Spring 2015 Medicinal Chemistry Approach to CHEM106H General Chemistry II 001 (Owens) Syllabus

To receive Honors credit, student must complete a separate QSAR project assigned during the second half of the semester.

This syllabus is a living document; students must check the syllabus posted on the Department web site http://chem.winthrop.edu/ for any changes prior to every class attendance

- Three lecture hours per week, three credit hours
- Dates reflect T,R lecture days for Spring 2015 semester

Instructor: Pat Owens (owensp@winthrop.edu) Phone: eight, zero, three, three, two, three, four, nine, two, five

- Office Hours: SIMS312A- MF 2:00-3:00 PM

Required Course Texts: Students are required to have their chemistry textbook from CHEM105

- *General Chemistry, 4th Edition*, McQuarrie, Rock and Gallogly, 2011

Course Objectives:

- Strengthen thinking skills, improve study habits, and demonstrate ability to learn fundamental principles from large amounts of scientific information.
- Develop a understanding of relevant chemistry in molecular medicine and neuroscience.
- Learn fundamental chemical science principles necessary to understand the scientific basis for molecular medicine

Course Outline: This is the second half of General Chemistry, an introductory chemistry course for science and engineering majors. This course focuses on learning chemistry by examining molecular medicine. Fundamental General Chemistry principles such as molecular structure, solubility, noncovalent interactions, thermodynamics, equilibria, kinetics, and electrochemistry represent the primary reasons for how and why drugs work. Students leave this course with both with a better understanding of relevant chemistry principles and fundamental insights into the scientific basis of modern medicines. This knowledge is useful for future science courses, is very helpful in better understanding human health at the molecular level, and is extremely important in being able to make informed decisions as scientifically literate citizens in a society increasingly engaged with molecular medicine.

Perhaps most importantly, molecules that enter our bodies are of tremendous human interest, whether these substances be medications, nutrients, toxins, or substances of abuse. Learning science by understanding how these molecules interact with and affect us can be a very rewarding and enriching experience. Such knowledge and insight can also lead to discoveries that help to improve the quality and length of human life.

The thematic approach being used in the course is organized in the following manner:

- The first third of this course reviews the fundamental chemical principles needed to be mastered to understand how drugs work.
- The middle third of the course examines anti-inflammatory therapeutics, steroids, cancer treatments,

and receptor drug targets. It begins with the mechanisms of action for medications used to treat inflammation; recent discoveries demonstrate that inflammatory processes are centrally important in cancer, cardiovascular disease and metabolic-syndrome related illnesses. This part of the course covers a broad array of receptor drug targets (nucleic acids, ion channels, GPCRs, kinase-linked receptors) and closely examines receptor-drug interactions and the design of medications to modulate these.

- The final third of the course centers on neuroscience; most drugs work by targeting nerve receptors; a good understanding of neuroscience is essential. The final half of this block covers a broad spectrum of classes of psychoactive drugs. Several classes involve drugs that are most widely abused in modern societies. Most of the other classes are used to treat mental illnesses. According to the National Institute of Mental Health, mental illness is the leading cause of disability for ages 18-44. Mental disorders are common in the United States and internationally. An estimated 26.2 percent of Americans ages 18 and older suffer from a diagnosable mental disorder in a given year. Understanding how these are being treated and the mechanism of action for these medications is an important part of becoming an educated citizen.

Schedule: Lectures are scheduled twice weekly at the appointed hour and location. The course syllabus provides the specific schedule as the semester progresses. All course information is posted on the chemistry department's web page (chem.winthrop.edu).

Final Exam: Students must take the final exam with their section.

- CHEM106 class that meets Tuesday at 12:30 PM will have its final exam at 11:30 AM, Thursday, April 30, 2015

Class Preparation: This is both a very interesting and a very challenging course. Once a principle is covered during a lesson, students will be expected to demonstrate an understanding of that concept throughout the remainder of the semester. Lecture discussions will assume that students understand material from previous lessons. Graded problems throughout the course often cannot be answered without being able to successfully apply previously discussed principles. It is very important for students to continuously review course material. Athletes practice every day, often for years, to master specific skills. Successful students (and faculty) have learned to continuously reexamine those topics and principles that are not completely clear to them. Students are also encouraged to study in groups; teaching peers is perhaps the most effective way to learn chemistry.

Students are responsible for all assigned study material and for all material discussed in lecture. A great deal of important information will be provided during lecture; take excellent notes!! Lectures are not designed to reiterate assigned readings but to focus on conveying important information from various sources to understand the General Chemistry concepts that represent the molecular basis of modern medicine. You are expected to spend whatever time it requires to develop and to demonstrate an understanding of these subjects and lecture materials. You must complete each reading and problem assignments **prior** to class. For each class I recommend that you do the following:

- Study previous lecture notes; you are strongly encouraged to organize and rewrite them immediately after each lecture.
- Study and review course material topics relevant to previous class discussions.
- Read assigned lesson for upcoming lecture, take notes and identify questions
- Work assigned problems

Student Competencies: Assigned chapters, class discussion, homework, problem sets, unannounced quizzes, announced quizzes, tests, and the final exam will all center on development and evaluation of student competencies. Students should expect to face challenging and unfamiliar questions on all graded work; this is done to focus attention on competencies that students have not yet fully mastered. Students can be evaluated five to six separate times on a given competency: homework problems, unannounced quizzes, problem sets, announced quizzes, tests, and the final exam. Students are urged to not fall behind and to master each competency as soon as it is first examined.

The course web site will itemize chapter sets of student competencies to more effectively focus student study and to allow student self-evaluation of progress. Links to quizzes given to date will be added to the syllabus schedule as they are returned. Solutions to problem sets and to quizzes will not be posted since more effective student learning occurs through working through these problems individually. Class time will be used to review the quiz and test questions that challenged students most. Periodically, as time allows, graded problem sets will be reviewed in class.

Graded Exercises

- Quizzes will be routinely be given, each be worth 30 points, and often be given at the beginning of class. These quizzes will include questions to evaluate understanding of material covered during the previous lecture as well as questions to evaluate competency in problem solving skills from sets due that day.
- ALEKS Objectives will be assigned weekly through spring break and will be each worth 30 points.
- Assigned problem sets will each be worth 15-30 points; only specific problems will be graded. Problem sets are due at the beginning of class; no credit will be given for sets turned in late.
- The assigned review paper will be weighted 75 points.
- Two tests will be given and be weighted approximately 150 points each.
- The cumulative final exam will be worth at least 300 points. You must score better than 50% on the final exam to pass the course. You must score an A on the final exam to earn an A in the course.

Grades: Percentages will be calculated based upon total earned points divided by total points tested. There will be no makeups for graded exercises. By May 4 2015, you must have mastered 85% of the assigned ALEKS topics to pass the course. You must also score better than 50% on the final exam to pass the course. You must score an A on the final exam to earn an A in the course. The following grade range will be used: A = 93.00-100%; A- = 88.00-92.99%; B+ = 85.00-87.99%; B = 80.00-84.99%; B- = 76.00-79.99%; C+ = 72.00-75.99%; C = 66.00-71.99%; D = 56.00-65.99%; F = <56.00%

Attendance: You are expected to attend all class meetings for the full scheduled time. A student who is absent for any reason is responsible for obtaining the assignments from the instructor or a classmate. Roll will be taken occasionally and the attendance practices of students will be taken into account when final grades are assigned. Absence from a test or quiz without a written doctor's excuse or similar external agency valid documentation is inexcusable. An unexcused student absence will result in a zero for the missed grade AND a deduction of 20-100 points (determined by the weight of the missed test) from the student's previously earned points in the course. For excused absences, missed exercises will not be included in neither the earned nor total points when calculating overall course grades.

