**BPS 2110 , Fall 2014 . Study Questions.**

**Question 1.**

a) What key questions are addressed in a Phase 1 Clinical Trial? In a phase II Clinical trial? In a Phase III Clinical trial? How many people are typically involved in each phase?

Phase 1: Involves healthy patients (about 20 volunteers) and determines safety.
Phase 2: Involves a small (<50) highly controlled group of patients and determines efficacy.
Phase 3: Involves a large diverse group of patients that mimics to a considerably extent the type of people who would use the drug and determines efficacy and safety.

b) Approximately what percent of drugs entering Phase I clinical trials are eventually approved by Regulatory agencies?

5%. 1000 compounds entering Phase 1 Clinical trials, only about 50 survive Phase III Clinical trials and are eventually approved by various regulatory agencies.

c) Which of the clinical trials is typically the longest in time and the costliest? Briefly justify your answer

Phase 3 is typically the longest in time and the costliest. Typically, Phase 3 takes 3-8 years and costs around $500 M. This is because this is the last phase to determine safety and efficacy before possible approval; therefore they need to be aware of all the possible adverse reactions and counter indications. They utilize a very large diverse group of patients, and need to monitor all the patients as well.

d) What is meant by the term **Post –marketing surveillance**? Why is this important in insuring drug safety?

Post-Marketing Surveillance is collecting data even after the drug has been put on the market, to see if there is anything that was missed in clinical trials. Certain counter indications or adverse reactions may come up after the drug has been put on the market, which can be a safety concern. If any new side effects emerge then companies may have to add a black box warning, or withdraw the drug all together and go back to the drawing board.

e) Despite the results of the clinical trial studies and the effort of regulatory agencies some drugs are withdrawn within a few years of approval. Explain why serious side effects are not always noted in Phase III Clinical trials.

Genetic diversity in large populations makes it hard to test against all the adverse effects. All clinical trials have a limited number of patients and are conducted under controlled conditions

for a limited period of time. Patients may also use complimentary natural health products, which cause drug-drug interaction. The use of other drugs at the same time may cause unexpected drug-drug interactions.

f) What is a typical cost of a Phase I, Phase II and Phase III clinical trials?

The typical cost of a Phase I clinical trial is approximately $15M, Phase II is $100M, and Phase III is $700M.

**Question 2.**

a) Give the names and headquarters country of three of the top ten pharmaceutical companies in the world.

Pfizer (US)
Johnson and Johnson (US)
Hoffmann-LaRoche (Swiss)
Novartis (Swiss)
GlaxoSmithKline (UK)

b) Which is currently the largest pharmaceutical company with headquarters in Canada?

Apotex

c) Which is the largest generic drug manufacturer in Canada?

Apotex

**Question 3.**

a) Why does Health Canada require Generic Drug Manufacturers to show that their drug is bio-equivalent to the brand name drug prior to giving marketing approval? What is meant by the term “bioequivalence”?

To ensure both safety and efficacy for all Canadians. Also to prove that the generic drug gives the same effects as the prescription drug, and the body will absorb the same amount of drug. Bioequivalence is the expected in vivo biological equivalence of two proprietary preparations of a drug. If two products are said to be bioequivalent it means that they would be expected to be, for all intents and purposes, the same.

b) What is a general estimate of the cost the work needed by a generic drug manufacturer in order to fulfill the requirement of “same bioequivalence”?

~10M$ vs ~700M$ for brand name.

**Question 4.**

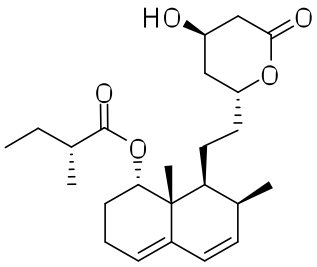
a) Explain the basic concept upon which the development of cholesterol lowering drugs (statins) is based.

The basic concept upon which the development of cholesterol lowering drugs is based is that a molecule with a similar structure to HMG-CoA could be expected to bind to the HMG-reductase enzyme and thus prevent it from converting HMG-CoA into mevalonate and eventually cholesterol. HMG reductase mediates the rate-determining step in cholesterol synthesis.

b) A Japanese company started to look for possible natural inhibitors of HMG -CoA reductase. Briefly explain why the looked first at metabolites produced by micro-organisms and not metabolites produced by plants.

Plants do not synthesize cholesterol, meaning looking at plants would be a waste of time.

c) Which part (s) of the structure of mevastatin are considered crucial for the inhibition of HMG-CoA –reductase? Explain by drawing chemical structure of a the natural ligand of this enzyme.



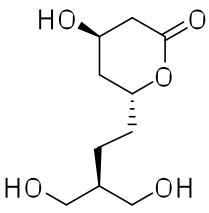

**mevastatin**
**- a potent inhibitor**
**of HMG-CoA reductase,**

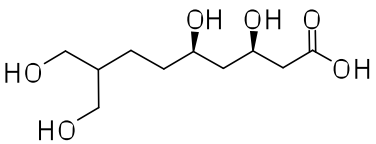
Lactone ring is the crucial structure.

See Wipebook.

**Question 6.**

a) Knowing the structure of the natural HMG-CoA reductase inhibitor shown in **Question 5**, would you expect the following two structures to be strong inhibitors of this enzyme? Give clear reasons for your decision.

