbon 2? **R**
3. How many aromatic rings are there? **4**
4. Is nitrogen 3 basic? **No**
5. What is the hybridization of nitrogen 4? **sp²**
6. pK_a of Lipitor is 4.46. What is the Gibbs free energy for this dissociation reaction at T=298K (R=8.314 J/molK)? (use 4 significant figures in your answer)

$$\begin{aligned}\Delta G &= -RT \ln K_a \\ &= -RT \ln 10^{-4.46} \\ &= -8.314 \frac{\text{J}}{\text{molK}} \times 298 \text{ K} \times \ln 10^{-4.46} \times \frac{1}{1000} \frac{\text{kJ}}{\text{J}} \\ &= 25.44 \text{ kJ/mol}\end{aligned}$$

7. Is this deprotonation reaction shifted to the left (protonated form) or to the right (deprotonated form)? **Left**

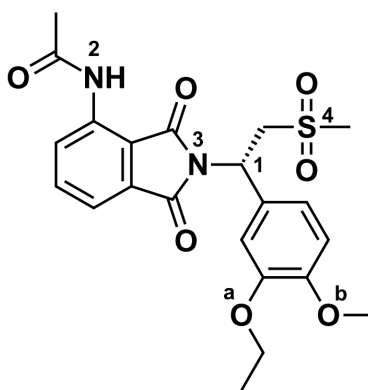
8. At what pH will the concentration of protonated Lipitor be 1000 times greater than that of deprotonated Lipitor? (use 3 significant figures in your answer)

$$K_a = \frac{[A^-][H^+]}{[HA]}$$

$$pK_a = pH - \log \frac{[A^-]}{[HA]}$$

$$pH = 4.46 + (-3) = 1.46$$

Problem 2. Otezla (apremilast; structure shown) is a phosphodiesterase inhibitor used to treat psoriatic arthritis. Answer the following questions about it:



1. Which nitrogen is part of an imide? **3**
2. What is the configuration at carbon 1? **S**
3. What is the name of the functional group that atom 4 is a part of? **Sulfone**
4. Which oxygen is part of an ethyl ether? **a**
5. pKa of this drug is 12.58. What is the concentration of NaOH solution in which 90% of Otezla would be in its negatively charged form? (give your answer with two significant figures)

$$\frac{A^-}{A^- + HA} = 0.9$$

$$1 + \frac{[HA]}{[A^-]} = \frac{1}{0.9}$$

$$\log \frac{[HA]}{[A^-]} = pK_a - pH$$

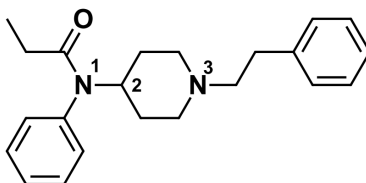
$$pH = 12.58 - \log \frac{1}{0.9} - 1 = 13.53$$

$$pOH = 14 - 13.53 = 0.466$$

$$[OH^-] = 10^{-0.466} = 0.34M$$

6. In blood ($\text{pH} = 7.4$), would most of Otezla molecules be neutral or charged? **Neutral**

Problem 3. Answer the following questions about fentanyl (structure shown):



1. Which nitrogen is basic? **3**
2. Is carbon 2 a stereogenic center? **No**
3. How many hydrogen-bond donors are there? **0**
4. How many hydrogen-bond acceptors are there? **2**
5. pK_a of fentanyl is 8.43. What percentage of this basic drug is neutral at $\text{pH} = 7.15$?

$$\log \frac{\text{B}}{\text{BH}^+} = \text{pH} - \text{pK}_a$$

$$\log \frac{\text{BH}^+}{\text{B}} = 10^{\text{pK}_a - \text{pH}}$$

$$\frac{\text{B}}{\text{B} + \text{HB}^+} = r$$

$$1 + \frac{\text{HB}^+}{\text{B}} = \frac{1}{r}$$

$$r = \frac{1}{10^{\text{pK}_a - \text{pH}} + 1}$$

$$= \frac{1}{10^{8.43 - 7.15} + 1}$$

$$= 0.0499 \approx 5\%$$

6. At what pH will the concentration of neutral and positively charged forms be equal?
 $\text{pH} = \text{pK}_a = 8.43$
7. Would solubility of fentanyl increase or decrease in more acidic medium? **Increase**