University Competencies: CHEM 106 and the co-requisite CHEM 108 together primarily develop students in the first University Competency: ***Winthrop graduates think critically and solve problems.*** *Winthrop University graduates reason logically, evaluate and use evidence, and solve problems. They seek out and*

assess relevant information from multiple viewpoints to form well-reasoned conclusions. Winthrop graduates consider the full context and consequences of their decisions and continually reexamine their own critical thinking process, including the strengths and weaknesses of their arguments. Some (but not all) of the ways that this competency is strengthened in CHEM106 include extensive quantitative problem solving, explanation of mechanisms of actions for complex human-drug intereactions, and the application of thermodynamics and electrochemistry to predict membrane potentials, spontaneity, and hyperpolarization effects across cell membrane ion concentration gradients.

General Education Requirements: CHEM 106 and the co-requisite CHEM 108 together fulfill four hours of general education requirement for natural sciences. Listed below are Winthrop's seven fundamental student learning outcomes for natural science courses as well as examples of how they will be fulfilled in CHEM 106 and 108.

Students should be:

1. *Conversant with a few fundamental concepts from among the three main areas of natural science, including earth, life, and physical sciences.* (e.g., enzyme kinetics, protein structure, mechanism of action for psychoactive substances, dose-response toxicological curves).

2. *Able to apply the scientific methodologies of inquiry.* (e.g., CHEM 108 laboratory exercises and experiments)

3. *Able to discuss the strengths and limitations of science.* (e.g., effectiveness and adverse side effects of medicine, limitations of medication, treating inflammation)

4. *Able to demonstrate an understanding of the history of scientific discovery.* (history of human substance abuse, development of aspirin and heroine by Bayer, initial inclusion of cocaine in Coke)

5. *Able to discuss the social and ethical contexts within which science operates.* (e.g., exposure of humans to known carcinogens; addiction to nicotine, toxicity testing and side effects).

6. *Able to communicate about scientific subjects including (lab courses only) the defense of conclusions based on one's own observations.* (e.g., CHEM 108 laboratory presentations and project reports)

7. *Able to discuss the application of scientific knowledge to the social sciences and to non-scientific disciplines.* (the entire course does this)

Students with Disabilities: Winthrop University is dedicated to providing access to education. If you have a disability and require specific accommodations to complete this course, contact the Office of Disability Services (ODS) at 803-323-3290. Once you have your official notice of accommodations from the Office of Disability Services, please inform me as early as possible in the semester.

Student Conduct Code: "Responsibility for good conduct rests with students as adult individuals." The policy on student academic misconduct is outlined in the "Student Conduct Code Academic Misconduct Policy" in the online *Student Handbook* (http://www2.winthrop.edu/studentaffairs/handbook/StudentHandbook.pdf).

Course Lecture Schedule

ALEKS Syllabus

L1 T 1/13	***Lecture 1. General Chemistry Review*** *Lewis Structures, Molecular Geometry, Arrhenius Equation, Second Law* *Text: Lewis Structures; Molecular Geometry; Chemical Kinetics; Acids & Bases, Chemical Thermodynamics* *Handout: Lewis Structure Methodology* *Wiki: Hybridization; Aromaticity; Arrhenius Equation; Second Law of Thermodynamics*
L2 R 1/15 PS 1 Due	***Lecture 2. Intermolecular Forces (Noncovalent Interactions)*** *Coulomb's Law, Electronegativity, Hydrogen Bonds, Van der Waals Forces, Dipole-Dipole & Ion-Dipole Interactions, Solvation, Hydrophobicity* *Wiki: : Electronegativity; Intermolecular Forces; London Dispersion Forces; Hydrogen Bonds; Coulomb's Law; Solvation; Hydrophobicity* *Text: Electronegativity, Intermolecular Forces (Hydrogen Bonding, Van Der Waals Forces, Dipole-Dipole & Ion-Dipole Interactions*
L3 T 1/20 PS2 Due	***Lecture 3. Solubility and Lipids*** *Thermodynamics of Liquid-Liquid Solubility, Octanol-Water Distribution Equilibrium Constants [Partition Coefficients (P)], Phospholipid Components and Structure, Cell Membrane Structure and Properties* *Wiki: Partition Coefficient;* *Link: UCSF Membrane Tutorial (Great resource!!)* *Reading: The Components and Properties of Cell Membranes* *Link: Kimball's Biology Pages: Fats (Unsaturated Fats, Trans and Omega Fatty Acids, Phospholipids*
L4 R 1/22 PS3 Due Quiz 1	***Lecture 4. Condensation and Hydrolysis Reactions*** *Alcohols and Carboxylic Acids, Triglyceride Formation, Polyphosphate and Phospholipid Formation* *Handout: Condensation Reactions*
L5 T 1/27 PS4 Due Quiz 2	***Lecture 5. Amino Acids*** *Structure, Chirality, Side Chain Polarity, Peptide Bond,Peptide Condensation and Hydrolysis, Henderson-Hasselbalch Equation, Charge and pH, Solubility and pH* *Wiki: Amino Acids; Chirality; Peptide Bond; Henderson-Hasselbalch Equation;* *Link: Amino Acid Structures at pH=7.4 Amino Acid Chart with pKa Table*
L6 R 1/29 PS5 Due Quiz 3	***Lecture 6. Protein Structure*** *Primary Structure, Disulfide Bonds, Secondary Structure - Alpha Helices and Beta Sheets, Tertiary/Quaternary Structures and Associated Noncovalent Interactions, Prions, PostTranslational Protein Modifications* *Wiki: Protein Structure Disulfide Bonds* *Kimball's Biology Pages: Proteins; Polypeptides;* *Kimball's Biology Pages: Protein Structure: Primary; Secondary; Tertiary; Quaternary*
7 T 2/3 Quiz 4	***Lecture 7. Enzymes: Structure and Function*** *Enzyme Catalysis, Mechanism of Action, Active Site, Substrate Binding, Catalytic Roles, Michaelis-Menton Kinetics, Lineweaver-Burk Plots, Km and Vmax Determination, Turnover Numbers, Km and Substrate-Enzyme Affinity* *Text: Michaelis-Menten Model of Enzyme-Catalyzed Reactions* *Kimball's Biology Pages: Enzymes* *Kimball's Biology Pages: Enzyme Kinetics*
L8 R 2/5 PS6 Due	***Lecture 8. Enzymes as Drug Targets*** *Active Site Inhibitors, Allosteric Inhibition, Competitive / Non-Competitive Inhibitors, Suicidal Substrates* *Wiki: Enzymes; Enzyme Inhibitors*