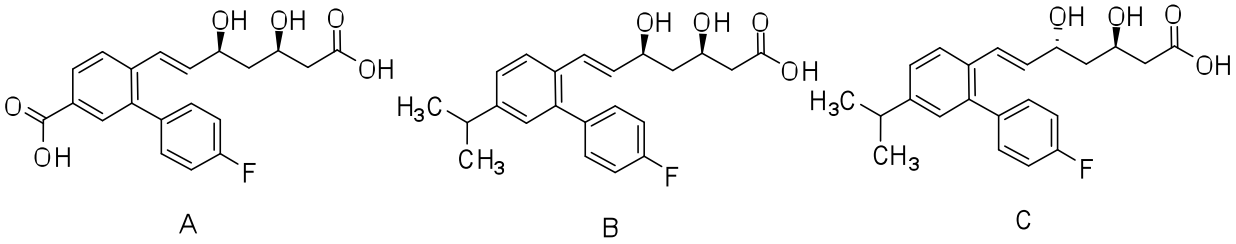


Although they both include the pharmacore, the rest of the molecule is very small and relatively polar, which will obstruct the molecule from working properly. For it to work properly a large, and hydrophobic compound must be attached to the pharmacore.

**Question 11**

b) Which of the following three structures would likely inhibit HMG-CoA-reductase most? Explain your reasons carefully. [Hint: Take into account the structure of mevastatin and its open chain form]




Structure B, because unlike structure C, it contains the pharmacore and unlike A is non-polar.

**Question 12.**

What is meant by the term "healer consensus"? **Give a plausible example**

All medicine men in South America tend to use the same compound even without communications. Ergo, it probably works.

**Question 13.**

Explain the process called "Bio-assay guided isolation" by describing its purpose and briefly outlining how it is carried out.

An example using a plant. Grind it up and place it in 95% ethanol, extract using various organic solvents, separation of biologically active materials, purification of biologically active materials by column, and finally testing for structure of compounds using NMR, mass spec, LCMS.

Bio-assay guided isolation processes are carried out when a plant extract is shown to have the desired activity for a certain drug. Examples of activity include antibiotic activity, anti-cancer activity, anti-fungal activity, or inhibition of an enzyme. Extracts have many component compounds, however, and the active component needs to be identified. The bio-assay guided isolation is a standard operating procedure to determine which is the active component.

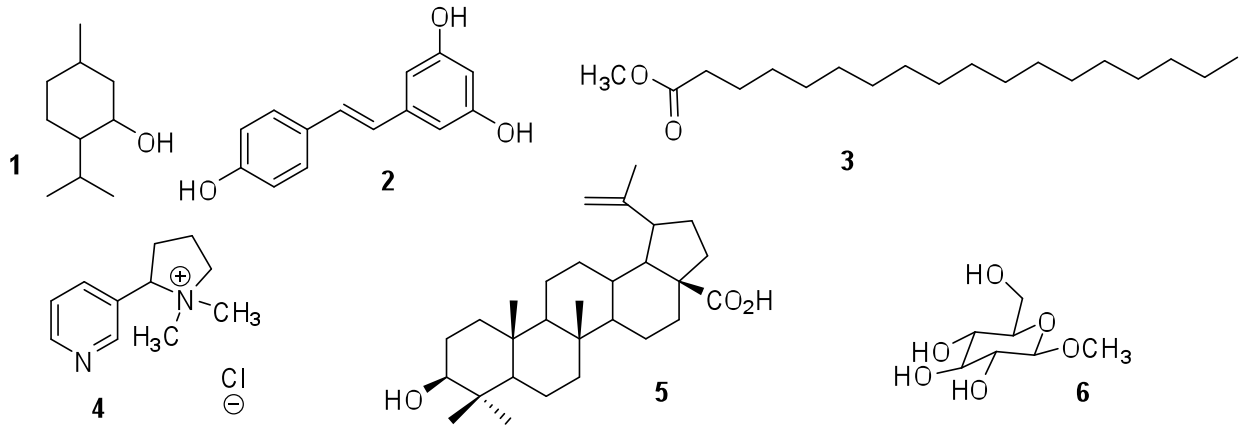
The extracts are typically prepared by grinding the plant sample, either fresh or dried with 95% ethanol, a highly polar solvent. They dissolve polar compounds present in the extract such as poly-hydroxy compounds, amino acid small peptides, and "small" carboxylic acids. Other organic solvents used are ethyl acetate and dichloromethane, which have intermediate polarity. These extract compounds with low and medium polarity. Often the active compounds are found in this fraction. Most alkaloids

(compounds which contain one or more basic nitrogen atoms) are of intermediate polarity and therefore are likely extracted with intermediate polarity solvents along with many other components. They can be separated form the other components by taking advantage of their basic character. Hexane is a non-polar solvent which best dissolves non-polar compounds such as glycerol esters of fatty acids or coloured hydrocarbons and terpenes with few polar bonds.

Chromatographic separation of the components of the mixture in the fraction with activity then occurs. Silica gel chromatography yields many individual fractions with different components (some single pure compounds, others still as mixtures). If the active fraction is a pure compound, then the process is complete. If it is still a mixture, then carry out a second, even third separation step until a pure active compound has been isolated. Structure determination can then occur by various techniques, including NMRS, MS, and X-Ray crystal structure determination.

**Question 14.**

a) A mixture of the following six compounds is shaken with water and ethyl acetate. Which of the six compounds do you expect to be found in the water layer? 2, 4, 6

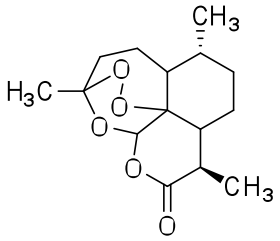



b) The ethyl acetate layer was placed in a flask and the solvent was removed under vacuum. The residue was then extracted with hexane. Which of the compound do you expect to be largely extracted with hexane? Which might be extracted to a small extent?

