MEDCHEM 562

First Midterm

October 26, 2015

Instructions:

• Exam packet totals 10 pages.

• If you need additional space go to the back of that page and tell me you did so.

• Write legibly and in complete sentences when indicated.

• Read the questions carefully and answer the questions you know first.
1. (33 points) Lipitor (atorvastatin) is an orally active drug that is given as a single isomer. This drug has a cLogP of 5.0 and a systemic drug bioavailability of 13%. The major pharmacological target is in the liver. The time to C$_{max}$ after a dose is 1-2 hours.

![Molecule Diagram]

a. Identify (circle) all the chiral centers in this molecule and show the partial structure of the active all-(R) isomer. (5 points)

b. Give approximate pKa values for any ionizable group(s) and indicate below by addition or removal of proton(s) and charge(s) (+/-) the predominant ionized state of this drug at pH 3, 7 and 11. (4 points)

![pH Diagrams]

pH=3  pH=7  pH=11

c. Based on first principles, where along the GI tract would you expect absorption to be most favorable? Is your expectation consistent with the time to C$_{max}$ given above? Explain in sentences. (5 points)

d. What condition is Lipitor used to treat? What is its mechanism of action? (Answer in sentences: (5 points)
e. The major metabolic routes for this drug begins with Phase I aromatic oxidation of the un-substituted aromatic ring by CYP3A4 to produce active metabolites. These metabolites are further altered by Phase II conjugation reactions (80% of dose). Show the partial structure of one of the possible Phase I metabolites of CYP3A4. Name one likely Phase II enzyme family that you would expect to be involved in further metabolism. (5 points)

f. Given all of the above information, briefly explain how it can be that 98% of the oral dose is found in the feces. Include the terms systemic bioavailability, first pass metabolism and percent absorbed in your answer. (Sentences: 5 points)

g. As discussed in class, lipitor is found in the blood as a mixture of a ring-opened and ring closed form. Show (using an abbreviated structure) the structure of the ring closed form (don’t worry about stereochemistry). Is the ring-closed form active or inactive? (4 points)

2. (17 points) Orphenadrine was originally developed and classified as an antihistamine but it is most commonly used to treat muscle spasms via its effect on acetylcholine receptors. It is approximately 50% as potent as atropine on a dose basis and binds somewhat selectively to the M_3 receptor. Thus the major indication for use has nothing to do with the histamine receptor. However, as one would expect, antihistamine side effects (dry mouth, constipation, dizziness) are a major problem. It has a pKa of 8.4, a LogP =3, a half-life of 15 hours and its major metabolite is formed by an N-dealkylation reaction.
a. Show above the partial structure of a major metabolite. What type of enzyme produces this metabolite. Comment on why it is particularly important to know if this general type of drug metabolite has pharmacological effects (4 points).

b. Calculate and show in a simple diagram how total orphenadrine is distributed amongst it’s various forms in the octanol and water phases at pH 7.4. (5 points).

c. Is orphenadrine a muscarinic receptor agonist or antagonist? How do you know this? (4 points).

d. Orphenadrine is a dirty drug in the sense that it binds to many different kinds of receptors in the body so its use is plagued with off target side effects. How might you seek to improve the M3 selectivity of orphenadrine without making new analogs? (3-4 sentences on how and why) (4 points).
1. (9 pts) Based on your knowledge of the role of vitamin A (and pro-vitamin A) in the visual cycle, **draw structures** in the boxes provided that represent:

a) **A** – the specific vitamer formed from α-carotene by the enzyme, BCMO. (3)

b) **F** – the vitamin A linkage to the visual pigment formed by reaction of E with opsin. (3) [Partial structure is OK here]

c) In which tissue in the body does the BCMO1-catalyzed event primarily occur? (1)

d) Which step; A → B, B → C, C → D, or D → E involves an isomerization? (2)
2. (9 pts) Photoactivation of 7-dehydrocholesterol results in the formation of Pre-vitamin D3.

\[
\text{7-Dehydrocholesterol} \rightarrow \text{Pre-vitamin D3} \rightarrow \text{Vitamin D3}
\]

a) Draw an **arrow-pushing mechanism** for the light-induced formation of pre-vitamin D3 and provide its structure in the space provided. (4)

b) Draw an **arrow-pushing mechanism** for the conversion of pre-vitamin D3 to vitamin D3. (4)

c) Is the process in b) above catalyzed by: [circle the correct answer below] (1)

- Light
- Heat
- Enzyme
3. (12 pts) The glutathione cycle, shown below, relies on several vitamins and minerals for its primary function of protecting the cell against peroxides, including hydrogen peroxide.

