

Heterocyclic Chemistry – Final Examination

June 12th, 2008

Professor Baran
Department of Chemistry
The Scripps Research Institute

Name: _____

Last 4 digits of your Social Security #: _____

This is an “open-notes” exam designed to last 2 hours that you have 5 hours to complete
Definition of "open notes": Only handwritten notes (from lectures and any other source), no copies allowed. Lecture summaries are the only handouts permitted during test.

Please present ONLY your FINAL answers on these sheets

Question 1 _____ < (40 points)

Question 2 _____ < (40 points)

Question 3 _____ < (20 points)

Question 4 _____ < (40 points)

Question 5 _____ < (40 points)

Question 6 _____ < (30 points)

Question 7 _____ < (20 points)

Question 8 _____ < (20 points)

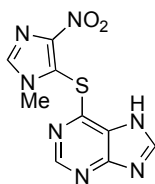
Question 9 _____ < (50 points)

Question 10 _____ < (50 points)

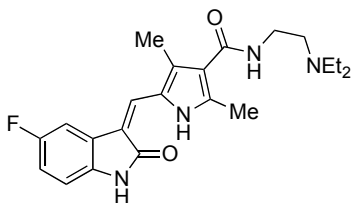
Bonus Question _____ < (30 points)

Total _____ out of 350 points

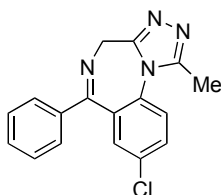
Question 1 (40 points – 10 each). Heterocyclic chemistry is indispensable in the production of medicinal agents. Below are four molecules from your recommended reading *Molecules in Medicine*. Provide viable routes to deliver these molecules using the chemistry you have learned in class.



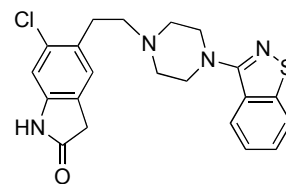
azathioprine (Imuran™)



sunitinib (Sutent™)

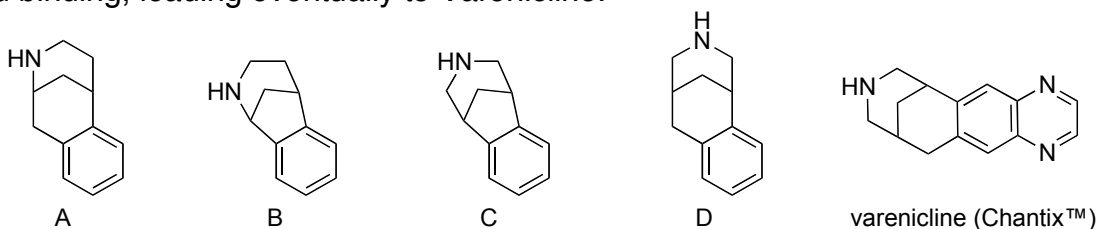


alprazolam (Xanax™)

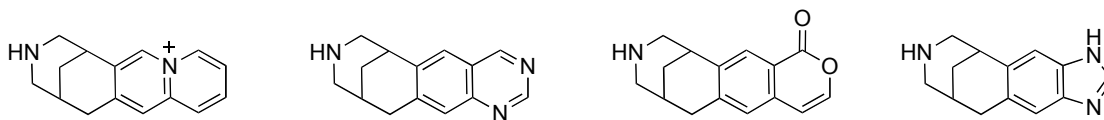


ziprasidone (Geodon™)

