Question 1

Which area of the following areas pharmaceutical industry holds the most promise for new drugs in the next ten years? Support your choice.

I believe that the fate of the pharmaceutical industry hold the most promise is the development of personalized drugs. Personalized drugs would be more relevant in today's drug research because it would mean the end of the "one-size-fits-all" approach to modern medicine. It is known that not all drugs interact with each individual equally and it is harder for a physician to prescribe the same drug for everyone while watching out for drug interactions and reactions with each patient. By developing personalized drugs, medication would better suit the patient's genetics and therefore more compatible than one-for-all drugs.

Question 2

A tremendous need and opportunity exists for developing new drugs to slow down rate of decline of patients suffering from dementia eg, Alzheimers disease.

Discuss the issues which made progress in this area slow at this time. What breakthrough(s) is (are) needed to change the situation?

Question 3

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

1. Pfizer – USA
2. Johnson and Johnson – USA
3. Holfmann-LaRoche – Switzerland

Question 4

Describe briefly the mode of action of Aspirin and explain why its action as an anti-inflammatory agent is accompanied in many patients by gastrointestinal bleeding.

Aspirin inhibits the formation of prostaglandins through the inhibitaiton of cyclo-oxygenase enzyme. NSAIDs like ASA aren't enzyme specific with the inhibition of COX I or COX II. COX I is important in the regeneration of the lining in the stomach. The compound would increase gastrointestinal toxicity because of this inhibition and therefore cause gastrointestinal bleeding via ulcers.

Question 5

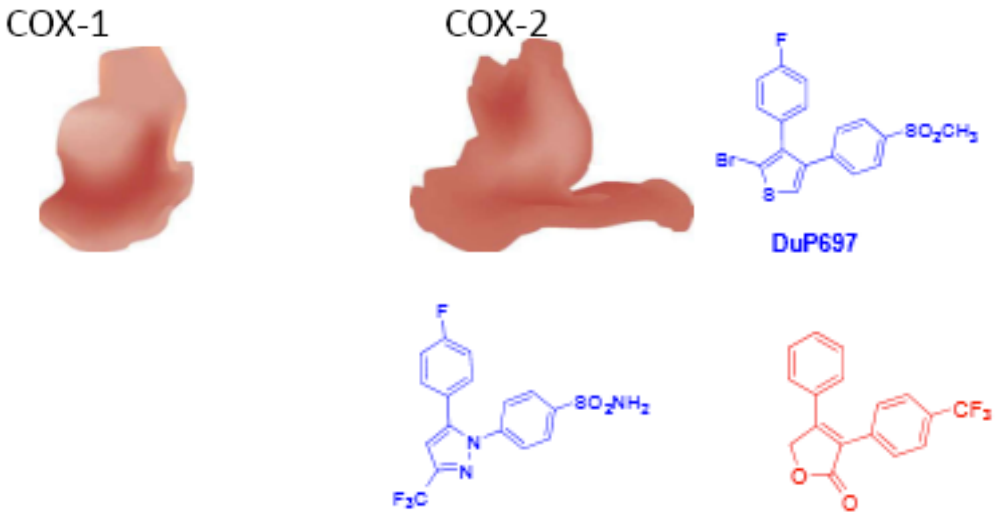
COX2 inhibitors were initially expected to act as anti-inflammatory agents without the typical side effects associated with Aspirin [ASA] and the other NSAIDs such as Ibuprofen

sold as Advil or Motrin. Explain the basis of this expectation.

Compounds such as Vioxx that inhibit COX II exclusively have little to no interactions with COX I. It has been studied in the 1980s that COX II is responsible for formation of prostaglandins while COX I was also responsible for important body functions such as renewal of the stomach and esophagus lining. COX II inhibitors have the most optimized structure to fit exclusively in COX II's active site and not COX I, which would lead to decreasing inflammation rather than disrupting gastrointestinal lining regeneration.

Question 6

Knowing the structure of lead structure published by the Dupont company, DuP697, 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 would obviously infringe on the Dupont patent.



Celebrex Vioxx

Question 7

Generic companies produce drugs whose patents have expired. In order to obtain permission from Health Canada to sell a particular drug what key property of the generic drug show compared to the originally approved drug.