3 will largely be extracted because it is the most non-polar of the bunch, and 5 will be extracted to a small extent because it is the most polar of the bunch.

**Question 15.**

a) The artemisinin structure is shown below. The peroxide bond is considered crucial to its activity. Identify this part of the molecule




Artemisinin

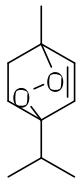
b) In the presence of iron (II) or potentially another catalyst the peroxide bond is cleaved. Show a reasonable mechanism for this reaction. See Notes

c) The product of reaction b) above is highly toxic. Explain why , either in words, or by drawing out the chemistry which is involved in the toxicity

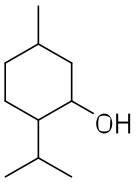
A very reactive oxide radical is formed. Radicals are very reactive and unstable (possess an unpaired electron making them highly reactive and able to damage all macro-molecules, including lipids, proteins, and nucleic acids.

**Question 16.**

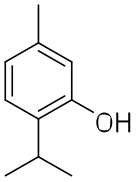
Which of the following three monoterpenes would you expect to most likely show toxicity in animals? Briefly explain why?




ascaridiol




menthol




thymol

Ascaridiol because of the possibility of the formation of an extremely reactive oxygen radical.

**Question 17.**

Describe briefly the mode of action of **Aspirin (acetyl salicylic acid; ASA)** and explain why its action as an anti-inflammatory agent is accompanied in many patients by gastrointestinal bleeding.

ASA inhibits the formation of prostaglandins from arachadonic acid (a poly-unsaturated fatty acid). Prostaglandins are lipid compounds and are mediators, with strong physiological effects in the body. The cyclo-oxygenase enzyme catalyzes the reaction of arachadonic acid to prostaglandins. COX-1 mediates the formation of prostaglandins associated with important body functions including renewal of the stomach and esophagus lining. Because ASA inhibits COX-1, the stomach and esophagus lining cannot properly be renewed, resulting in gastrointestinal bleeding.

**Question 18.**

COX2 inhibitors were initially expected to act as anti-inflammatory agents without the typical side effects associated with Aspirin [ASA] and the other NSAIDs such as Ibuprofen sold as Advil or Motrin. Explain the basis of this expectation.

COX2 inhibitors were initially expected to only act as anti-inflammatory agents without the gastro-toxicity exhibited by ASA and other NSAIDs, as it is only inhibiting the COX-2 enzyme as opposed to both the COX-1 and COX-2 enzyme. This is essentially the same pathway as ASA, but rather just inhibiting one enzyme rather than two.

**Question 19.**

Knowing the structure of lead structure published by the Dupont company, DuP697, [**See lecture notes**] and suggest two additional compounds that you would expect to have significant COX-2 vs COX-1 selectivity. Your compounds cannot have a sulfur containing ring since such compounds likely infringe on the DuPont patent. **If I were to ask this question on an exam, I would draw the structure of the compound on the questionnaire**.

See Wipebook.

**Question 20.**

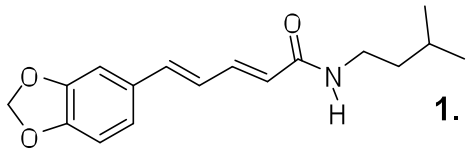
a) What are the two primary requirements for a strong patent in the pharmaceutical area?

   New and not obvious. It needs to have composition of matter and use. Without a use or plausible use it cannot be patented.

b) What is the length of a patent in Canada under current law?

   20 years

c) Suppose you were to patent a family of compounds as insecticides based on the core structure **1**.




**1.**

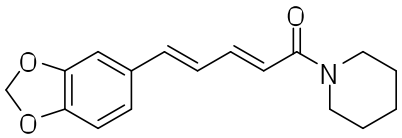
Suggest a series of structure changes that could be made to structure **1** which would lead to a library of at least 40 compound {you should propose at least two or tree modifications}.

Turn the long chain into a ring. Add substituents. Shorten the chain, as long as the required functional group is not removed.

**Question 20.**

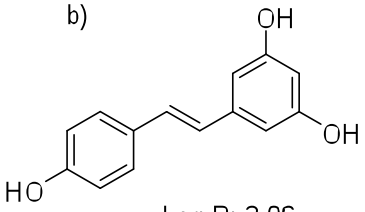
a) Apply the Lipinski rules to the following structures and decide whether they follow all four of the rules and are potential drugs (drug –like molecules)

a)



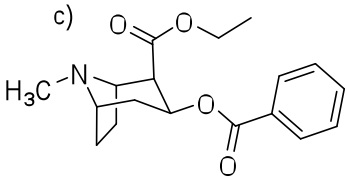
Log P: 2.78

b)



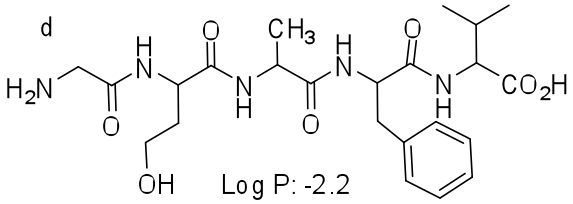
Log P: 3.06

c)



Log P: 2.15

d



Log P: -2.2

a) MW = 285.34
Log P: 2.78
H-Bond Donors: 0
H-Bond Acceptors: 4
Answer: Yes, follows all 4 rules and potential drug.

b) MW: 228.24
Log P: 3.06
H-Bond Donors: 3
H-Bond Acceptors: 3
Answer: Yes, follows all 4 rules and potential drug.

c) MW: 317.38
Log P: 2.15
H-Bond Donors: 0
H-Bond Acceptors: 5
Answer: Yes, follows all 4 rules and potential drug.

c) MW: 493.55
Log P: -2.2
H-Bond Donors: 7
H-Bond Acceptors: 10
Answer: No, does not follow all 4 rules. Not likely to be a potential drug.

