

Avg 75, 25% of class 90-100, 50% of class 80-100. Nice work.

1. (10 pts) Use the data provided in the table of LogP values to calculate the substituent constant (π_x) for the bromine substituent, —Br. Show your reasoning.



$1.74 - 0.5 - 0.5 = 0.74$

or



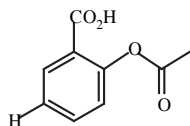
$0.41 - (-0.17) = 0.58$

Other similar calculations would also work

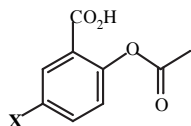
2. (10 pts) (a) Define: Pharmacokinetics - **ADME**. Absorbtion, distribution, metabolism and excretion. The path that the drug travels to its cellular target... and away from its cellular target.

(b) Define: Pharmacodynamics - The interaction of the drug with its medically-relevant cellular target (receptor, enzyme, DNA, etc).

3. (10 pts) Use the data in the tables attached at the end of the exam to help answer this question. Suggest an identity for the substituent —**X** that would give compound "B" increased lipid solubility compared to compound "A". Briefly explain your reasoning.



"A"

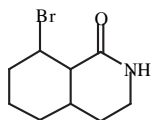


"B"

(discussed in lecture, textbook, exam 2003, problem 2, 2004 exam, problem 7)

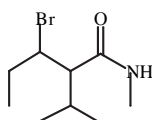
Any substituent in LogP table with a positive LogP/ π_x value. For example, — CH_3 , — $\text{CH}_2\text{CH}_2\text{NO}_2$, etc

4. (10 pts) Consider the drugs shown below, along with their binding constants for their interaction with a receptor. (a) Which drug displays more effective binding to the receptor? (b) Suggest the molecular reason *why* this analog binds more tightly to the receptor.



"P"

$K_B = 1 \times 10^8 \text{ M}^{-1}$



"Q"

$K_B = 2 \times 10^5 \text{ M}^{-1}$

(a) Which Drug is "Better"?

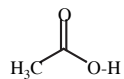
(b) Why?

(discussed in lectures about morphine pharmacophore and Lipinski's rules, Homework #1, question 11, 2003 exam, question 10)

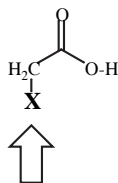
(a) P is a better binder. Larger K_B = better binder... $1/K_B = K_D$... smaller K_D = better binder.

(b) The ring structures in P make the compound more rigid, preorganized for interaction with receptor. Pays a smaller entropic penalty for binding to the receptor.

5. (10 pts) In our discussion of the development of cimetidine, we considered how electron-withdrawing groups and electron-donating groups can alter the acid-base properties (pK_a) of functional groups. The pK_a of acetic acid is 5. Use the data provided in the tables at the end of the exam to choose a substituent for **X** that would yield an acetic acid derivative that is *more acidic* than acetic acid. Briefly explain your reasoning.



Acetic Acid
 $pK_a = 5$



Select a Substituent
That Will Yield a
More Acidic Acetic
Acid Derivative

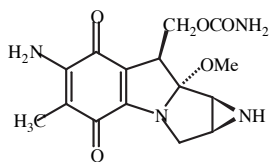
As we saw with the acidity of benzoic acid (discussion of Hammett Equation) and the urea-type functional groups in cimetidine, and electron withdrawing group can stabilize an anion. Hammett sigma values tell us whether a given functional group is ewg. Anything with a positive Hammett sigma value is ewg and should increase the acidity of acetic acid. (discussed in lecture regarding cimetidine and prilosec, homework #2, problem 5)

6. (10 pts) State Lipinski's "rule of fives".

Rule: A drug is likely to be poor if *two or more* of the following are true...

1. MW > 500
2. Log P > 5
3. H-bond donors > 5
4. H-bond acceptors (N,O) > 10
5. Number of freely rotating bonds > 10

7. (10 pts) Mitomycin C is a clinically used anticancer drug. Does Lipinski's rule of fives predict that this compound will be a good drug? Briefly explain your answer.



Mitomycin C
MW = 334.13
LogP = 0.44

(discussed in lecture, 2004 exam, question 11, homework #1 question 17)

MW < 500 (OK)

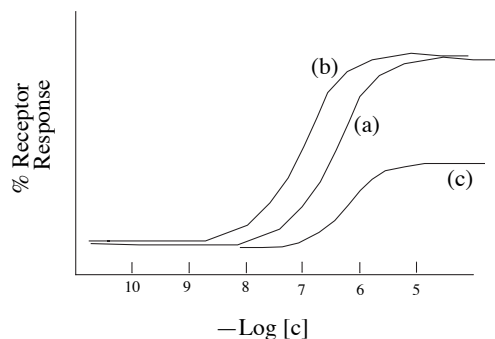
Log P < 5 (OK)

H-bond donors = 3 (OK)

H-bond acceptors = 9 (OK)

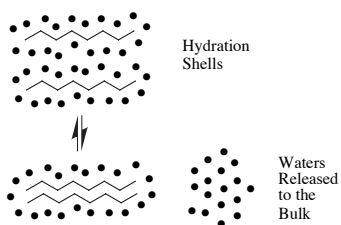
freely rotating bonds = 4 (OK)

8. (10 pts) Draw (AND CLEARLY LABEL) the dose-response curves for (a) an autocoid, (b) an agonist that is *more potent* than the autocoid, (c) a partial agonist.



(discussed in lecture - handout - and textbook pages 132-134, Homework 2 problems 2 and 3.)

9. (8pts) Briefly discuss the nature of the enthalpic (ΔH) and entropic (ΔS) contributions to the "hydrophobic effect".



What are the thermodynamic reasons underlying the fact that the association of hydrocarbons is greatly favored in water?