(a) Identify W, X, Y and Z in the blanks in the scheme below (8).

W -

X -

Y -

Z -

b) Show where the mineral, selenium and the water-soluble vitamin, riboflavin play critical roles in maintaining the glutathione pathway (4)
Questions 4-13 (20 pts); 2 points per question.

**Read the following statements (i – iii) and circle the best answer (A-D).**

4. The Daily Value for vitamins is;
   i) sufficient to meet nutritional requirements for 97-98% of the population,
   ii) based on a 2,000 calorie/day diet,
   iii) sufficient to meet the requirements of half of healthy individuals,
   iv) equal to the Reference Dietary Allowance (RDA).

   **A** if only (i) is correct
   **B** if only (ii) is correct
   **C** if only (iii) is correct
   **D** if only (iv) is correct

5. If the EAR for a vitamin is 50 µg/day then the RDA is:
   i) 50 µg/day
   ii) 60 µg/day
   iii) 75 µg/day
   iv) none of the above

   **A** if only (i) is correct
   **B** if only (ii) is correct
   **C** if only (iii) is correct
   **D** if none are correct

6. All-trans retinoic acid;
   i) effects transcription by binding to RAR-RXR
   ii) is synthesized from all-trans retinaldehyde by CYP26
   iii) is effective in the treatment of promyelocytic leukemia

   **A** if only (i) is correct
   **B** if only (i) and (ii) are correct
   **C** if only (i) and (iii) are correct
   **D** if only (ii) and (iii) are correct
7. Acitretin (structure below)

![Acitretin structure](image)

i) is a second generation retinoid  
ii) is a pro-drug for etretinate  
iii) was withdrawn from the market due to a high risk of birth defects.

A if only (i) is correct  
B if only (ii) is correct  
C if only (iii) is correct  
D if none are correct

8. CYP24A1 is responsible for formation of;
   i) calcidiol  
   ii) calcitriol  
   iii) calcitroic acid

A if only (i) is correct  
B if only (ii) is correct  
C if only (iii) is correct  
D if none are correct

9. The vitamin D plasma level;
   i) found in healthy adults with good sun exposure is 50-70 ng/ml  
   ii) needed to prevent rickets is at least 15 ng/ml  
   iii) cut-off for deficiency is <20 ng/ml

A if (i) and (ii) are correct  
B if (i) and (iii) are correct  
C if (ii) and (iii) are correct  
D if all are correct
10. Menadione
i) is found predominantly in hydrogenated vegetable oils
ii) is converted to vitamin K1 by reaction with geranylgeranylphosphate
iii) is also known as vitamin K3

A if only (i) is correct
B if only (ii) is correct
C if only (iii) is correct
D if none are correct

11. Vitamin K
i) deficiency is associated with a high PIVKA-II value
ii) has a Daily value of 90 micrograms/day
iii) has an Upper Limit of 1000 micrograms/day

A if only (i) is correct
B if (i) and (ii) are correct
C if (ii) and (iii) are correct
D if none are correct

12. For vitamin E,
 i) bleeding can be an adverse effect
 ii) deficiency causes neurological problems in humans.
 iii) αTTP selectively transfers α-tocopherol and α-tocotrienol into lipoproteins

A if (i) and (ii) are correct
B if (i) and (iii) are correct
C (ii) and (iii) are correct
D if all are correct

13. The Haber-Weiss reaction;
 i) consumes superoxide anion and hydrogen peroxide
 ii) generates hydroxyl radical
 iii) requires Fe for catalysis

A if (i) and (ii) are correct
B if (i) and (iii) are correct
C if (ii) and (iii) are correct
D if all are correct