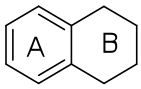
b) Which aspect of the ADME properties do the Lipinski rules address?

Mainly A & D. The molecular weight requirements address the bioavailability by ensuring that the molecule is small enough to be absorbed and pass through pores in the gut. The logP

ensures that the molecule is soluble enough in water and can be distributed throughout the body. The number of H-bond donators and acceptors ensure that the molecule does not interact too strongly with water. If it interacts strongly with water, it is hard to break the hydrogen bonds and the molecule will not react with the enzymes or other compounds that it needs to in order to be bioactive.

**Question 22.**

Consider the tetrahydronaphalene shown below.




a) What is the most likely monohydroxylation product if the oxidation occurs at ring A?

An alcohol in place of one of the hydrogens.

b) What is the most likely monohydroxylation product if the oxidation occurs at ring B?

A ketone replacing two of the hydrogens.

c) What is the structure of the key intermediate in process a)

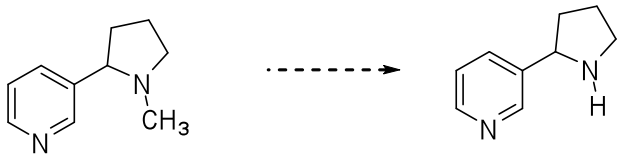
Peroxide radical? If not then none.

d) What is the structure of the key intermediate in process b)

Peroxide radical? If not that then a diol on a carbon replacing the two hydogens (it is a diol – two consecutive OH groups).

**Question 23. ***

Explain why an alkaloid such a nicotine, A, is readily metabolized by N-demethylation

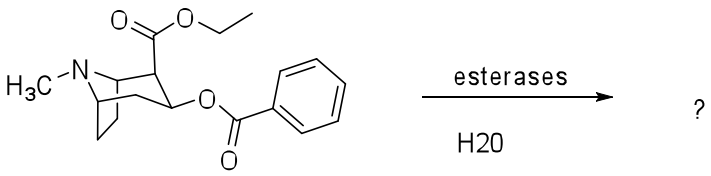



Nicotine

Weak O-H bond due to the electronegative Nitrogen, as well as the radical would be resonance stabilized (the hydrogens are weakly bonded compared to those on the ring because of the electronegative Nitrogen pulling the electrons, allowing for easier formation of the carbon radical intermediate. Not only that, but the carbon radical intermediate is also stabilized through resonance with the nitrogen.

**Question 24.**

What is the expected structure of the product when the molecule cocaine, shown below is exposed to esterase enzymes in the presence of water?




An esterase is a hydrolase enzyme that splits esters (double bonded oxygen to an OR group) into an acid and an alcohol in a chemical reaction with water called hydrolysis.

**Question 25.**

a) Define the term "therapeutic index"

Therapeutic index is a comparison of the amount of a therapeutic agent that causes the therapeutic effect to the amount that causes death or toxicity. It is calculated by dividing the toxic dosage for 50% of patients by the therapeutic dosage for 50% of the patients, or TD50/ED50. Ideally it will be a large number, where there is low toxicity relative to effective dosage. If less than 5 it gives a narrow window and a small margin of error for safety.

b) A drug compound has a therapeutic index of 4 and is known to be metabolized by CYP3A4. The patient receiving this drug drink s grapefruit juice every day. What might be the consequence of this combination of action?

If the drug has a therapeutic index of 4 then it is a narrow window and there is a small margin of error for safety. Grapefruit juice inhibits the CYP3A4 enzyme, reducing the rate of metabolism of the drug. This means there is increased concentration of the drug in the body, and it is eliminated more slowly. With a narrow safety window, this could be quite dangerous, and the concentration of the drug rises to the toxic level.

c) Explain why drug- drug interactions are most critical when one the drug in question has a low therapeutic index.

When the drug in question has a low therapeutic index, then there is high toxicity relative to effective dosage. This means that the difference between the effective dosage and the toxic dosage is very small, and if the patient is not careful with their medication, then the toxic dosage could be reached more easily than a drug with a high therapeutic index. Drug-drug interactions are thus more critical, because if the metabolic enzymes are inhibited, then the drug concentration will increase and the toxic level can be reached.

d) Explain how a compound, for example one of the components of grape fruit juice can act as a drug sparing agent.

If a drug is rapidly metabolized into an inactive compound by CYP3A4, then the patient needs to take this drug many times and at relatively large dosage to achieve the desired therapeutic level. If the patient drinks grapefruit juice, which inhibits CYP3A4, then the concentration of the drug rises to the desired therapeutic level, and smaller amounts of the drug need to be taken, resulting in less cost.

e) Extracts from the herb 'St. John's wort" upregulate CYP3A4. How would the blood concentrations of a drug metabolized by CYP3A4 change if it is taking with St. John's wort? Explain.

Since St. John's wort upregulates CYP3A4 activity, the drug is metabolized more quickly and this may reduce the drug concentration below therapeutic values, due to the shorter half-life and thus faster elimination from the body.

**Question 26.**

Explain why people of Asian origin are more likely to have problems associated with taking the anti-coagulant drug Plavix compared to those of European origin.

In Asians, rougly 12% to 23% are poor metabolizers for CYP2C19, an enzyme which activates the pro-drug Plavix by oxidation. This means this percentage of Asians carrie two copies of a variant allele. Only about 3% to 5% of Caucasians lack functioning genes for the synthesis of CYP2C19.