L9 T 2/10 Quiz 5	***Lecture 9. Medical Approaches to Inflammation I*** *Cyclooxygenase Case Study* *Reading: Protein Function – Section III Cyclooxygenase (COX): An Example of How Enzymes Function* *Wiki: NSAIDs; COX-2 Inhibitors* *Reading: Molecular Basis of Inflammation*
L10 R 2/12 PS7 Due	***Lecture 10. Medical Approaches to Inflammation II*** *Steroids - Structure, Intracellular Receptors, Anti-Inflammatory MOA* *Reading: Molecular Basis of Inflammation* *Reading: Protein Function – Section II Nuclear Receptors: An Example of How Proteins Function* *Reading: Kimball's Biology Pages: Steroid Hormone Receptors and their Response Elements* *Wiki: Steroid ; Zinc Finger; Complex Ion ; d-Orbitals*
L11 T 2/17 Quiz 6	***Lecture 11. Receptors as Drug Targets I*** *Neurotransmitters & Hormones, Agonists, Antagonists, Partial Agonists, Inverse Agonists,* *Treatment of Hormone-Dependent Breast Cancers* *Wiki: Neurotransmitters; Hormones; Receptors; Antagonists; Agonists; Partial Agonists; Inverse Agonists;* *Ligands; Tamoxifen; Aromatase Inhibitors;*
L12 R 2/19	***Lecture 12. Receptors as Drug Targets II*** *Desensitization & Sensitization; Tolerance & Dependence; Receptor Types & Subtypes; Affinity, Efficacy, & Potency; Ligand-Receptor Dissociation Equilibria, EC50, IC 50* *Wiki: Efficacy; Dose-Response Curve; EC50; IC50; Therapeutic Index;* *Scribd: Sensitization and Desensitization;*
L13 T 2/24 Quiz 7	***Lecture 13. Nucleic Acids as Drug Targets*** *Structure of DNA, Central Dogma, Intercalating Drugs, Alkylating & Metallating Agents, Cisplatin, 5-FU* *Wiki: Akylating Agents; Sulfur Mustard; Cisplatin;*
C1 R 2/26	***Compensatory Time for Review Paper Preparation***
T1 T 3/3 Midterm	***Mid-Term Examination on Material from Lectures 1-13*** A Few Practice Problems....
L14 R 3/5	***Lecture 14. Receptor Structure and Signal Transduction I – Overview of Ion Channel Receptors*** *Ion Concentration Gradients, Ion Channel Structure and Mechanisms of Action, Ligand-Gated and* *Voltage-Gated Ion Channels, Cell Membrane Potentials, Nernst Equation and Membrane* *Equilibrium Potentials, Ion Movements and Resulting Inhibitory/Excitatory Potential Changes,* *Wiki: Ion Channels; Nernst Equation; Action Potential ; K+ Ion Channel Nobel Chemistry Lecture (Video)* *UCSF Reading: "Diffusion and Transport Across Membranes" Section on Ion Channels (pages 80-86)*
L15 T 3/10 PS8 Due	***Lecture 15. Receptor Structure and Signal Transduction II – Thermodynamics of Ion Channels*** *Sodium-Potassium-ATP Pump Mechanism, Cell Membrane Potentials, Nernst Equation and* *Membrane Equilibrium Potentials, Free Energy Changes of Ion Movement across Voltage and Concentration* *Gradients, Ion Movements and Resulting Inhibitory/Excitatory Potential Changes* *UCSF Reading: "Diffusion and Transport Across Membranes" Section on ATP-Driven Ion Pumps (pages 73-77)*

	Wiki: Neuron; Membrane Potential; Na+/K+-ATPase *McGraw-Hill: Sodium-Potassium-ATP Pump*
L16 R 3/12	***Lecture 16. Receptor Structure and Signal Transduction III – G-Protein Coupled Receptors (GPCRs)*** *G-Protein Coupled Receptor Structure, Evolutionary Tree of GPCRs, GPCR Signaling Mechanism of Action* *2012 Nobel Chemistry - Nobel Lecture Rob Lefkowitz Nobel Lecture Brian Kobilka* *Wiki: G-Protein Coupled Receptors (GPCRs);*
L17 T 3/24 Quiz 7	***Lecture 17. Cholinergics I*** *Nervous System, Cholinergic System, Acetylcholine Structure & Receptor Binding*
L18 R 3/26	***Lecture 18. Cholinergics II*** *Cholinergic Antagonists, Acetylcholinesterase Inhibitors*
L19 T 3/31	***Lecture 19. Adrenergics*** *Geometry of Adrenergic Receptors, Main Types of Norepinephrine Receptors, Interaction of Adrenergic Receptors with Neurotransmitters, MOA of Activated Receptors*
L20 R 4/2	***Lecture 20. Psychoactive Drugs I: Stimulants and Tranquilizers*** *Handout:*
L21 T 4/7	***Lecture 21. Psychoactive Drugs II: Anti-Depressants*** *Handout:*
L22 R 4/9	***Lecture 22. Psychoactive Drugs III: Anti-Psychotics and Hallucinogens*** *Handout*
L23 T 4/14	***Lecture 23. Psychoactive Drugs IV: Cannabinoids, Opium & Opioid Analgesics*** *Cannabinoids, Source and History of Opiates, Structure of Opioids and Opioid Receptors,* *Endogenous Opioids, Side Effects of Opiates* *Text Assignment: MedChem – Chapter 21*
L24 R 4/16	***Lecture 24. Chemistry of Local & General Anesthetics*** *MOA for Local Anesthetics, pKa Relevance, History of Cocaine Use by Humans, MOA for General Anesthetics, Molecular Structures of Widely Used General Anesthetics* *Handout: Local and General Anesthetics*
T2 T 4/21	***Test 2 Concepts***
R1 R 4/23 Paper Due	***Review***

ALEKS® Course Syllabus

Course Name:	CHEM106 Owens S15	**Course Code:**	XDJ66-6J9VH
ALEKS Course:	General Chemistry (Second Semester)	**Instructor:**	Prof. Owens
Course Dates:	Begin: 01/12/2014 End: 05/09/2015	**Course Content:**	127 topics
Textbook:	McQuarrie et al.: General Chemistry, 4th Ed. (University Science Books, Paperback)		

Dates	Objective
01/13/2014 12:01 AM - 01/16/2015 11:59 PM	**1.** Intermolecular Forces IMF (12 topics)
01/16/2015 11:59 PM - 01/23/2015 11:59 PM	**2.** Thermodynamics, Sig Fig (14 topics)
01/23/2015 11:59 PM - 01/30/2015 11:59 PM	**3.** Acids&Buffers-Metric Sys (13 topics)
01/30/2015 11:59 PM - 02/06/2015 11:59 PM	**4.** Kinetics-Dimensi Analysis (12 topics)
02/06/2015 11:59 PM - 02/13/2015 11:59 PM	**5.** Molarity and Precipitation Reactions (10 topics)
02/13/2015 11:59 PM - 02/20/2015 11:59 PM	**6.** Enthalpy & Heat Capacity (10 topics)
02/20/2015 11:59 PM - 02/27/2015 11:59 PM	**7.** Acid/Base & Redox Rxns (7 topics)
02/27/2015 11:59 PM - 03/13/2015 11:59 PM	**8.** Electrochemistry (7 topics)
03/13/2015 11:59 PM - 04/24/2015 11:59 PM	**9.** Exam Review (1 topic)

Intermolecular Forces IMF (12 topics, due on 01/16/2015, 11:59 PM)