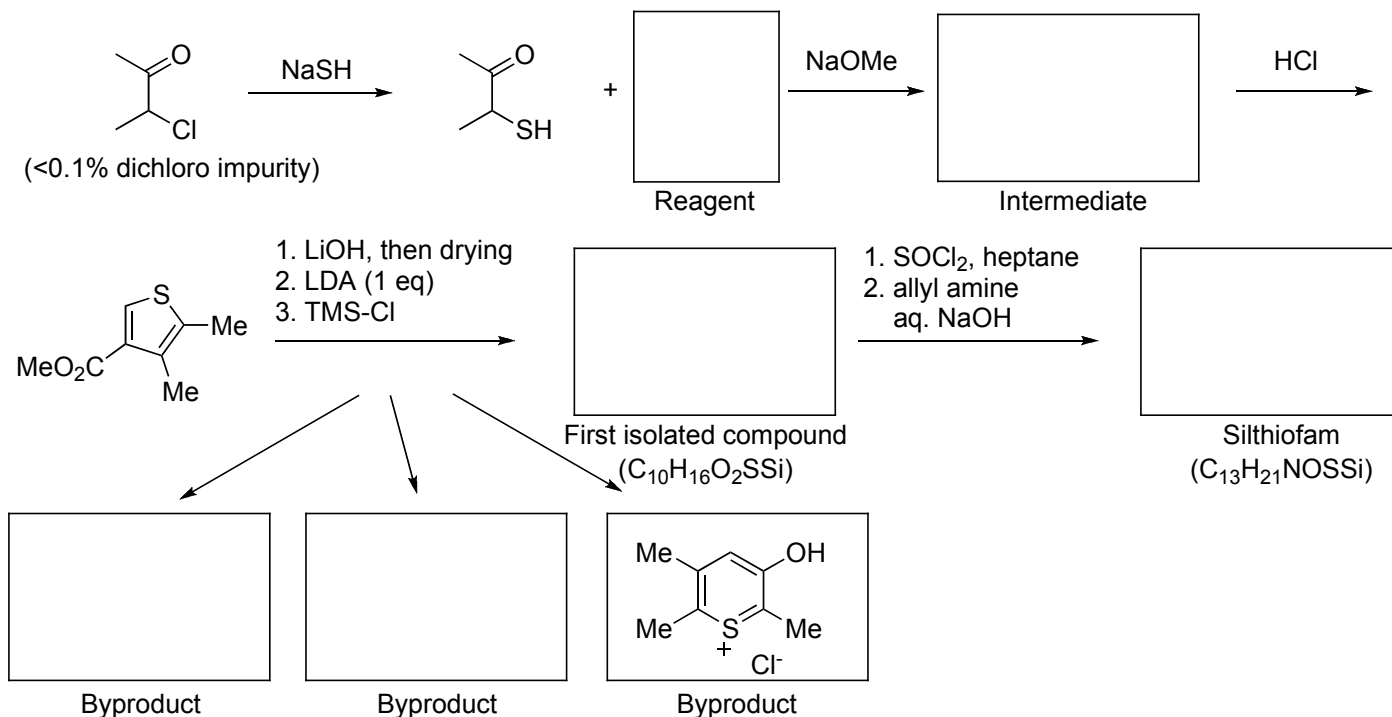
Question 2 (40 points – 10 points each). Very minor constitutional changes in the cores of molecules can greatly affect their pharmacologies. A striking example of this is the Varenicline story. In your assigned reading, you were acquainted with the Pfizer team led by Jotham Coe that observed that morphine analogs A and B displayed similar antinociceptive behavior that analog C did not share. The key observation was that known cytosine analog D, which had minor nicotinic antagonist activity, closely resembled C. When C was studied, it was found to share activity with D, and information from SAR studies showed that an EWG on the aromatic ring would increase activity and binding, leading eventually to Varenicline.



