MEDICINAL CHEMISTRY 402

Exam 1

October 21, 2005

Please write neatly

NAME ________________________________
I. Tamsulosin (Flomax) is a relatively new drug for the treatment of benign prostatic hypertrophy (BPH), a condition common in older males in which urine flow is restricted.

1. (6 pts) Circle any group on the structure of Tamsulosin that is ionizable under physiological conditions and estimate the pKa of the protonated forms.

2. (5 pts) Tamsulosin is administered orally as its hydrochloride salt. Explain why a salt form is used.
   The salt form will dissolve more rapidly and completely from its oral dosage form into physiological fluids. This can result in an increased rate and extent of drug absorption, and both of these factors can decrease intersubject variability in drug absorption.

3. (6 pts) Show the structure of the hydrochloride salt of Tamsulosin on or next to the structure above (partial structure is o.k.)

4. (8 pts) Would you expect that a large fraction of an oral dose of Tamsulosin would be absorbed in the stomach (pH=1)? Explain by using your estimation of the pKas of the ionizable groups on Tamsulosin, and by calculating the fraction of unionized drug in the stomach.

\[ 10^{(pH-pKa)} = \frac{\text{[unprotonated]}}{\text{[protonated]}} \]

For the sulfonamide: \[ 10^{(1-11)} = 10^{(-10)} = \frac{1}{10^{10}} = \frac{\text{[unprotonated]}}{\text{[protonated]}} = \frac{\text{[ionized]}}{\text{[unionized]}} \]

For the alkylamine: \[ 10^{(-9)} = 10^{-8} = \frac{1}{10^8} = \frac{\text{[unprotonated]}}{\text{[protonated]}} = \frac{\text{[ionized]}}{\text{[unionized]}} \]

Despite the fact that the sulfonamide group will be mostly unionized at pH=1, the quinolamine group will be mostly ionized at pH=1; the drug molecule as a whole will be mostly ionized and not absorbed to any significant extent in the stomach.
II. Diltiazem (Cardizem®) is a calcium channel blocker used to treat various heart conditions.

1. (6 pts) The drug literature describes Diltiazem as the (+)-cis isomer. What does this tell you?
   The (+) indicates asymmetry in the structure based on the physical chemical property of the drug to rotate plane polarized light in a dextrorotatory fashion.
   The cis designation indicates that there is a geometric isomer in the structure in which two larger groups are cis to each other rather than two smaller groups.

2. (6 pts) The only active isomer of Diltiazem has the stereochemistry shown above, what is the absolute configuration at the two chiral centers, A and B? Both A (see #5 in squares) and B (see #7 in circles) have the R configuration.

3. (7 pts) Although Diltiazem itself is active as a calcium channel blocker, so is its deacetylated metabolite. Thus, Diltiazem is both a drug and a prodrug. Below show the mechanism of general base-catalyzed hydrolysis of an acetyl ester.

4. (6 pts) Several interactions occur between Diltiazem and its calcium channel protein receptor that lead to its blockade. Circle ionizable sites on the structure above, draw arrows to two different kinds of hydrogen bond acceptors, and put squares around two different kinds of hydrophobic sites.

See above
III. Tramadol is a non-narcotic analgesic drug.

1. (4 pts) Circle chiral carbons on the structure above.

2. (7 pts) Show below the mechanism for oxidative N-demethylation of Tramadol (partial structures are o.k.).

3. (6 pts) On or next to the structure above show two different additional possible phase I metabolites of Tramadol.  See above

4. (6 pts) Next to the structure above draw two possible phase II metabolites of Tramadol itself.  See above

5. Tramadol is an inhibitor of CYP2D6, and the anticoagulant drug warfarin is oxidized to inactive metabolites in part by this P450 isoform.

a. (5 pts) If a patient who you knew was stabilized on the drug warfarin came in with a prescription for Tramadol, what should you do and why?

   Ask the patient if they are being carefully monitored (Protime) for anticoagulation status, because Tramadol could↑ concentrations of the active anticoagulant parent drug, warfarin, that could→ internal bleeding if the blood is too thin.

b. (2 pts) Would a patient who was genetically a fast or slow CYP2D6 metabolizer be at more risk of the interaction?  Slow CYP2D6 metabolism

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IV. Sevoflurane (A) is a newer general anesthetic that does not cause immune-mediated liver damage as does halothane. A partial scheme for oxidative metabolism of sevoflurane is shown below.

1. (5 pts) Show mechanistically (arrow convention) how the intermediate metabolite B is converted to ester C, and give the structure of by-product D.

2. (2 pts) The entire process of going from sevoflurane to metabolites C and D is called **oxidative dehalogenation**.

3. (5 pts) Show mechanistically how C is converted to a tetrahedral intermediate E, and draw the structure of E.

4. (5 pts) Show mechanistically how E breaks down to alcohol F and product G, and draw the structure of G.

5. (3 pts) The reactive metabolite of halothane that binds to proteins is trifluoroacetyl chloride. Therefore, trifluoroacetyl chloride is a **hapten**. Are any of the products of metabolism of sevoflurane as reactive as trifluoroacetyl chloride? **No**