**Question 27**.

a) What is the US definition of an Orphan Disease?

An Orphan Disease is a disease or disorder that affects fewer than 200,000 people in the US.

b) What is the purpose of the US Orphan Drug program?

The Orphan Drug Designation Program provides orphan drug status to drugs and biological which are defined as those intended for the safe and effective treatment, diagnosis or prevention of rare diseases/disorders that affect fewer than 200,000 people in the US, or that affect more than 200,000 persons but are not expected to recover the costs of developing and marketing a treatment drug. The **purpose** is to facilitate the development of drugs for relatively rare diseases and provide the potential for financial reward.

c) Why does the development of an orphan drugs require special considerations?

The development of orphan drugs requires special considerations because they are intended for relatively few patients, and thus developing a drug might lose money for the company. Phase II and III clinical trials are carried out with fewer participants, and regulatory decisions are generally made more quickly. They are also usually more expensive

for patients since the cost of development per potential patient is much less than that for a drug with potential use by the general population.

d) Give two specific examples of successes of this program.

Before 1980, cystic fibrosis patients typically died before age 20. Pulmozyme and Tobramycin were both developed with aid from the ODA, and significantly improved the quality of life for CF patients and extended life expectancy.

Wilson's Disease is a rare hereditary disease that can lead to a fatal accumulation of copper in the body. Penicillamine was developed with aid from the ODA, and was also later found to be effective in treating arthritis.

Prior to 1983 only 38 drugs were approved in the US for treatment of orphan diseases. Between 1983 and 2010, 353 orphan drugs were approved. By 2010, 200 of the roughly 7,000 officially designated orphan diseases have become treatable.

e) Give two examples of orphan diseases

Two examples of orphan diseases are cystic fibrosis, Wilson's Disease, and homozygous familial hypercholesterolemia.

**Question 28**.

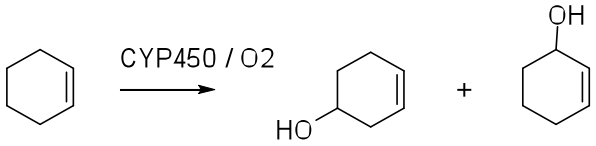
What is the cause of most of the orphan diseases?

Most orphan diseases are hereditary abnormalities such as genetic mutations.

**Question 30.**

First pass metabolism refers to metabolism by the family of cytochrome P450 enzymes in the liver. These enzymes introduce hydroxyl groups into drug molecules.

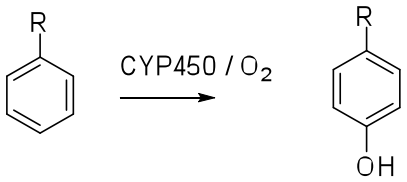
a) Give the key steps, by drawing the key intermediated involved, in the conversion of an aliphatic C-H bond into an O-H bond. Use the molecule cyclohexene as a simple substrate.
b) The following products are possible. Which is the more likely? Explain why.



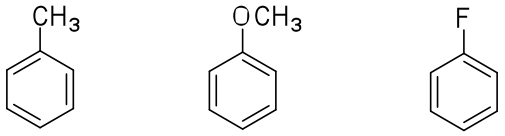

The second is more likely as it will be stabilized through resonance.

**Question 31.**

a) Give the structure of the intermediate in the metabolism of the aromatic substrate into the hydroxy derivative.




b) Which of the following substrates would be expected to be metabolized more rapidly according to the above pathway? Explain your choice.




The middle would be metabolized more rapidly because it has an EDG allowing for increased reactivity of the aromatic ring by increasing the electron density. F is an EWG and would decrease the reactivity because it decreases the electron density of the ring.

**Question32.**

Esomeprazole (Nexium) is an inhibitor of the enzymes CYP2C19 and CYP2C9, and may therefore interact with drugs that depend on them for metabolism.

a) Plavix is an inactive pro-drug that depends on CYP2C19 for conversion to its active form. Will the concentration of Plavix be increased or decreased if used concomitantly with esomeprazole? Explain, briefly.

Since Esomeprazole is an inhibitor of the enzyme CYP2C19, which is required for activation of Plavix , there will be a reduced rate of metabolism of Plavix, resulting in an increased concentration of the drug in the body due to a longer half-life (thus slower elimination). Thus, there will be an accumulation of the inactive pro-drug, and the concentration of Plavix will be increased if used continuously with esomeprazole.

**Question 33.**

Define the term –"pro-drug"

A pro-drug is a compound that is not a drug, but is converted to the active drug by a chemical reaction in the patient. This conversion may be the result of an enzyme reaction, by a metabolic process, or a reaction of the drug with acid in the stomach.

**Question 34.**

a) Based on the Lipinski rules the compound Taxol was not a likely candidate to be a useful drug. Nevertheless it has become an important anti- cancer drug. How was this accomplished?

Taxol was isolated from the bark of the Pacific yew tree, and identified as cyto-toxic in a cancer screen. It would likely not have been proposed as a drug had it not been shown to have good *in*

*vitro* activity. Taxol vioalated the molecular weight and the hydrogen bond acceptor rules. It was extremely insoluble in solvents. It was eventually formulated with a combination of ethanol and cremophor, however along with this came side effects.

b) Taxol can be isolated in small quantities from the bark of the Pacific yew tree. This source was found to be inadequate for widespread use in cancer chemotherapy. Discuss , in general terms, the resolution of this problem.