Section 0-6 (2 topics)

- Understanding that opposite charges attract and like charges repel
- Sketching polarization induced by a nearby charge

Section 7-9 (1 topic)

- Predicting the relative electronegativities of atoms

Section 7-10 (3 topics)

- Predicting bond polarity
- Sketching the electrostatic potential map of a molecule

- Identifying a molecule from its electrostatic potential map

Section 8-9 (1 topic)

- Predicting whether molecules are polar or nonpolar

Section 15-4 (5 topics)

- Identifying hydrogen-bonding interactions between molecules
- Identifying the important intermolecular forces in pure compounds
- Predicting the relative strength of the dispersion force between molecules
- Predicting the strength of intermolecular forces from an electrostatic potential map
- Identifying the intermolecular forces between atoms, ions and molecules

Thermodynamics, Sig Fig (14 topics, due on 01/23/2015, 11:59 PM)

Section 1-8 (5 topics)

- Counting significant digits
- Rounding to a given significant digit
- Counting significant digits when measurements are added or subtracted
- Counting significant digits when measurements are multiplied or divided
- Adding or subtracting and multiplying or dividing measurements

Section 23-3 (2 topics)

- Predicting qualitatively how entropy changes with mixing and separation
- Qualitatively predicting reaction entropy

Section 23-5 (1 topic)

- Calculating reaction entropy using the standard molar entropies of reactants

Section 23-6 (5 topics)

- Using the general properties of Gibbs free energy
- Calculating dG from dH and dS
- Using the conditions of spontaneity to deduce the signs of ΔH and ΔS
- Calculating standard reaction free energy from standard free energies of formation
- Estimating a phase transition temperature from standard thermodynamic data

Section 23-8 (1 topic)

- Calculating reaction free energy under nonstandard conditions

Acids&Buffers-Metric Sys (13 topics, due on 01/30/2015, 11:59 PM)

Section 1-4 (8 topics)

- Knowing the dimension of common simple SI units
- Understanding the purpose of SI prefixes
- Knowing the value of an SI prefix as a power of 10
- Interconversion of prefixed and base SI units
- Addition and subtraction of measurements
- Multiplication and division of measurements
- Calculating mass density
- Using mass density to find mass or volume

Section 20-4 (1 topic)

- Understanding the effect of induction on acidity

Section 20-7 (1 topic)

- Interconverting Ka and pKa

Section 21-1 (2 topics)

- Identifying the major species in weak acid or weak base equilibria
- Calculating the pH of a buffer

Section 21-2 (1 topic)

- Calculating the composition of a buffer of a given pH

Kinetics-Dimensi Analysis (12 topics, due on 02/06/2015, 11:59 PM)

Section 1-9 (4 topics)

- Interconversion of prefixed SI units
- Interconverting compound SI units
- Interconverting derived SI units
- Predicting the units of the solution to a basic quantitative problem

Section 17-3 (3 topics)

- Using a rate law
- Using reactant reaction order to predict changes in initial rate
- Deducing a rate law from initial reaction rate data

Section 18-2 (2 topics)

- Interpreting a reaction energy diagram
- Relating activation energy to reaction rate

Section 18-3 (3 topics)

- Understanding the qualitative predictions of the Arrhenius equation
- Using the Arrhenius equation to calculate k at one temperature from k at another
- Using the Arrhenius equation to calculate Ea from k versus T data

Molarity and Precipitation Reactions (10 topics, due on 02/13/2015, 11:59 PM)

Section 10-9 (3 topics)

- Identifying combination, decomposition, single and double displacement reactions
- Writing net ionic equations
- Predicting precipitation

Section 12-2 (5 topics)

- Calculating molarity using solute moles
- Using molarity to find solute moles and solution volume
- Calculating molarity using solute mass
- Using molarity to find solute mass and solution volume
- Dilution

Section 12-5 (2 topics)

- Solving for a reactant in solution
- Solving limiting reactant problems in solution

Enthalpy & Heat Capacity (10 topics, due on 02/20/2015, 11:59 PM)

Section 14-2 (3 topics)

- Understanding the definition of enthalpy
- Using the general properties of reaction enthalpy
- Calculating the heat of reaction from molar reaction enthalpy and the mass of a reactant

Section 14-5 (3 topics)

- Interconverting calories and joules
- Writing a standard formation reaction
- Calculating a molar heat of reaction from formation enthalpies

Section 14-7 (4 topics)

- Calculating specific heat capacity
- Calculating molar heat capacity
- Using specific heat capacity to find heat
- Using specific heat capacity to find temperature change

Acid/Base & Redox Rxns (7 topics, due on 02/27/2015, 11:59 PM)

Section 10-10 (1 topic)

- Predicting the products of a neutralization reaction

Section 10-11 (6 topics)

- Identifying precipitation, combustion and acid-base reactions
- Assigning oxidation numbers
- Recognizing reduction and oxidation
- Identifying oxidizing and reducing agents
- Identifying oxidized and reduced reactants in a metal-nonmetal reaction
- Identifying oxidized and reduced reactants in a single-displacement reaction

Electrochemistry (7 topics, due on 03/13/2015, 11:59 PM)

Section 25-4 (2 topics)

- Recognizing consistency among equilibrium constant, free energy, and cell potential
- Using the Nernst equation to calculate nonstandard cell voltage

Section 25-5 (2 topics)

- Designing a galvanic cell from two half-reactions
- Analyzing a galvanic cell

Section 25-7 (1 topic)

- Calculating standard reaction free energy from standard reduction potentials

Section 25-8 (2 topics)

- Using the Faraday constant
- Calculating the mass of an electrolysis product from the applied current

Exam Review (1 topic, due on 04/24/2015, 11:59 PM)

Section 0-1 (1 topic)

- Simplifying a fraction

Review Paper Requirement

1. For this requirement, you are to write a 5-page review paper that focuses on a current medicinal chemistry topic or on a specific class of psychoactive substances.
2. If applicable to the chosen topic, the paper should provide:
    a. An historical perspective
    b. The relevance and societal impact
    c. A clear and detailed description of the molecular mechanisms of action
    d. A discussion of side effects
    e. An overview of the most significant structures
    f. A description of similar substances that may have antagonistic or agonistic activity
    g. An assessment of future activity, needs, or research
3. You must use citations from a minimum of three references from recent journals and books for this paper. A copy of the most important reference must be attached to your paper. Internet citations must be limited to published reports and articles. Use APA or MLA style documentation. The Winthrop Writing Center has excellent resources for research papers and styles of documentation.
4. The paper must be five full pages, exclusive of the reference list, using 12 point font, double spaced, and one inch margins.

Topic selection: Pick an area you would like to learn more about. Develop two to three ideas, survey the literature to ensure sufficient references are available, and submit a prioritized list of possible topics to me by the end of March.

