This is an “open-notes” exam (designed to last 2 hours) that you have 4 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  _____ < (20 points)
Question 2  _____ < (25 points)
Question 3  _____ < (50 points)
Question 4  _____ < (40 points)
Question 5  _____ < (10 points)
Question 6  _____ < (30 points)
Question 7  _____ < (20 points)
Question 8  _____ < (20 points)
Question 9  _____ < (30 points)
Question 10 _____ < (30 points)
Question 11 _____ < (25 points)

Bonus Question  _____ < (44 points)

Total  _____ out of 300 points
Question 1a (10 points). Provide a reasonable mechanism for the recently described synthesis of furans from alkynylloxiranes, typified by the following reaction (J. Org. Chem. 2009 ASAP).

Question 1b (10 points). A Russian research group recently reported a novel synthesis of fluorine-containing nicotinic acid derivatives (Tetrahedron 2008 10172). Provide a reasonable mechanism for the conversion of pyran 1 to pyridine 2.
Question 2 (25 points). Omeprazole (3), a proton pump inhibitor, is converted to pyridinium sulfenamide 4 when it encounters acidic media in the gastric chamber (J. Med. Chem. 1986 1327). Delineate a mechanism for the conversion of 3 to 4, and draw the covalent adduct resulting from interaction of 4 with H⁺/K⁺–ATPase (abbreviated here as Enzyme–SH).

![Diagram of omeprazole (3) and 4 with covalent adduct]

omeprazole (3)  
Prilosec®

4  
covalent adduct
**Question 3 (50 points).** A process research group at Abbott has devised routes for efficient access to the following thienopyridine 5, which was required for their multitarget kinase oncology program (*J. Org. Chem. 2009* ASAP). Devise the following: i) a medchem route, ii) a process route, iii) a route for incorporating $^{14}$C at the indicated (*) carbon atom.
Question 4 (40 points). Propose a reasonable synthesis of pyridynitrile 6, and suggest reagents and conditions for converting 6 to the fused heterocycles (7, 8, 9, and 10) depicted in the scheme (Heterocycles 2009 PrePress).
Question 5 (10 points). In a study of the enolization of phenacetylpyrazine in aqueous solution, it was found that metal ions are more effective catalysts than protons. The converse is observed for phenacetylpseudine (*J. Org. Chem. 2009 ASAP*). Explain.
Question 6 (30 points). A Taiwanese research group identified a facile approach to the [1]pyrindine ring system, which is embodied by the microbial metabolite streptazolin (11) (Org. Lett. 2004 3453). Devise a synthesis of 11.
**Question 7 (20 points).** Ofloxacin (12), a second-generation fluoroquinolone, is a broad-spectrum antibiotic (*Chem. Pharm. Bull.* 1986 4098). As of October 2008, the labeling now includes a black box warning that states: “**Fluoroquinolones, including FLOXIN®, are associated with an increased risk of tendinitis and tendon rupture in all ages.**” Devise a synthesis of 12.
**Question 8 (20 points).** Sunitinib (13) is a receptor tyrosine kinase inhibitor approved by the FDA for the treatment of renal cell carcinoma and gastrointestinal stromal tumor (*J. Med. Chem.* **2003** 1116). Devise a synthesis of 13 that can be used in medchem and transitioned quickly to process development.

![Sunitinib (13)](image-url)
**Question 9 (30 points).** During salinosporamide A fermentation development at Nereus Pharmaceuticals (San Diego), lymphostin (14) was observed. It is a lymphocyte kinase inhibitor, first isolated from *Streptomyces* sp. (*J. Antibiotics* **1997** 543). Propose a synthesis of 14.
**Question 10 (30 points).** Off the shores of Okinawa, the marine sponge *Aaptos aaptos* produces aaptamine (15), and many approaches to its chemical synthesis have been reported (*Tetrahedron* 2009 4257). Devise your own approach to 15, and illustrate it below.
Question 11 (25 points). Each of the following is worth 5 points.

a) \((C_{15}H_{13}NO)\) Obtained by reacting 2-benzyloxy-6-nitrotoluene with DMFDMA then treating the resulting product with \(H_2/Pt\).

b) \((C_{10}H_{12}O_2S)\) Obtained upon treatment of cyclohexanone with POCl₃/DMF followed by methyl 2-mercaptoacetate.

c) \((C_5H_5ClS)\) Obtained by reaction of thiophene with formaldehyde and HCl at 0 °C.

d) \((C_6H_5NO_2)\) Obtained by reaction of 3-methylpyridine with \(O_2\) and potassium tert-butoxide at room temperature in DMF.

e) \((C_{12}H_{13}NO_3)\) Obtained by reacting p-benzoquinone and ethyl 3-aminocrotonate in boiling acetone.
**Bonus Question (2 points each, 44 points maximum).** Authors of the article “Heteroaromatic Rings of the Future” (*J. Med. Chem. 2009 ASAP*) used computational techniques to survey chemical space for small aromatic ring systems. They estimate that there are over 3,000 unpublished, but synthetically tractable, ring systems. You have the opportunity to be the first person to conquer these heterocycles! See Figure 6 in the attached article (also included below), and propose syntheses for as many of these ring systems as you can!