A key property of the generic drug the generic companies need to prove to obtain permission from Health Canada to sell a particular drug is how the drug is bioequivalent with the brand name drug. This is an important consideration because it ensures the industrial standards are kept. It also ensures that the generic drug has the same bioavailability of the active ingredient and properties as the brand name drug.

Question 8

a) What key questions are addressed in a Phase 1 Clinical Trial? In a phase II Clinical trial? In a Phase III Clinical trial?

   Phase I addresses the safety of the compound. Phase II addresses the efficacy of the compound. Phase III addresses the safety and efficacy in a somewhat diverse group of patient that mimics the type of people who would use the drug.

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

   70% of drugs end up passing Phase I

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

   The longest and costliest phase in clinical trials is Phase III. This is because developers are determining the efficacy of the drug to targeted patients. If it isn't effective, they would need to tweak and improve the drug and therefore have to go through all of the other processes again.

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

   Post-marketing surveillance is when the drugs are available to the general public and doctors and specialists assess how the drug performs in the general demographic. This phase is important in insuring the drug's safety as not all side effects are discovered in clinical trials.

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.

   Serious side effects are not always noted in Phase III clinical trials because the genetic diversity in a large population makes it almost impossible to test against all adverse effects.

Question 9

a) Explain the basic concept used to develop the cholesterol lowering drugs, the statins.

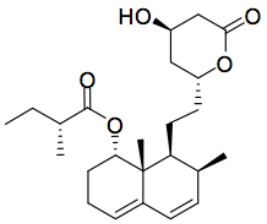
   The statins generally work by imitating the natural ligand, HMG-CoA, which will inhibit the enzyme of the rate-determining step called HMG reductase when in abundance. Statins work by directly inhibiting the active site of HMG reductase

and therefore preventing the creation of cholesterol's precursor compounds.

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

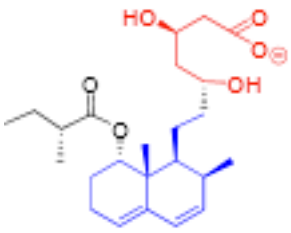
Cholesterol is predominately found in animals and not in plants. Micro-organisms were found to produce inhibitors of HMG-CoA reductase as a form of defense.

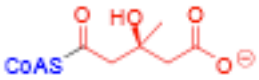
c) Which part (s) of the structure of mevastatin are considered crucial for the inhibition of HMG-CoA –reductase? Explain by drawing chemical structures of relevant molecules



mevastatin
- a potent inhibitor
of HMG-CoA reductase,

The ester group on the top of the inhibitor is a crucial component. That portion unraveled simulates HMG-CoA

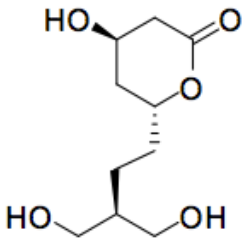


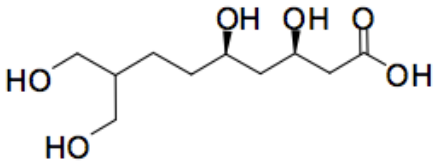


HMG-CoA

Question 10

Knowing the structure of the natural HMG-CoA reductase inhibitor shown in Question 9, would you expect the following two structures to be strong inhibitors of this enzyme? Give clear reasons for your decision.



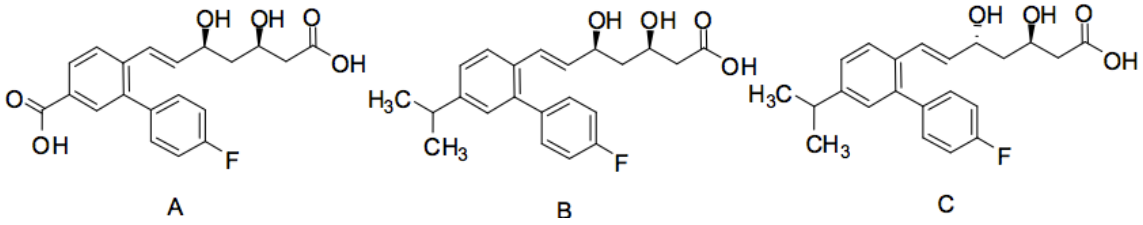


I would propose that the first compound would be the best candidate to be a strong

inhibitor of HMG-CoA reductase. This is because the compound includes the crucial component required to mimic the properties of HMG-CoA. The first is more lipophilic in polarity and the second has an extra hydroxyl group.