CHEM106 General Chemistry II Course Competencies

Lsn 1: General Chemistry Review: *Lewis Structures, Molecular Geometry, Arrhenius Equation, Second Law of Thermodynamics*

- *Electronegativity, charge distribution, and molecular bonding structure*
  - Demonstrate an understanding of electronegativity; understand and be able to clearly explain the basis for electronegativity periodic trends in terms of fundamental laws of electrostatic interactions (Coulomb's Law).
  - Understand how to use relative electronegativities of atoms to clearly depict charge distribution across chemical bonds. Be able to quickly predict the important partial charges on atoms within given molecules.
- *Electron configuration*
  - For a given atom or ion, use the periodic table to quickly list its specific electron configuration
  - Understand the valence electron configuration of atoms and ions
- *Molecular structure*
  - Draw molecular structures showing all bonds from a given molecular representation
  - Quickly draw complete Lewis structures, to include all nonzero formal charges, for a given molecule or ion
  - Predict electron arrangement, molecular geometry, hybridization, and bond angles around given atoms in molecules
- *Multiple bond structure*
  - Know and discuss double/triple bond geometry and hybridization
  - Outline and diagram cis/trans geometry about carbon-carbon double bonds
  - Outline, discuss, and use aromatic electronic structure and geometry
- *Distribution of molecular kinetic energies*
  - Calculate fractions of molecules having kinetic energies greater than a given energy at a given temperature
  - Graphically represent and be able to clearly explain the distribution of kinetic energies of a collection of molecules at various temperatures
  - Understand the kinetic energy conversions into potential energy necessary to separate molecules, to break bonds, or to react molecules
- *Chemical thermodynamics and equilibria*
  - Understand and diagram the relationship between reaction spontaneity and reactant to product free energy changes.
  - Understand enthalpic and entropic contributions to changes in Gibbs free energy
  - Use thermodynamic data to predict phase change temperatures
  - Know what equilibria constants are; be able to relate equilibria constants to changes in Gibbs free energy

Lsn 2: Intermolecular Forces (Noncovalent Interactions)*: Ionic Interactions, Hydrogen Bonds, Van der Waals Interactions, Dipole-Dipole and Ion-Dipole Interactions, Repulsive Interactions, Water Solvation, and Hydrophobic Interactions*

- *Noncovalent interactions and intermolecular forces*
  - Understand and be able to clearly discuss and diagram the basis for attractions between molecules/ions to

include ion hydration, hydrogen bonding, London dispersion, dipole-dipole, ion-dipole, and cation-p electron interactions.

- Understand and use the relative magnitude (in kJ/mole) of chemical bonds (e.g. ionic, covalent and metallic) vs intermolecular forces (hydrogen bonding, London dispersion, dipole/dipole) interactions.
- Quickly draw diagrams that clearly show appropriate partial charges and intermolecular interactions among a given set of molecules or ions.
- Predict points of potential H-bond donors and acceptors for any given molecular structure.
- Predict and discuss relative boiling points (also vapor pressure, melting points, viscosity, surface tension) from molecular structure

Lsn 3: <u>Solubility and Lipids</u>: *Thermodynamics of Liquid-Liquid Solubility, Octanol-Water Distribution Equilibrium Constants [Partition Coefficients (P)], Phospholipid Components and Structure, Cell Membrane Structure and Properties*

- *<u>Solubility, thermodynamics, and equilibria</u>*
  - Understand and be able to clearly explain the thermodynamics of solution formation
  - Know what equilibria constants are; be able to relate equilibria constants to changes in Gibbs Free Energy
- *<u>Partition coefficients (P)</u>*
  - Understand what is meant by the octanol-water partition coefficient (P) and clearly describe its significance
  - Solve problems involving P, log P, and drug concentrations or amounts distributed across water and 1-octanol phases
  - Be able to predict relative polarities and solubilities (hydrophilic/hydrophobic, lipophilic/lipophobic) of a given molecular structure
- *<u>Phospholipids</u>*
  - Understand and be able to quickly draw molecular structures of components within phospholipid molecules
  - Relate the structure of phospholipids molecules to solubility
- *<u>Membranes</u>*
  - Understand and draw the molecular structure of membranes
  - Understand and describe the forces that hold membranes together
  - Predict and explain how membrane fluidity changes with temperature, degree of saturation, and fatty acid chain length.
  - Clearly outline the role of cholesterol in cell membranes
  - Predict relative membrane permeability for a variety of types of molecules or ions
- *<u>Fats, oils, and fatty acids</u>*
  - Know the structure of saturated, monounsaturated, polyunsaturated, and trans fats; describe associated health effects
  - Relate the melting points of fats and oils to molecular structure
  - Understand and explain what is meant by omega fatty acids

Lsn 4: <u>Condensation and Hydrolysis Reactions</u>: *Alcohols and Carboxylic Acids, Triglyceride Formation,*

Polyphosphate and Phospholipid Formation

- *Molecules: carboxylic acids, fatty acids, amino acids, and alkaloids*
  - Outline the structure of a carboxylic acid functional group and diagram its acid/conjugate base forms
  - Be able to draw the structure for fatty acids, to include those having one or more points of unsaturation
- *Condensation reactions*
  - Use partial charges within molecules to outline the basic mechanism for condensation reactions
  - Outline the chemical reactions and mechanisms for the formation of phospholipids from molecular subcomponents
  - Predict and outline fundamental mechanisms for condensation reactions such as those between
    - Acids and alcohols
    - Phosphates and alcohols
    - Amino acids
- *Hydrolysis reactions*
  - Outline the reactions involved in phospholipid hydrolysis
  - Outline peptide hydrolysis chemical equations

Lsn 5: Amino Acids: *Structure, Chirality, Side Chain Polarity, Peptide Bond and Resonance, Peptide Condensation and Hydrolysis, Henderson-Hasselbalch Equation, Charge and pH, Solubility and P*

- *Amino acids*
  - Know and be able to quickly draw the general molecular structure of amino acids and be able to clearly diagram the acid/conjugate base forms for both the carboxylic acid and the amine functionalities
  - Be able to quickly draw the complete molecular structure showing all bonds for all of the following amino acids:
    - AA's with nonpolar side chains [Alanine(Ala,A), Valine(Val,V), Leucine(Leu,L), Isoleucine(Ile,I), Phenylalanine(Phe,F)]
    - AA's with polar uncharged side chains [Glycine(Gly,G), Serine(Ser,S), Threonine(Thr,T), Tyrosine(Tyr,Y), Cysteine(Cys,C), Asparagine(Asn,N), Glutamine(Gln,Q)]
    - AA's with carboxylic acid side chains [Aspartic Acid(Asp,D), Glutamic Acid(Glu,E)]
    - AA's with basic side chains [Lysine(Lys,K), Arginine(Arg,R), Histidine(His,H)]
  - Understand and explain amino acid chirality
- *Peptides*
  - Understand how peptide bonds are formed and draw appropriate resonance structures to explain peptide bond geometry
  - Diagram and understand the mechanisms for condensation and hydrolysis reactions of peptides
- *Acid-base systems*
  - Predict reactions of acids with water; predict reaction of bases with water.
  - Write and use equilibria expressions for dissociation of weak acids and bases, K_a and K_b; pKa's
  - Know the Henderson-Hasselbalch equation: be able to understand and use.
  - Predict predominant (and relative amounts) of acid/base forms (e.g. $COOH/COO^-$, $NH_3^+/\text{-}NH_2$) present at a given pH.
  - Know what an alkaloid is and be able to quickly draw acid/conjugate forms of a given alkaloid.