A realistic possibility was found in another natural source. *Taxus canadiensus* needles and European ornamental yew shrubs were found to contain small amounts of Taxol and much larger amounts of a related compound called baccetin III. The challenge was then how to semi-synthesize Taxol from Baccatin III. A professor from Florida State University applied beta lactam chemistry to this problem, and the chemistry along with the new sourcing of Baccatin III solved the Taxol supply problem.

**Question 35.**

a) Explain why the World Health Organization is concerned with the indiscriminate use of artimisinin as a single anti-malarial drug. What are the advantages of the treatment called ACT (artimisinin combination therapy)

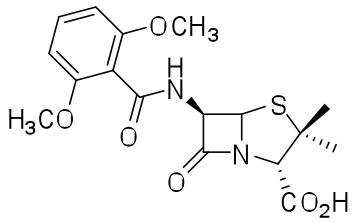
The WHO is concerned with the indiscriminate use of artimisin because it could lead to resistance which is what happened with chloroquine. WHO therefore mandated that artemisinin should not be used as a single drug, and instead recommends artemisinin-combination therapy (ACT). Combination therapy is considered best for malaria management, and ACTs are highly effective and may help to delay development of resistance.

**Question 36.**

Knowing the structure of Penicillin G and V and **understanding why** Pen V is orally bio-available and Pen G is not, decide whether the following penicillin called Methicillin could be effectively administered orally or would need to be injected**. (You should be able to answer this type of question with some structure variation) On an exam, I would supply all structures!**

Methicillin would be orally inactive as it has a substituent that is an electron donating group, which helps stabilize the (+) and allows the intermediate to form more readily. This causes less acid stability.

**b)** Incidentally: Methicillin is considered an important penicllins since for a long time most bacteria which had become resistant to other penicillins remained sensitive to Methicllin. More recently types of Methicillin resistant bacteria have appeared. These are called MRS : Methicillin Resistant ***Staphylococcus***. strains of bacteria **.**




**Question 37**

Describe and very briefly explain two key advantages of natural product compounds as**.** potential drugs.

More likely to be bio-active and bio-available. Are also produced as single isomers. A second isomer can have no biological activity, other biological activity, or can be toxic. They are more likely to be bioactive because they are produced in biological systems and are produced to have some biological function, thus they will be less likely to do noting in the body. In additional, because they are produced in biological mediums, they are more likely to be stable in biological mediums such as the cells of the body, making them more bioavailable to carry out their function.

**Question 38**

Consider the structure of quinine and chloroquine. Discuss the common structural features including respect to hydrogen bond donor, hydrogen bond acceptor sites. What is the shape of the quinoline [bicyclic aromatic] ring system? **Here again, if this question, or a closely related one, were asked on the test the structures would be included.**

3 acceptors, 1 donor.

Quinine is a bicyclic tertiary amine with a basic nitrogen, and contains a quinoline ring. Chloroquine also contains a quinoline ring, and is a 4-aminoquinoline, where the amino group is at the 4-position of the quinoline.

**Question 39.**

a) What are the two major goals of the Natural Health Product Division of Health Canada with respect to the sale and distribution of NHPs?

To protect public safety and help insure quality control and monitor efficacy claims.

b) Indicate several ways which are used to reach these key goals

Evidence of identity and quality is required, site license for manufacture is required, active post market “pharmacovigalence” for AR reports, and rapid assessment and response of reported ARs. Must also be backed by 50 years worth of scientific literature. Little testing of products is actually performed unless ARs are reported.

Question 40.

a) Give an estimate of the number of orphan diseases, world wide.

5000-7000

b) Discuss two incentives given to pharmaceutical companies which have helped convince companies to initiate such research.

Financial incentives and extended (patent) exclusivity periods.

c) What is the name of the orphan disease associated with the "Philadelphia chromosome and the first successful drug developed to treat it?

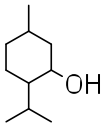
Chronic myelogenous leukemia, Gleevec.

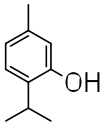
**Question 41.**

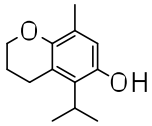
a) Keeping in mind the context of this course, what is meant by the term anti-oxidant?

An antioxidant is a molecule that inhibits the oxidation of other molecules. Oxidation is a chemical reaction that transfers electrons or hydrogen from a substance to an oxidizing agent. Oxidation reactions can produce free radicals. In turn, these radicals can start chain reactions. When the chain reaction occurs in a cell, it can cause damage or death to the cell. Antioxidants terminate these chain reactions by removing free radical intermediates, and inhibit other oxidation reactions. They do this by being oxidized themselves, so antioxidants are often reducing agents.

b) Which of the following structures do you expect would act to act as the most potent anti-oxidant and which would not act as an anti-oxidant. Justify your choices!

1) 

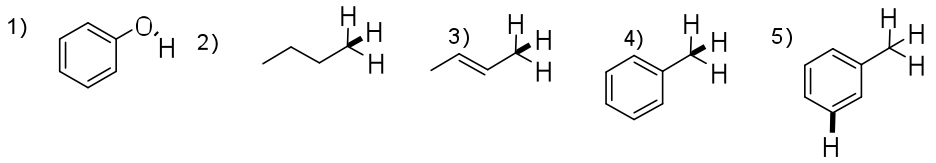

2) 


3) 


3 most potent, 1 least. 1 doesn't have any EDG, and doesn't have any double bonds to interact with the OH.

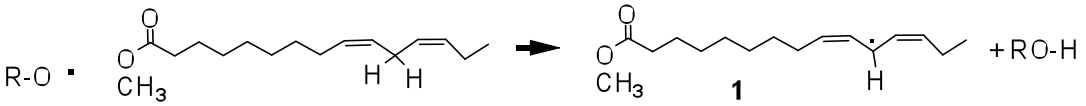
**Question 42.**

a) What is the bond dissociation energy in Kcal/mole of the indicated(Bold) bond in each of the following structures? [The number should be within several Kcal/mole compared to the usually accepted value].