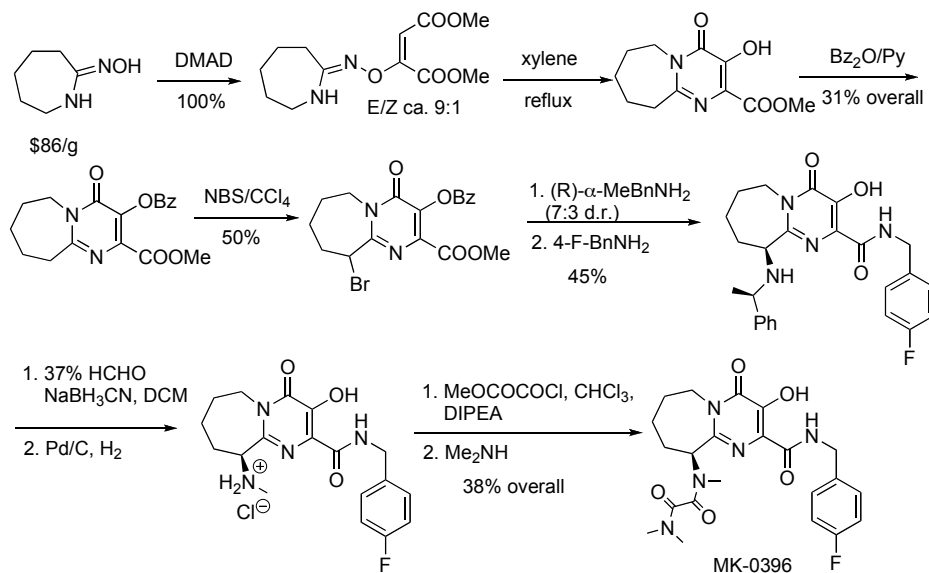
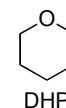
The year is now 2015, and you are Coe's replacement at Pfizer. Chantix™ was recalled from the market by the FDA in 2013 due to "suicidal inclinations" exhibited by some patients. You have been charged with the task of coming up with a replacement drug to save your company. Below are four candidates that you have chosen, you just need to show your team how to make them:




Question 3 (20 points). On a process scale, every impurity and every percent yield lost can cost your company millions of dollars. Equally, identification of byproducts can lead to optimization that can save your company \$\$\$ and get you a raise. You have been acquainted through your assigned reading with the story of Silthiofam, in which Pharmacopia researchers were optimizing the reaction seen below. Although initial attempts provided the desired product in >90% yield, it was further optimized by identification of the byproducts. Provide the missing structures in the boxes. Also, postulate a mechanism for the formation of the thiopyrillium byproduct found in the crude mixture with the first isolated compound.

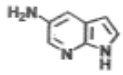
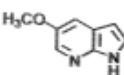
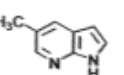
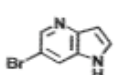
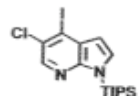
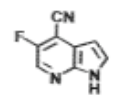
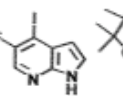
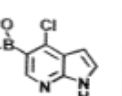
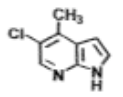
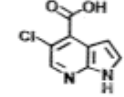
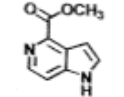
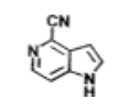
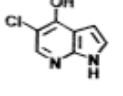
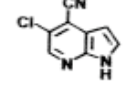
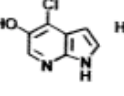
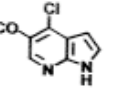


Question 4 (40 points). The following medicinal chemistry route provided access MK-0396, an HIV inhibitor developed by Merck, as seen in a recent guest lecture. As with many med. chem. routes, when MK-0396 proved to be a promising lead, a new and improved process route was required. Point out the distinct problems with the med. chem. route and propose a process route that will circumvent all of these problems starting from DHP, including mechanisms of key steps that might confuse the TA's.



Question 5 (40 points – 3 points each plus bonus). You are a team leader at Adesis Inc., a start-up company that has been placing ads in C&E news for aza-indole derivatives that you will make for your clients (see below). However, your sales and marketing department is way ahead of your process plant, and none of the compounds have even been made yet. Please save your company by providing routes to the following 16 compounds as quickly as possible.

