

Matching (22 pts). Place the Letter of the Best Answer in the Blank on the Left

1. Pharmacokinetics __N__

2. Pharmacodynamics __J__

3. Pharmacophore __L__

4. Autocoid __C__

5. X-ray crystallography __F__

6. Covalent Bond __H__

7. van der Waals interaction __D__

8. Hydrogen Bond __R__

9. Ionic Bond __G__

10. QSAR __P__

11. K_B __A__

A. $= 1/K_D$

B. Any compound used to cure, mitigate, prevent, or diagnose a disease or physical malady

C. Endogenous ligand for a receptor

D. Strength varies as $1/r^6$ (r = distance)

E. $= [D][R]/[D \cdot R]$

F. Can provide a three-dimensional picture of a macromolecular drug target

G. Strength varies as $1/r^2$ (r = distance)

H. Stable bond at room temp. Worth 85 kcal/mol

I. Stable bond at room temp. Worth 8.5 kcal/mol

J. Interaction of drug with its biological target

K. Quantitative system to assay receptors

L. Core set of functional groups required for biological activity within a structural group of molecules

M. Often thermoneutral a vacuum

N. Absorption, distribution, metabolism, excretion, and toxicity

O. Favored by electron withdrawing groups

P. Quantitative structure-activity relationship

Q. Qualitative stereochemistry assessment ratio

R. Strongest when bond angle is 180°

12. (5 pts). Why were almost all early, successful medicines derived from plants?

Answer: See class notes regarding the early history of medicinal chemistry

13. (6 pts). List one advantage and two disadvantages of an in vivo bioassay for lead discovery.

- i. **Answer:** See class notes regarding bioassays.
- ii.
- iii.

14. (5 pts). Addition of an ionic interaction worth -6.8 kcal/mol will alter the binding constant of a drug by a factor of about (circle the best answer and *briefly* show how you calculated your answer):

Answer: 100,000. Must show equation that you used to calculate. See handout on $K_{eq}/\Delta G$

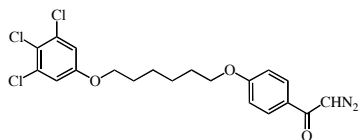
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15. (5 pts). How are molecules like the one shown below used in diversity-oriented synthesis (combinatorial chemistry)? A complete answer will show a chemical reaction along with a short written explanation.



Answer: See class notes on combinatorial chemistry.

16. (10 pts). A combinatorial library of tripeptides containing Gly, Phe, Leu, Glu, Trp and Gln was constructed using Merrifield's resin and Still's tagging method for encoding.

(a) How many peptides are possible in this library? (Show the equation you used to calculate this number, please.)

$$N = b^x \text{ (} b = \text{\# of building blocks, } x = \text{\# of cycles)}$$

The active bead was isolated, tags removed by photolysis, and identified by electron capture gas chromatography to give the following result: **Tags 1, 2, 5, and 8 were detected.**

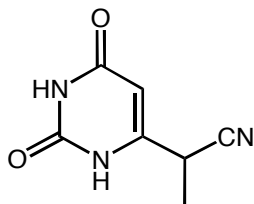
(b) Use your knowledge of Still's encoding method to determine the structure of the active peptide on the polymer bead (please indicate the carboxy and amino ends on your answer).

Assume the following "code":

$$100 = \text{Gly} \quad 010 = \text{Phe} \quad 001 = \text{Leu} \quad 110 = \text{Glu} \quad \text{Trp} = 101 \quad 111 = \text{Gln}$$

Answer: See assigned problems in textbook. Also see classnotes and posted exam keys for previous years.

17. (5 pts). Calculate Log P for the molecule shown below.



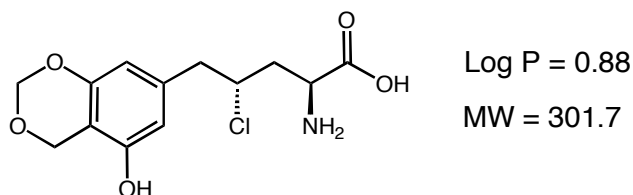
18. (5 pts). Why is a Log P > 5 detrimental to the pharmacokinetic properties of a drug candidate?

Answer: see class notes regarding Log P and Lipinski's Rule of Fives

19. (5 pts). State Lipinski's Rule of Five.

Answer: See class notes and publications posted on the course website.