110, 98, 98, 98 , 110

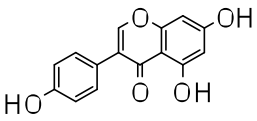
b) Generation of RO. (oxygen centered radicals) in the presence of the unsaturated fatty ester, shown below, leads to R-O-H and the radical **1** as the most likely result. Explain why by drawing the electron movement using the fishhook presentation to rexplain this transformation.




c) The reaction of **1** with oxygen results in the formation of a hydroperoxide. Draw the structure of the hydroperoxide and the fishhook arrows to show how this product is formed.

**Question 43.**

Genistein, is known to be a weak estrogen agonist.



genistein

a) Define the term agonist.

Agonist is a chemical that binds to some receptor of a cell and triggers a response by that cell.

b) What structural features of genistein most likely account for its estrogenic activity?

Two hydroxyl groups.

**Question 44**

The development of typical pharmaceutical drugs requires careful Clinical trials including the practice of blind and double blind studies.

In contrast clinical trials with NPHs are often not carried out or are often of poorer quality than those involving new pharmaceuticals. What are several of the most common problems associated with clinical trials involving NHPs.?

Clinical trials for NHPs are not funded as well as clinical trials for drugs. Clinical trials for NHPs are subjective and not regulated as well. There are often differences in the herbal products tested and

how the studies were done by different companies. Since there is no standardization for NHP clinical trials, results are often inconsistent. Also patients may be taking other NHPs and the source of the beneficial effects cannot be credited to the NHP being tested as it may be a result of the other NHPs.

**Question 45**

a) What health issues are typically addressed by NHPs?

Treat or prevent disease, restore or correct function, maintain or promote health.

b) What health issues cannot by claimed by NHPs without the same relatively rigorous clinical trials as are required for typical pharmaceuticals?

Prevent, treat, or cure any **specific** disease.

c) Which governmental organization in Europe is considered to be a very reliable source of information concerning the use of NHPs?

Commission E

**Question 46.**

Complementary and Alternative Medicines, including **homeopathy**, are included in the mandate of the NHP branch of Health Canada and US Food and Drug Aministration –National Center for Complementary and Alternative Medicine despite the following statement on the website of the US organization. "**There is little evidence to support homeopathy** as an effective treatment for any specific condition".

a) What is the definition of homeopathy?

A system of medical practice that treats a disease especially by the administration of minute doses of a remedy that would in larger amounts produce in healthy persons symptoms similar to those of the disease.

b) Why is such a treatment included in NHP regulations?

Because they're claiming health benefits, therefore despite being classified as foods, they are included in NHP regulations due to the claims of health benefits.

**Question 47.**

Many plants make a number of analogs of a basic structure often as a protective measure. For example ginger roots contain at least three closely related gingerols.

a) What term is used to describe this phenomenon?

Phytochemical redundancy.

b) Suggest a possible reason why a plant might make a series of analog compounds.

Helps to prevent or delay build up of resistance in the pant to fungi or parasites.

**Question 48**.

a) Give an example of an off-label use of an approved drug.

Gabapentin.

b) Under what conditions can a doctor use a drug for an off-label use?

Whenever they feel like.

c) Under what conditions can a company promote the off-label use of a drug?

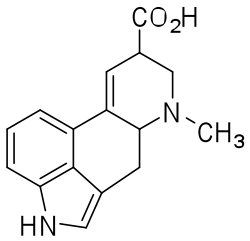
Only after the clinical trials have been complete.

**Question 49**

a) What are the common structure elements of typical natural product derived CNS drugs.

Aromatic ring(s) with amine group.

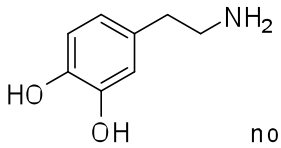
b) Lysergic acid has CNS activity; its diethylamide is much more potent. The structure of lysergic acid is shown below. Show that it has the common element that you have defined in a) above.




lysergic acid

**Question 50**.

Monoamine oxidases are important enzymes in animals, including humans since they metabolize rapidly a variety of CNS active compounds including nor-epinephrine.




nor-eprinephrine

a) What product is formed when nor-epinephrine is metabolized by a MAO?

Replace the NH2 with carboxylic acid.

b) Why is the efficient metabolism of compounds such as epinephrine (adrenaline) and nor epi-nephrine (nor-adrenaline) important?

Information: Adrenaline and nor-adrenaline are also inactivated by an enzyme called Catechol-O methyl transferase (COMT). This converts the OH meta to the side chain into O-CH3 and provides an alternate method of removing this compound from the system.

**Question 51**.

Fractioning of ginseng roots into fractions soluble in hot methanol and hot water yields two products.

a) What are the major constituents of each fraction?

b) What is the major use reasonably well-documented use of the water soluble fraction?

c) The methanol soluble fraction contains compounds called ginsenosides. What are the two major structure components of the ginsenosides? What biological properties, if any, have been attributed to the ginsenosides?

**Question 52**.

Feverfiew is the basis of an NHP used in the treatment of migraines.

a) Describe how evidence was obtained to support this claim.

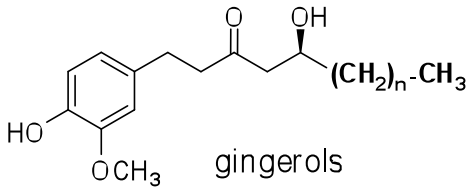
A survey of 270 people with migraines in Great Britain found that more than 70% of them felt much better after taking an average of 2-3 fresh feverfew leaves daily.

b) What is considered the active ingredient in feverfiew?