Question 11

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



B would be the best likely inhibitor of HMG-CoA reductase as it is more similar to the diastereomer of mevastatin that is effective. A wouldn't be as the carboxylic group may change the polarity of the molecule and HMG-CoA is lipophilic. C wouldn't be the best candidate as it has a different diastereomer of mevastatin.

Question 12

What is meant by the term "healer consensus" ?

Travelling to see different healers and try to see similar natural ingredients found in other cultures to see the effectiveness for therapy. Example of this is willow bark. Healer consensus is a term used when a natural ingredient is found to have therapeutic qualities used by shamans or traditional doctors and accepted across the culture.

Question 13

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

Bio-assay guided isolations are useful for extraction of the active ingredient in either dried or fresh plants. The process involves grinding the plant in a compatible solvent to filter out the active ingredient from the rest and repeated until the active ingredient is completely isolated. The activity of the extraction is tested through chromatographic separation and by checking the fractions. If the active fraction is a pure compound then the process is complete.

Question 14

a) Define the therapeutic index either in words or via an equation.

The therapeutic index is the ratio between the toxic dosage for 50% of patients and the therapeutic dosage for 50% of the patients. The high the index, the more effective the drug is.

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

Some drugs may inhibit the key CYP enzyme in the liver and reduce the rate of metabolism of the prescribed drug. If the drug has a low therapeutic index, then the intended metabolism of the drug is lengthened, this would increase the concentration of the drug and its toxic properties to be in the system longer and can cause more unfavourable effects in the system.

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

Grapefruit juice is known to decrease the enzymatic activity of CYP enzymes and therefore lower the metabolic rate of drugs and toxic compounds.

d) Explain why the drug Plavix, which prevents platelet aggregation should not be taken with grapefruit juice.

Plavix is known as a "pro-drug" and requires CYP metabolism in order to become active. Drug sparing agents such as grapefruit juice is known to reduce the activity of CYP enzymes and therefore reduce metabolism of the pro-drug to the active metabolite.

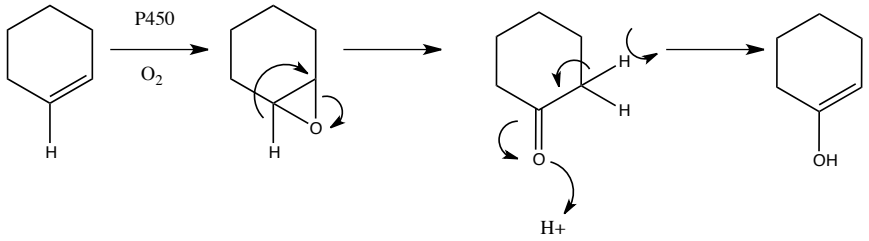
e) Extracts from the herb "St. John's Wort" upregulates CYP3A4. How would the blood concentrations of a drug metabolized by CYP3A4 change if it is taking with St. John's wort? Explain.

If St. John's Wort upregulates CYP activity, the blood concentrations of the drug would decrease as more of the drug would be metabolized by the CYP enzyme. The enzyme would push more of the drug to the product's side.

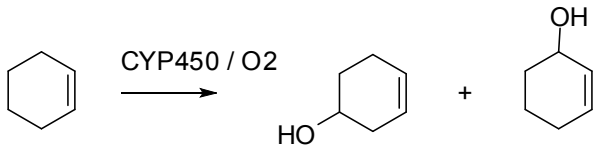
Question 15.

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 intermediates involved, in the conversion of an aliphatic C-H bond into an O-H bond. Use the molecule cyclohexene as a simple substrate.



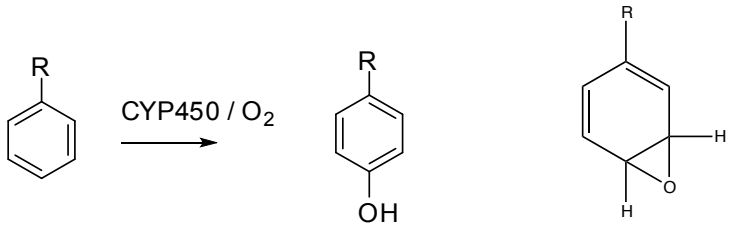
b) The following products are possible. Which is the more likely? Explain why.