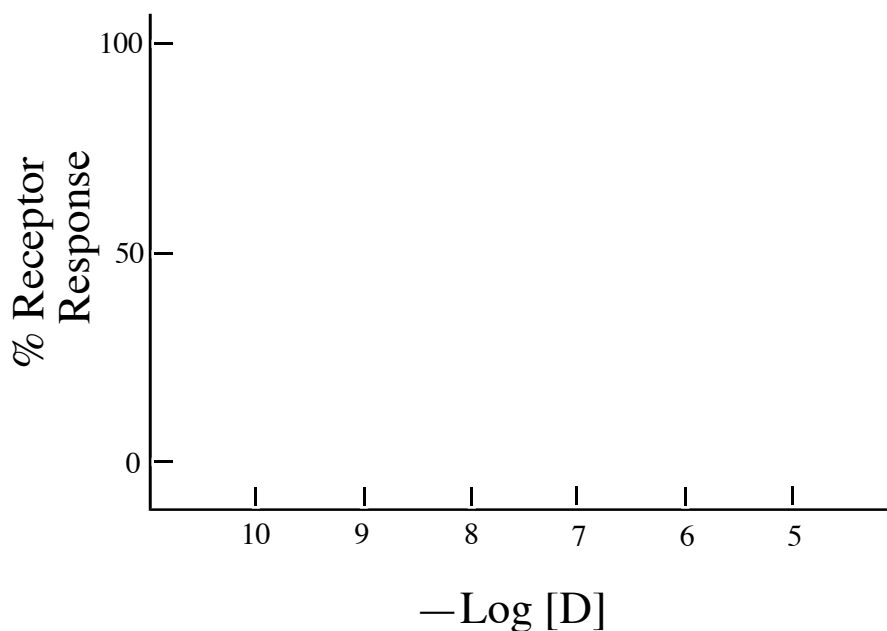
20. (5 pts). According to Lipinski's Rule of Five, does the compound shown below have a chance to display acceptable bioavailability? Show your "numbers" in each category.



MW 301.7... OK; Log P < 5... OK; H-bond donors = 4... OK; H-bond acceptors = 6 if you just count N, O... but we should also count Cl... so, I'll say "7"... OK; rotatable bonds = 5... OK.

21. (9 pts). Draw AND CLEARLY LABEL the dose-response curves for:

- (a) An agonist with $K_D = 1 \times 10^{-6}$ M
- (b) An agonist with $K_D = 1 \times 10^{-8}$ M
- (c) A noncompetitive antagonist

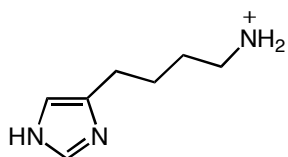


Answer: See previously posted exam keys.

22. (5 pts). Regarding lead optimization: Provide an argument based upon thermodynamic consideration of drug-target interactions that explains why a chain→ring modification of a lead compound might yield a more active compound. Your answer must fit in the space below (compose your answer before you begin writing).

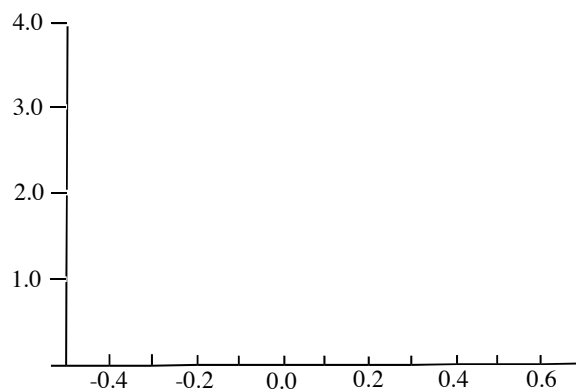
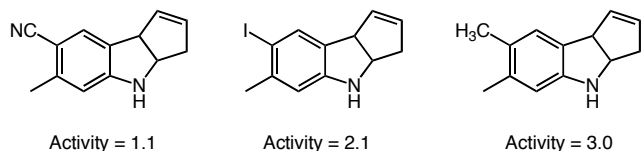
Rigid compounds, if designed properly, are “preorganized” for binding to the target site on the biological macromolecule. Thus, they do not pay an entropic penalty upon binding to the target. This is reflected in a “better” ΔG of binding and a “better” equilibrium binding constant K .

23. (5 pts). Draw a stable analog of the compound shown below that contains one bioisosteric substitution. Please propose *only one* analog.



Many possible. See handouts on isosteric substitutions. See class notes on the development of cimetidine.

24. (8 pts). The biological activities of three drug candidates are shown below.



Axes... Log activity (vertical) and sigma (horizontal).

a) Sketch a Hammett plot on the graph above. Label the axes and show the data points. The points do not need to be highly accurate. Is the Hammett rho value (ρ) positive or negative?

Negative

b) Use your Hammett plot to suggest an analog that is likely to have *higher activity* than any of those shown above. Draw the complete structure of your analog below **and** *briefly explain your choice*.

NH₂, OH, OCH₃, CO₂-, t-Bu, Et Any of these should be better.

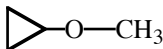
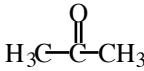

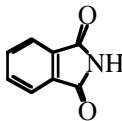

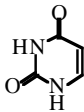
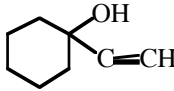

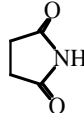
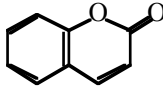
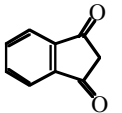
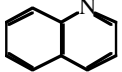
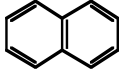
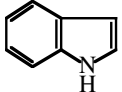
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Log P Values From Leo, A.; Hansch, C.; Elkins, D. *Chem Rev.* **1971**, *71*, 525.

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

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