Parthenolide. It has a reactive electrophilic centre.

**Question 53**.

Ginger is used by many people throughout the world for a variety of purposes including as a spice in baking. The major bioactive constituents of ginger are called gingerols, structure 53. Gingerols have a rather strong pungent taste. Gingerbread cookies have a much milder taste due to a heat or possibly base catalyzed reaction of the gingerols. All gingerols have zingerone. What is the structure of zingerone and how is it formed?



gingerols

The removal of the alcohol chain to produce an enol at the Ketone.

**Question 54.**

Shaogol10, obtained the from the related gingerol by heating with base or with acid, has been shown to inhibit COX2 with an IC50 of approximately 7.5 uM. It does not appear to inhibit COX1.

a) Suggest a potential application of this compund

   This compound after a few more modifications to allow possibility for patenting, could replace ASA and its derivatives to treat inflammation with no risks.

b) Even though this evidence was available a number of years ago, shaogols have not been developed for this purpose. Give possible reasons why this has not happened.

   Unable to patent, meaning no money.

c) Define the term IC50. Suppose compound a) inhibits a particular enzyme with an IC50 of 15 uM and a second compound b) shows an IC50 of 5 uM. Which is the more potent compound?

**Question 55**.

The off-label use of the anti-diabetic drug Metformin for potential cancer prevention treatment is being actively investigated. Most of the researchers in the field and many highly recognized research organizations have become involved in extensive clinical trials.

a) Discuss the type of evidence that is available which has been used to justify the effort and expense of these trials.

   A comprehensive literature search and meta-analysis of epidemiologic studies was conducted to assess the effect of metformin on cancer incidence and mortality in diabetic patients. Eleven studies were selected in terms of intervention, population studied, independence, and reporting of cancer incidence or mortality data. A 31% reduction in overall summary relative risk was found in subjects taking metformin compared with other anti-diabetic drugs.

   A prospective study with a median follow-up time of 9.6 years reported that patients with T2D who were not taking metformin showed an increased cancer mortality ratio compared with that for the general population. The mortality of patients taking metformin was comparabl with that for the general population. A reduced cancer risk for patients taking metformin compared with patients taking a sulfonylurea drug.

b) Which people are most likely the benefit if the trials give positive results?

   Those who have T2D and are taking metformin.

**Question 56**.

Metformin has also been reported to reduce heart disease. Indicate a fundamental reason why this could be a plausible outcome.

Generally, many of the characteristics common to diabetes and heart failure, such as insulin resistance, endothelial dysfunction, inflammation, and oxidative stress, are improved by metformin. At a more fundamental level, the contracting heart appears to elaborate most of its energy from the metabolism of non-esterified fatty acids, an adaptation that may be further heightened in the insulin-resistance diabetic heart due to an increased availability of this substrate.

**Question 57.**

According to statistics, Canadian physicians prescribe drugs for off label uses about 10% of the time. Discuss both the positives and negatives surrounding this practice.

Negatives: Carries health risks, and legal liability.
Positives: Drug could be useful in treating certain patients or diseases for which it was not intended. The drug company might not have run large-scale clinical trials for certain reasons (e.g. companies have been historically reluctant to include children in clinical trials).

**Question 58**.

St. John's Wort is often used as an example of a natural health product interfering with the activity of a prescribed drug.

a) Explain carefully at least two types of problems seen when patients take St. John's Wort.

   SJW and Hyperforin can interact strongly with drugs. Hyperforin stimulates the pregnane X receptor that induces the drug metabolizing enzyme CYP3A4. Interaction can cause antiretroviral drug or plasma levels to fall below the therapeutic levels – potentially life threatening! Interactions with other SSRIs may cause serotonin syndrome (high serotonin), which includes mental confusion fever and muscle twitch. However, SJW is safe if taken alone.

b) What is the major medical use of St. John's Wort as an NHP? How well is it supported by scientific data?

   Mild to moderate depression.

c) How is the quality of St. John's Wort determined?

   Standardized to hyperforin (5%) as selective serotonin re-uptake inhibitor. Hyperforin in St Johns Wort has a similar effect to conventional antidepressants. 27 trials have been conducted including a total of 2291 patients. Major controversy after a 2002 Journal of the American Medical Association stud showed that STJ was not effective in severe depression.

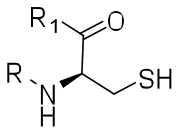
**Question 59**.

What benefits have been ascribed to Flax seed used as a "functional food"?

Flax seeds contain two essential fatty acids, as well as fiber and vitamins.

**Question 60**

a) Discuss, via equations the mechanism by which of the tripeptide glutathione acts as anti-oxidant in cells. A simplified structure of glutathione is shown below.




**Question 61**.

What are the three common and typically operation anti-oxidants in the human body?

Vitamin E, K, C, and Glutathione.

**Question 62**.

Many plants and fruits contain excellent anti-oxidant compounds. Since radical quenching is undoubtedly important for cell survival one would assume that consuming anti-oxidants would produce important health benefits. Yet some recent epidemiology studies do not show significant benefits arising from consuming anti-oxidants. Suggest possible explanation(s) for these results.

**Question 62**.

Capsaicin is the active ingredient in a number of pain medications, both prescription and over the counter.

a) What is the source of capsaicin?

   Hot chiles.

b) Which well known medical organization has carried out much of the research concerning the use of this material for the treatment of pain, including arthritic pain?

   American Institute for Cancer Research