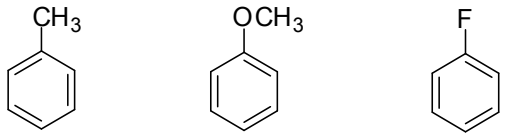
The second product is more likely as it is ortho to the alkene. The alkene allows the protons on the ortho position to be removed as there is more electron density around that portion of the cyclohexene. When epoxidation occurs, that proton would be the best candidate to be removed.

Question 16.

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.

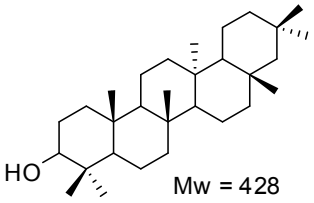


The second substrate would be metabolized more rapidly as the methoxy group is the better activating group compared to the others. Activating groups would also promote nucleophilic attack of the epoxide components at the ortho and para (which is the desired one) to be formed.

Question 17.

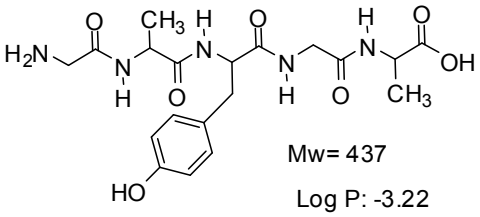
a) Which of the following compounds are likely to be reasonable drug candidates?

Explain your choice in terms of the Lipinski rules.



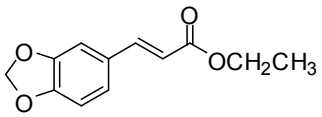
Mw = 428

Log P: 8.9



Mw= 437

Log P: -3.22



Mw= 220

Log P: 2.31

Lipinski's rules: MW less than 500, logP of < 5, < 5 H-bond donor and receptors

A) 428 < 500 ! ; logP 8.9 < 5 X ; 1 P-donor < 5 ! ; 1 P-receptor < 5 ! – POSSIBLE

B) 437 < 500 ! ; logP -3.22 < 5 ! ; 7 P-donor > 5 X ; 10 P-receptor < 5 X – NOT POSSIBLE

C) 220 < 500 ! ; logP 2.31 < 5 ! ; 0 P-donor < 5 ! ; 4 P-receptor < 5 ! – POSSIBLE

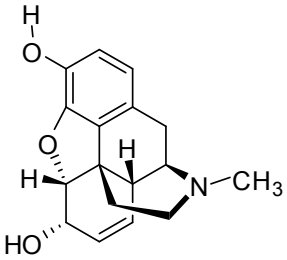
Question 18.

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"?

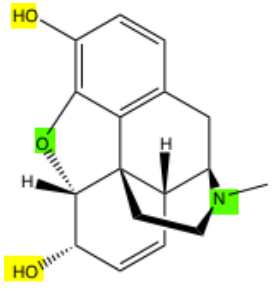
A key property of the generic drug the generic companies need to prove to obtain permission from Health Canada to sell a particular drug is how the drug is bioequivalent with the brand name drug. This is an important consideration because it ensures the industrial standards are kept. It also ensures that the generic drug has the same bioavailability of the active ingredient and properties as the brand name drug.

Question 19.

Identify clearly all the hydrogen bond donor and all of the hydrogen bond acceptor sites in the morphine structure.



Morphine



Yellow = donor/acceptors

Green = Acceptor

Question 20.

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

Will the concentration of these drugs increase or decrease in they are used concomitantly with esomeprazole? Explain, briefly

The concentrations of these drugs will increase because the metabolism of the drugs is lowered. This will therefore allow accumulation of the drug to occur within the system and therefore increase the concentrations.

b) Plavix is an inactive pro-drug that partially 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.

The concentration of the pro-drug would increase as the formation of the active drug is reduced. This would lower the effectiveness of the treatment and will not allow the patient to use the therapeutic properties of the drug.

Question 21.

Define the term –"pro-drug"

A pro-drug is a precursor drug of the active metabolite. Sometimes time elapsed drugs or drugs that require to be activated in localized areas require the ingestion of the drug in an inactive state. Enzymes like within the liver metabolize these pro-drugs into their activated state. An example of this is codeine and morphine.