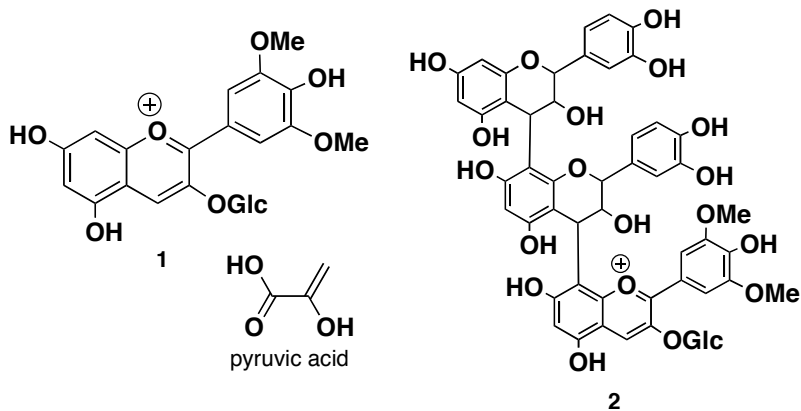

Catalog of Advanced Intermediates
 Custom Synthesis • FTEs

 4-127	 4-131	 4-203	 4-216
 4-291	 4-268	 4-270	 4-284
 4-281	 4-280	 4-295	 4-286
 4-278	 4-267	 4-279	 4-274

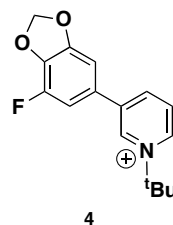
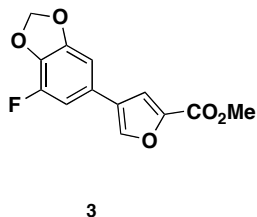
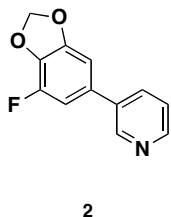
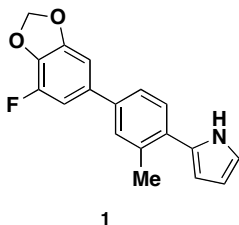
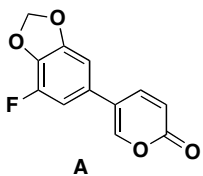
REQUEST MORE AT ADINFONOW.ORG

Adesis Inc. Phone: 800-429-0116
 27 McCullough Drive email: info@adesisinc.com
 New Castle, DE 19720 eCommerce: www.adesisinc.com

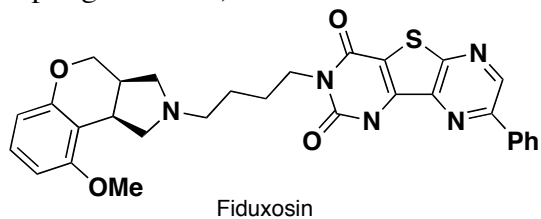
Question 6 (30 points). Anthocyanins (e. g. malvidin, **1**) are the principal constituents that give red wine its initial color. Over time the color of red wine changes as a result of the formation of secondary metabolites by reacting with tannins to form products of type **2** or by reacting with pyruvic acid to give **X**. Propose a synthesis of **1** and **2** and propose a structure of **X**.



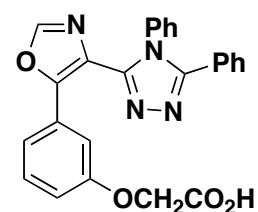
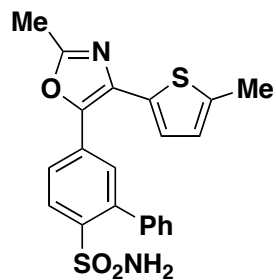
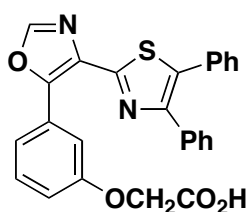
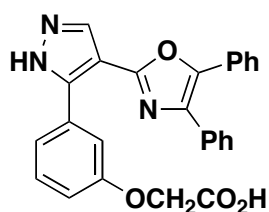
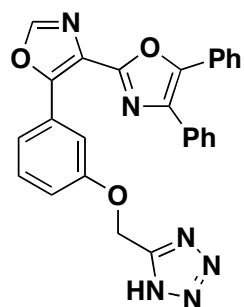
Question 7 (20 points – 5 points each). You have run out of starting material to make **A**, but have 100 mg of that compound. You must make compounds **1-4** for an SAR study by the end of the week. Propose routes from **A** to make compounds **1-4**.