- *Acid-base properties of amino acids*
    - Predict acid-base forms of amino acids present at various pH's
    - Relate pH to amino acid functional group solubility in lipids or water

***Lsn 6: Protein Structure**: Primary Structure, Disulfide Bonds, Secondary Structure - Alpha Helices and Beta Sheets, Tertiary/Quaternary Structures and Associated Noncovalent Interactions, Prions, PostTranslational Protein Modifications*

- *Protein structure*
    - Know the primary structure of peptides
    - Understand protein secondary structure; draw diagrams to represent the underlying reason for the formation of alpha helices and beta sheets
    - Understand the various types of interactions that can occur between side chains; draw appropriate diagrams and clearly discuss these
    - Understand protein tertiary and quaternary structures
    - Understand the underlying reasons for the structure of globular proteins

***Lsn** 7**: Enzymes: Structure and Function:** Enzyme Catalysis, Mechanism of Action, Active Site, Substrate Binding, Catalytic Roles, Michaelis-Menton Kinetics, Lineweaver-Burk Plots, Km and Vmax Determination, Turnover Numbers, K_M and Substrate-Enzyme Affinity, Factors Affecting Reaction Rates, Rate Law, Arrhenius Equation, Activation Energy, Kinetic Molecular Distribution*

- *Enzyme-substrate interactions*
    - Be able to draw and to clearly explain reaction energy diagrams for enzyme-substrate interactions
    - Understand the effects of inhibitors and what is specifically meant by IC50
    - Understand and clearly explain the basis for important types of noncovalent enzyme-substrate interactions
    - Clearly describe the enzyme inhibition process
- *Michaelis-Menton kinetics*
    - Write equilibria associated with enzyme-substrate interactions
    - Understand how reaction order changes with substrate concentration
    - Be able to use the Lineweaver-Burke relationship to calculate V_{max}, turnover number, and K_M
    - Understand the significance of K_M; understand the relation of K_M to enzyme-substrate complex stability and to maximum reaction rate
- *Chemical kinetics*
    - Understand the two fundamental requirements for a chemical reaction to occur…
    - Draw reaction coordinate-energy profiles and clearly label activation energies, and heat gained or lost
    - Understand and be able to clearly explain the role of catalysts
    - Understand and be able to use fundamental principles to clearly describe the dependence of reaction rate changes with temperature
- *Arrehenius equation*
    - Know and be able to use the Arrehenius equation for rate constant determination
    - Demonstrated the ability to calculate relative rates of reactions for different activation energies or temperatures

- Understand and be able to calculate a reaction's activation energy from given rate constants at different temperatures
- Understand relative impacts of temperature changes on rates for chemical reactions with low and high activation energies
- Be able to use activation energies to predict rate constants at different temperatures

- *Rate law*
  - Understand what is meant by the rate law and outline the experimental procedures and methodology to determine reaction order
  - Use a given rate law to calculate rate constants and their associated units

Lsn 8: Enzymes as Drug Targets: *Active Site Inhibitors, Allosteric Inhibition, Competitive / Uncompetitive / Non-Competitive*

Inhibitors, Suicidal Substrates

- *Enzyme inhibition*
  - Understand and fully explain the basis for competitive enzyme inhibition
  - Understand and fully explain the basis for noncompetitive enzyme inhibition
  - Illustrate and discuss the effects of various types of inhibition on maximum reaction velocities and on substrate concentrations required to achieve half of the maximum reaction velocities
  - Discuss what is meant by suicidal inhibitors and use your understanding of condensation reactions to predict the specific mechanism of action for a given active site and inhibitor structures.

Lsn 9: Medical Approaches to Inflammation I: Nonsteroidal Anti-Inflammatory Drugs (NSAID's)

- *Inflammation*
  - Understand the overall molecular basis of inflammation
- *Cyclooxygenase (COX) inhibitors*
  - Understand the mechanism of action of cyclooxygenase (COX) inhibitors
  - Identify key structural features of NSAIDs and understand of specific important interactions with COX enzymes
  - Understand the specific interaction between the NSAID carboxylic group and the COX Arg-120 side chain; describe and effectively explain the effect upon K_M values that occur when neutral glutamine is substituted for Arg-120
  - Understand and clearly discuss aspirin's unique mechanism of action for irreversible COX inhibition
- *COX-2 Inhibitors*
  - Understand key differences between COX-1 and COX-2 enzymes, their physiological roles, and their respective inhibitors
  - Clearly describe the rationale for the development of COX-2 inhibitors
  - Explain the structure differences between nonspecific COX inhibitors and COX-2 specific inhibitors; relate these differences to active site geometries of thee two enzymes
  - Use COX-1 and COX-2 IC50 values for various substances to evaluate their respective potential for therapeutic development

Lsn 10: Medical Approaches to Inflammation II: Steroidal Anti-Inflammatory Drugs

- *Steroid structure and properties*
  - Understand and draw the skeletal structure for steroids
  - Discuss and predict the lipophilic/lipophobic properties of steroids
  - Outline where steroids are produced, what their sources are, and how they work hormones in the human body
- *Inflammation and steroids*
  - Understand the overall molecular basis of inflammation
  - Explain the molecular mechanism of action for steroids as anti-inflammatories
  - Understand the emerging relevance of inflammatory processes in various diseases
- *Central dogma*
  - Understand and clearly describe how genetic information is encoded in DNA
  - Explain what a gene is, what it does, and the two roles of the major regions (promoter and coding) of DNA gene templates
  - Generate a possible DNA sequence for the coding of a given peptide
  - Interpret a DNA or RNA sequence to generate an amino acid sequence that is coded for by this
- *Complex ions*
  - Understand the structure of complex ions and be able to explain the basis for their interaction
  - Relate Lewis acid/base chemistry to complex ion components
  - Clearly explain why complexes are colored and demonstrate an understanding of relevant molecular orbital energies
  - Understand and describe the structure of important biochemical complexes such as iron in hemoglobin.
- *Intracellular Receptors and Zinc fingers*
  - Diagram and discuss the structure of zinc fingers; clearly show the amino acid residues that interact with the zinc ion and how zinc fingers affect protein shape
  - Explain the underlying basis for the zinc finger mechanism of action in steroidal interactions with DNA
  - Discuss a new area of drug research that targets the zinc fingers in estrogen receptors to treat breast cancer

***Lsn 11: Receptors as Drug Targets I**: Neurotransmitters and Hormones, Receptor-Ligand Interactions, Agonists, Antagonists, Partial Agonists, Inverse Agonists, Treatment of Hormone-Dependent Breast Cancers, Mechanisms of Actions for active ingredients in Advair*

- *Drug-receptor binding*
  - Understand and clearly discuss the ligand-receptor interactions; know the underlying physical principles that govern these interactions
  - Understand chirality, enantiomers, racemic mixtures, and the chiral specificity of many drug receptors
  - Know, diagram, and explain the equilibrium constant expression for K_d, the dissociation constant for drug-receptor complex dissociation
- *Receptors*
  - Understand and describe some of the various classes of drug receptors present within the human body
  - Understand the various types of receptor responses

- Understand receptor response differences to agonists, partial agonists, antagonists, and inverse agonists

Lsn 12: <u>Receptors as Drug Targets II</u>: *Affinity, Efficacy, and Potency; Sensitization, Tolerance, and Dependence, Dissociation Binding Equilibria, EC50, IC 50*