Thermodynamic analysis of the "oil and water" phenomenon. ΔH - van der Waals interactions are gained when hydrocarbons associate with each other. Increased H-bonding opportunities between the waters released to the bulk. ΔS - Association of two hydrocarbons with each other is entropically disfavored; however, water molecules that were "frozen" in the hydration shell around the hydrocarbons are released

into the bulk solvent. The disorder (entropy) of these released waters is greatly increased. In many cases, increases in entropy provides the thermodynamic driving force behind the hydrophobic effect.

(This material was discussed in lecture, 2004 Exam question 5, Homework One problems 11d and 21)

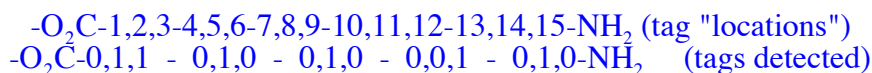
10. (12 pts) A combinatorial library of pentapeptides (peptides containing five amino acids) containing His, Ala, Asp, Arg, Lys, and Met was constructed using Merrifield's resin and Still's tag method for encoding. (a) How many peptides are possible in this library?

$$N = b^x \quad N = 6^5 = 7776$$

(discussed in lecture and textbook page 35)

An "active bead" was isolated and photolyzed, and electron capture gas chromatography gave the following result: **Tags 2, 3, 5, 8, 12, and 14 were detected.** (b) Use your knowledge of Still's encoding method to determine the structure of the active peptide on the polymer bead (please indicate the carboxy and amino ends on your answer).

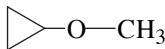
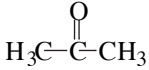

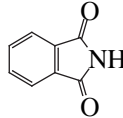

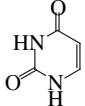
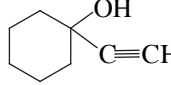

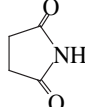
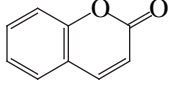
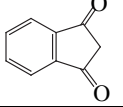
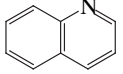
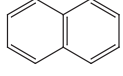
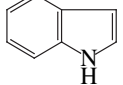
The following "codes" were used: His=001, Ala=010, Asp=100, Arg=011, Lys=111, Met=110



(2004 exam question 12, homework question #10 in textbook, page 101.)

Log P Values From Leo, A.; Hansch, C.; Elkins, D. *Chem Rev.* **1971**, *71*, 525.

Table courtesy of Prof. Richard B. Silverman

Compound	log P _{oct}	Compound	log P _{oct}	Compound	log P _{oct}
CH ₃ OH	-0.66	CH ₂ =CHCOOH	0.43		1.20
CH ₃ NH ₂	-0.57	CH ₃ CH ₂ CN	0.16	CH ₂ =CH-OCH ₂ CH ₃	1.04
CCl ₃ COOH	1.49		-0.24	CH ₃ CH ₂ CH ₂ COOH	0.79
BrCH ₂ COOH	0.41	CH ₂ =CHCH ₂ OH	0.17	CH ₃ CH ₂ CH ₂ CH ₂ OH	0.83
ClCH ₂ COOH	0.47	CH ₃ CH ₂ CHO	0.38	CH ₃ CH ₂ OCH ₂ CH ₃	0.77
FCH ₂ COOH	-0.12	CH ₃ CO ₂ Me	0.18	CH ₃ CH ₂ OCH ₂ CH ₂ OH	-0.54
ICH ₂ COOH	0.87	CH ₃ CH ₂ COOH	0.33	CH ₃ CH ₂ NHCH ₂ CH ₃	0.57
CH ₃ CN	-0.34	CH ₃ OCH ₂ COOH	-0.55		0.85
CH ₃ CHO	0.43	CH ₃ CH ₂ CH ₂ Br	2.10	CH ₃ CH ₂ CH ₂ CH ₂ CH ₂ F	2.33
CH ₃ COOH	-0.17	CH ₃ CH ₂ CH ₂ NO ₂	0.65	PhCH ₂ OH	1.10
HOCH ₂ COOH	-1.11	CH ₃ OCH ₂ OCH ₃	0.00	PhCH ₂ NH	1.09
CH ₃ CH ₂ Br	1.74	CH ₃ OCH ₂ CH ₂ OH	-0.60		1.15
CH ₃ CH ₂ Cl	1.54	Me ₃ N	0.27	PhCH ₂ COOH	1.41
CH ₃ CH ₂ I	2.00	CH ₃ I	1.69	PhOCH ₂ COOH	1.26
CH ₃ CONH ₂	-1.46	CH ₃ NO ₂	-0.33		2.13
CH ₃ CH ₂ NO ₂	0.18		-1.07		1.73
CH ₃ CH ₂ OH	-0.32	HOOCCH=CHCOOH	0.28		0.81
Me ₂ NH	-0.23		-1.21		1.39
CH ₃ CH ₂ NH ₂	-0.19	CH ₂ =CH-O-CH=CH ₂	1.81		0.61
HOCH ₂ CH ₂ NH ₂	-1.31	CH ₃ CH=CHCOOH	0.72		2.03
HC≡CCO ₂ H	0.46	HOOCCH ₂ CH ₂ COOH	-0.59		3.37
CH ₂ =CHCN	-0.92	CH ₂ =CHCH ₂ OCH ₃	0.94		2.00
-CH ₂ - (π _x)	0.50	-CH ₃ (π _x)	0.50		
Branching	-0.20	-H ₂ C=CH-CH=CH ₂ - (π _x) "two thirds of benzene"	2/3(2.13) =1.36	H ₂ C=CH- (π _x) "one third of benzene"	1/3(2.13) =0.71