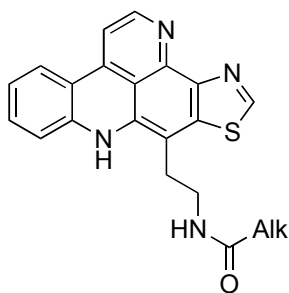
Question 8 (20 points). Please propose a racemic route to prepare *multi-kilogram quantities* of Fiduxosin.
(Note: no metal-mediated cross-coupling reactions)



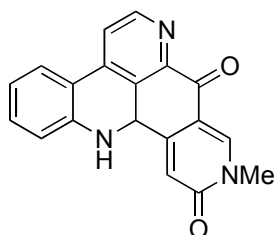
Question 9 (50 points – 10 points each). A large number of research studies have been performed to identify vicinal diaryl heterocycles that may act as COX-2 inhibitors. Provide routes to the following potential oxazole-derived leads, which you should be familiar with from your assigned reading. (Note: no metal-mediated cross-coupling reactions)



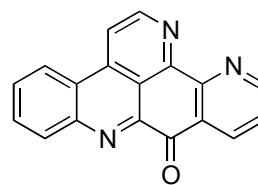
Question 10 (50 points). The pyridoacridine alkaloids are a diverse and structurally intriguing class of heterocycles that have been extensively reviewed (including a guest appearance in your required reading). Many of these molecules have notable biological activities, including a cytotoxic pathway involving the intercalation of DNA. Below are three pyridoacridine alkaloids that have been postulated to arise in nature from tryptophan. Provide a divergent biogenic hypothesis to access these three molecules starting with tryptophan. Feel free to use amino acids, acetic acid, and GABA. Once you have completed this task, propose a way to make these molecules in the laboratory.



kaunoniamines B – D

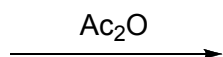
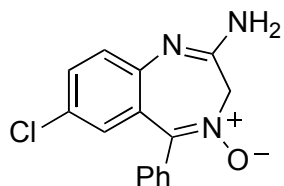


amphimedine



ascididemin

Bonus Question (30 points). Benzodiazepines exhibit some of the most exciting chemistry of any class of heterocycles. Below are some rearrangements of benzodiazepines from the Leo H. Sternbach review that you read for class. Please provide the structure and plausible mechanism of formation for each product below.



Contains an oxazole.
 $\text{C}_{19}\text{H}_{14}\text{ClN}_3\text{O}_2$

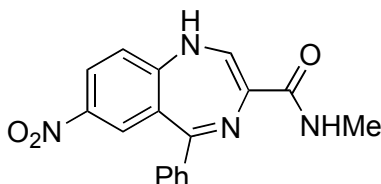
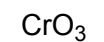
+



Contains IR bands at 1675 cm^{-1}
 and 1680 cm^{-1} .
 $\text{C}_{19}\text{H}_{16}\text{ClN}_3\text{O}_3$



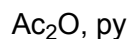
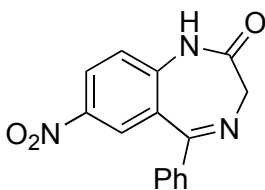
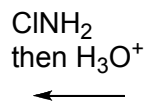
A quinazoline.
 $\text{C}_{16}\text{H}_{12}\text{N}_4\text{O}_3$



Contains a heteroatom proton
 at 8 ppm, and an aromatic singlet.
 $\text{C}_{14}\text{H}_{10}\text{N}_2\text{O}_2$



Contains a heteroatom–
 heteroatom bond.
 $\text{C}_{13}\text{H}_9\text{N}_3\text{O}_2$



Has an aromaticity value
 less than indole.
 $\text{C}_{16}\text{H}_{12}\text{N}_2\text{O}_3$