- *<u>Affinity, Efficacy and Potency</u>*
  - Define, illustrate and demonstrate an understanding of affinity, efficacy, and potency
- *<u>Sensitization, Tolerance, and Dependence</u>*
  - Illustrate, describe, and discuss the mechanism of action of the desensitization process that can occur due to prolonged receptor activation by an agonist
  - Illustrate, describe, and discuss the mechanism of action of the sensitization process that can occur due to prolonged receptor binding of antagonists
  - Discuss the molecular basis for tolerance and dependence.
- *<u>Neurotransmitter molecular structures</u>*
  - Acetylcholine
  - Dopamine, norepinephrine, epinephrine, and serotonin [5-Hydroxytryptamine (5-HT)]
  - Glutamate, GABA (gamma-aminobutyric acid)

Lsn 13: N<u>ucleic Acids as Drug Targets</u>

- *<u>Nucleic acid structure</u>*
  - Understand the structure of DNA and RNA to include the major components and specific features
  - Understand the condensation mechanism of action to form phosphate diester polynucleotides
  - Clearly explain the underlying physical basis for the attractions between the two strands of double helix DNA
- *<u>Cancer Chemotherapy Treatments</u>*
  - Outline the mechanism of action for platinum compounds [e.g. cisplatin $PtCl_2(NH_3)_2$] as chemotherapeutic agents for cancer patients
  - Describe the historical development of and outline the mechanism of action for nitrogen mustards as chemotherapeutic agents for cancer patients
  - Describe the mechanism of action for 5-Fluorouracil (5-FU) as a chemotherapeutic agent for cancer patients

Lsns 1-13: <u>Mid-Term Examination</u>

Lsn 14-15: <u>Receptor Structure and Signal Transduction I-II - Overview and Thermodynamics of Ion Channels</u>: *Ion Concentration Gradients, Cell Membrane Potentials, Nernst Equation and Membrane Equilibrium Potentials, Ion Movements and Resulting Inhibitory/Excitatory Potential Changes Ion Channels, Sodium-Potassium-ATP Pump Mechanism, Free Energy Changes of Ion Movement across Voltage and Concentration Gradients*

- *<u>Ion Channels</u>*
  - Understand the relative intracellular and extracellular concentrations of sodium, potassium, calcium, and

chloride ions
    - Understand the sodium-potassium pump mechanism to maintain ion concentration gradients and the array of energetics associated with this
    - Describe what an ion channel is and the specific properties of the substance that forms the channel
    - Outline the difference and define what is meant by voltage-gated and ligand-gated ion channels.
    - Describe the structure of voltage gated sodium ion channels and potassium ion channels to explain how they work. Understand the role of these ion channels in moving nerve pulses down an axon
    - Understand the role and the basic general mechanism of G-Protein Coupled Receptors (GPCR) in cell signaling processes; explain the importance of these receptors in the pharmaceutical industry
    - Understand and be able to clearly explain the physical basis for the selectivity of sodium and potassium ion channels
    - Understand how increased permeability can affect voltage-gated ion channels
- *Neurochemistry*
    - Be able to relate concentrations to associated electric potentials (e.g. Nernst Equation) and changes in Free Energy
    - Demonstrate the ability to calculate Free Energy changes, equilibrium constants, and electric potentials associated with given reactions
    - Explain and calculate cell membrane potentials associated with ion concentration gradients
    - Relate resting membrane potential to ion permeability and to intracellular/extracellular concentrations
    - Calculate Free Energy changes necessary to move substances across concentration gradients and to move ions across potential gradients
- *Thermodynamics*
    - Understand and be able to use the Second Law of Thermodynamics to predict reaction spontaneity
    - Clearly explain how spontaneity is related to Free Energy change.
    - *Explain Free Energy changes associated with ATP-ADP interconversion; discuss and effectively use the concept of coupled reaction energetics*

Lsn 16: Receptor Structure and Signal Transduction III – GPCR's: *G-Protein Coupled Receptors Signaling Mechanism of Action*

- Understand the role and the basic general mechanism of G-Protein Coupled Receptors (GPCR) in cell signaling processes; explain the importance of these receptors in the pharmaceutical industry

Lsn 17: Receptor Structure and Signal Transduction IV – Kinase-Linked Receptors: *General Principles, Structure and Activation Mechanism of Tyrosine-Kinase Receptors, Tyrosine Kinase-Linked Receptors, Signal Transduction Involving Kinase-Linked Receptors*

Lsn 18: Cholinergics I: *Nervous System, Cholinergic System, Acetylcholine Structure & Receptor Binding*

- Outline and clearly explain the steps that occur to pass a nerve impulse from one neuron to another
- Know the structure of acetylcholine and explain how it is synthesized and hydrolyzed
- Clearly explain the two major mechanisms used to reduce neurotransmitter concentration levels at nerve synapses
- Understand the two (nicotinic and muscarinic) major classes of cholinergic (acetylcholine) receptors and the mechanism of action for each

Lsn 19: <u>Cholinergics II</u>: *Cholinergic Antagonists, Acetylcholinesterase Inhibitors*

Lsn 20: <u>Adrenergics</u>: *Geometry of adrenergic receptors, main types of norepinephrine receptors, interaction of adrenergic receptors with neurotransmitters, MOA of activated receptors*

- Describe the geometry of adrenergic receptors
- Classify the role of the three main types of norepinephrine receptors (alpha, beta 1, and beta 2)
- Describe the interaction of adrenergic receptors with neurotransmitters
- Discuss the mechanism of action of activated adrenergic receptors
- Be familiar with medications that target adrenergic receptors and discuss their mechanism of action

Lsn 21: <u>Psychoactive Drugs I -- Stimulants and Tranquilizers</u>:

Lsn 22: <u>Psychoactive Drugs II – Anti-Depressants</u>:

- Understand how PCP (angel dust) and Memantine (Namenda) affect the glutamate receptor NMDA (N-Methyl-D-Aspartate)
- Understand the synthesis steps involved in the production of L-DOPA, dopamine, norepinephrine, and epinephrine
- Understand the role of glycine and GABA receptors
    - Be able to explain the electrochemical basis for their inhibitory effects
    - Clearly explain how each of the following substances affects the GABA-ergic system: ethanol, barbiturates, strychnine, diazepam (valium), and caffeine
- Explain the role of monoamine oxidase (MAO) for catecholamine neurotransmitters; identify the role of MAO inhibitors.
- Explain the effect of dopamine levels on brain activity
    - Explain the effects of cocaine and of amphetamines on the dopaminergic system
    - Outline the role of seratonin and identify the substance from which it is produced
        - Explain what SSRI's are and what they are used for

Lsn 23: <u>Psychoactive Drugs III – Anti-Psychotics and Hallucinogens</u>:

Lsn 24: <u>Psychoactive Drugs IV – Cannabinoids, Opium & Opioid Analgesics</u>:

- Relate the structure of opioid receptors to opioid ligand geometry and identify key features of each
- Understand the history of opioid use and development by humans
- Understand the side-effects of opioids
- Describe the structure of natural opioids found in the human body and be familiar with its historical discovery

Lsn 25: <u>Chemistry of Local and General Anesthetics</u>:

- Understand the mechanism of action for local anesthetics
- Relate pK_a's to local pain anesthetics
- Understand the history of cocaine use by humans
- Describe the mechanism of action for general anesthetics
- Be familiar with the molecular structures for the more widely used general anesthetics

Lsns 14-25: Second Half-Term Examination

Lsns 1-25: Comprehensive Final Examination

Antioxidant properties of phenolic compounds

Background:
Resulting from an excess of reactive oxygen species (ROS), states of oxidative stress are known to be causative factors in a number of human illnesses. Antioxidants are substances that are easily oxidized. Antioxidants react quickly to scavenge the free radicals generated by ROS; this lessens the chemical damage associated with free radical induced oxidation of proteins, nucleic acid, and lipids.