Question 22.

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 on its own is not a very effective drug. When mixed with ethylene oxide and Castor oil, the solvents give the drug its ability to become more bioavailable in the system. The increase of bioavailability can bypass the requirements outlined by the Lipinski rules and makes Taxol an important anti-cancer drug.

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 the resolution of this problem.

Taxol extraction gives extremely low yields from the Yew tree to allow the drug widespread use in cancer chemotherapy. An alternative method of synthesis was to prepare Taxol from baccetin III using a beta lactam ring containing the acid derivative as suggested by Holton.

Question 23.

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)

WHO recommends using ACT treatment as this would prevent artemisinin resistant parasites. By using the combination therapy, the parasite couldn't just form a resistance to the artemisinin.

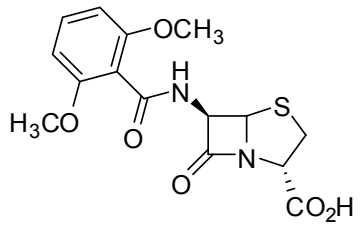
b) What is the pharmcophore in the anti-malarial drug – artimisinin? Suggest a relatively simple organic compound that you might reasonably expect to have anti-malarial activity.

The pharmcophore in the anti-malarial drug artimisinin is the peroxide structure. This would give rise to the formation of free oxide radicals, which binds to Heme in blood and kills the parasite. Another substrate could be benzoyl peroxide as it will degrade to radical benzoate.

Question 24.

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 Meticillin 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!**

Incidentally: Meticillin is considered one of the important penicllins since for a long time most bacteria which had become resistant to other penicillins remained sensitive to Meticllin. More recently types of Meticillin resistant bacteria have appeared. These are called MRSA: Methicillin resistant Staph. A**.**



Electron rich substituents with an electron-withdrawing group tend to increase the stability of a compound within acidic conditions. This is why Pen G is not effective when ingested orally. Knowing this, Meticillin would not be an orally active drug.

Question 25.

What are the key structural features of typical central nervous system drugs?

Key structural features of typical central nervous system drugs are substituents with an aromatic ring, 2 methyls and a amine. Another are indoles.

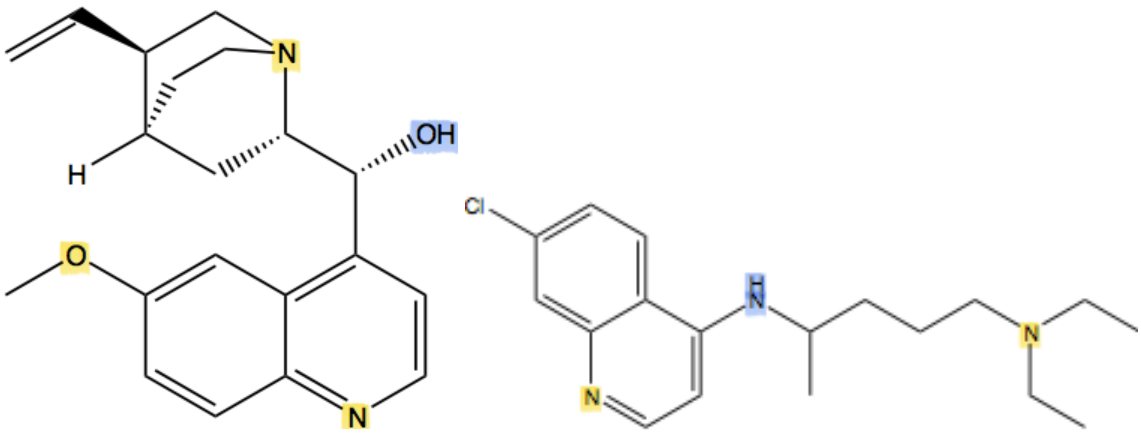
Question 26.

Describe and very briefly explain some of the key advantages of natural product compounds as potential drugs.

Natural products are produced by biological systems and a therefore more likely to be bio-active as they can be absorbed better within the system. Natural products are also presented as a single isomer so toxic properties found within the other isomers wouldn't be an issue.

Question 27.

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.**



Quinoline is a bicyclic structure