Phenolic compounds are well known antioxidants; many of the nonalcohol-related health benefits of wine consumption have been attributed to the presence of polyphenolic substances. It is generally considered that the primary mechanism of the radical scavenging activity of polyphenols is hydrogen atom donation. The corresponding antioxidant radical formed (from hydrogen donation) is either unreactive, often as a result of steric hindrances, or undergoes a subsequent electron rearrangement to a more stable form.

Quantitative Structure Activity Relationships (QSAR) represent a widely used approach to predict chemical or biological properties using a set of compound-specific set of variables that often include chemical/physical properties or quantum-chemical computed parameters. Previously published studies have shown that phenolic oxidation potentials (E) are closely correlated with experimentally observed antioxidant properties.

Objective:
This project involves the development and validation of a QSAR model to predict antioxidant properties of phenolic substances. Using reported oxidation potentials for a range of phenolic structures, a data set of properties for each of these structures has been generated. These data have been divided into two subsets: one that will be used to develop a mathematical model to predict oxidative potentials and a second smaller subset that will be used to test the model's effectiveness. Based upon the model developed, new phenolic structures having improved antioxidant properties will be explored and evaluated with the developed QSAR model.

Data Matrix Development: The first step in QSAR is to develop a data matrix of sample compounds and property variables. By convention, each matrix row corresponds to a different sample (compound) and each data matrix column corresponds to a different variable (property or computed molecular parameter). QSAR models are often designed for prediction of a biological effect such as enzyme inhibition or toxicity (QSAR has been particularly effective for lessening the degree and the extent of required animal toxicity testing).

Biological Effect (dependent variable): For this project, the predicted (dependent) variable to evaluate biological effects for phenolic compounds will be oxidation potentials; these potentials are closely correlated with experimental antioxidant properties. ***Table 1*** presents oxidation potential data that have been reported for 41 phenolic compounds having various substituent groups on a phenol backbone (***Figure 1***). The oxidation potential, E_7, is an indication of the voltage required to remove an electron from the oxygen atom present within the phenolic backbone.

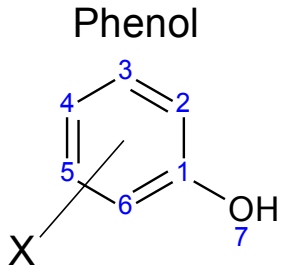

Figure 1: *Phenol backbone structure being used for this study*

Compound	***X Substituent***	***E_7 (Volts)***	***Compound***	***X Substituent***	***E_7 (Volts)***
1	4-NO_2	1.23	22	3-OH	0.81
2	3-Cl, 5-Cl	1.15	23	2-OCH_3	0.77
3	4-CF_3	1.13	24	4-OCH_3	0.73
4	3-NO_2	1.13	25	3-OCH_3, 4-OCH_3	0.67
5	4-COPh	1.12	26	3-OCH_3, 4-OCH_3, 5-OCH_3	0.66
6	3-CN	1.11	27	Sesamol	0.62
7	4-COOH	1.04	28	2-OH, 4-COOH	0.6
8	3-$COCH_3$	0.98	29	2-OCH_3, 6-OCH_3	0.58
9	4-H	0.97	30	2-OH, 3-OH	0.58
10	4-Br	0.96	31	2-OH,3-OH, 5-$COOCH_3$	0.56
11	4-Cl	0.94	32	3,4-Dihydrocynnamic acid	0.54
12	4-F	0.93	33	2-OH	0.53
13	Tyrosine	0.89	34	2-OH, 4-CH_3	0.52
14	3-OH, 4-$COCH_3$	0.89	35	4-OH	0.46
15	4-CH_3	0.87	36	4-NH_2	0.41
16	3-OCH_3, 5-OCH_3	0.85	37	4-CN	1.17
17	3-CH_3	0.85	38	4-$COCH_3$	1.06
18	3-OH, 5-OCH_3	0.84	39	4-t-Butyl	0.8
19	3-CH_3, 5-CH_3	0.84	40	2-CH_3, 6-CH_3	0.77
20	4-Phenyl	0.84	41	2-OCH_3, 4-CH_3	0.68
21	2-CH_3	0.82			

Table 1: *Table of oxidation potentials for 41 phenolic compounds having various X substituents on a phenol backbone (**Figure 1**).*

QSAR Independent Variables (physical/chemical properties, computed quantum mechanical parameters)
This project incorporates a number of **computated** molecular properties—determined using either Chemsketch or Spartan software--to explore as possible variables to use for predicting oxidation potentials. These include: Log P, Polarizability, Surface Tension, Index of Refraction, Density, Vertical (Koopman's) Ionization energy ($-E_{HOMO}$), Charge on the O_7 atom, O_7-H vibrational frequency, Energy of LUMO-r (of radical form), Electron Affinity, Vertical Ionization Potential, Molecular Area, Molecular Volume, Dipole Moment, Electronegativity, Hardness, Softness, and Electrophilic Index.

QSAR Model Development Requirement

Overall Goal: Develop and evaluate a three-variable mathematical model to predict phenolic antioxidant activity (quantified by the oxidative potential) in the form:

Oxidative potential = a * variable1 + b* variable2 + c * variable3 + d

- ***Data Set***: You are being provided a data set for the 41 compounds with their respective oxidative potential along with 18 other properties/variables—5 determined using ChemSketch, 13 obtained from Spartan quantum chemistry methods using Spartan software or calculated from Spartan results.

- ***Requirements***:

    - Use these data to generate a correlation matrix (***Tools, Data Analysis, Correlation***) that shows the correlation coefficient for all pairs of these 19 parameters. The correlation coefficients vary between -1 to +1; an r value of 0 indicates no correlation and thus little utility in predicting E….

    - Identify the variable with the best correlation to the oxidative potential E. Conduct a linear regression (***Tools, Data Analysis, Regression)*** to predict E using this independent variable. Identify the Coefficient of Determination R^2 that represents the fraction of the overall variability accounted for by this single variable model.

    - Identify other variables that work well with the initially selected variable; conduct a series of exploratory regressions using two independent variables (one being the first selected) and find which pair gives the highest Coefficient of Determination R^2 for predicting E. The best two pairs will provide the 2nd and 3rd best variable to use in your final model.

    - Conduct a three independent variable model using the selected variables to predict E.

- ***Documentation***:
    - Write an abstract giving a brief introduction, outlining what you did, and summarizing the results you obtained. The results should include an equation for each of your three models, the corresponding coefficients of determinations, and the respective root-mean-square errors from both the calibration and test sets.
    - Provide a spreadsheet that clearly shows:
        - A table showing the correlation matrix that you determined.
        - Three plots of experimental vs predicted values for each of your three models.