The University of British Columbia - Faculty of Pharmaceutical Sciences

Midterm Examination 2013 – March 5, 2013

PHAR 220: Physicochemical Properties of Drugs

Total Marks: 50 **Time: 1 hour, 50 minutes**

STUDENT NAME: **ANSWER KEY**

Please Print

STUDENT NUMBER:

STUDENT SIGNATURE:

THIS EXAMINATION CONSISTS OF **10 QUESTIONS** and **13 PAGES.** IN A SEPARATE HANDOUT YOU WILL FIND **7 TABLES/SCHEMATICS/APPS** REQUIRED TO COMPLETE THE EXAM QUESTIONS. CHECK TO ENSURE THAT THIS PAPER IS COMPLETE. ANSWER ALL THE QUESTIONS ON THE EXAMINATION PAPER.

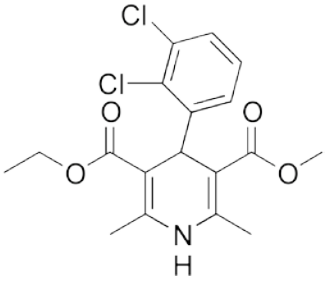
Instructors: S. Albon

RULES GOVERNING EXAMINATIONS:

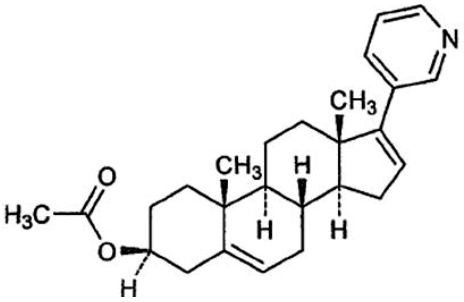
1. Each candidate should be prepared to produce, upon request, his/her library AMS card.
2. **READ AND OBSERVE THE FOLLOWING RULES**:
   No candidate shall be permitted to enter the examination room after the expiration of one-half hour, or to leave during the first half-hour of the examination.
   The use of any device capable of containing user stored memory is prohibited.
   Candidates are not permitted to ask questions of the invigilators, except in the cases of supposed errors or ambiguities in examination questions.
   CAUTION: Candidates guilty of any of the following, or similar, dishonest practices shall be immediately dismissed from the examination and shall be liable to disciplinary action.
   a) Making use of any book, papers or memoranda, other than those authorized by the examiners.
   b) Speaking or communicating with other candidates.
   c) Purposely exposing written papers to the view of other candidates. The plea of accident or forgetfulness shall not be received.
3. During all examinations, the following routines will be followed:
   a) Calculators and their cases or any other items the candidate has at the desk may be checked at any time.
   b) Examination papers may be scrutinized at any time.
   c) Students may be asked to move to another seat at the discretion of the invigilator at any time.
   d) Students are prohibited from sharing calculators or any other instrument with other students.
   e) At the beginning of each examination, it is the responsibility of each student to deposit all books, extra clothing, baseball caps, bags, and other paraphernalia at a site remote from student access: for example either at the very front of the examination room or at the back of the room.

Instructor:	TOTAL
Possible Mark:	50
Obtained:	

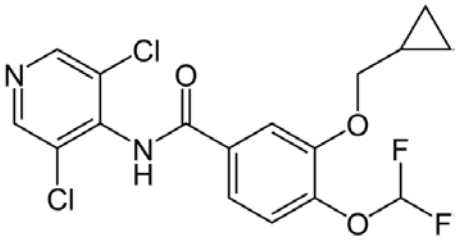
Drugs **A-I** shown below represent a few of the many drugs that are either currently on the market, have recently been approved for therapy, or are in the final stages of clinical trials in Canada and the US. These drugs are to be used to answer exam questions 1-10 that follow.



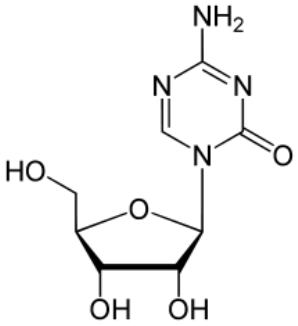
A. Felodipina (calcium channel blocker; antihypertensive agent; MW 384.3 g/mol)



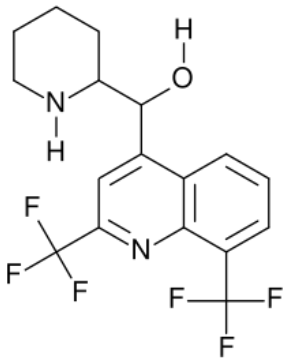
B. Abiraterone (CYP17A1 inhibitor; blocks testosterone production in prostate cancer; MW 391.6 g/mol)



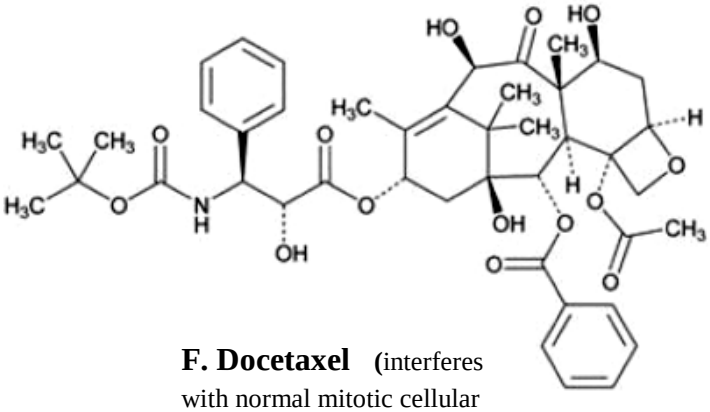
C. Romfluilast (phosphodiesterase 4 inhibitor; anti-inflammatory used to treat COPD; MW 403.2 g/mol)



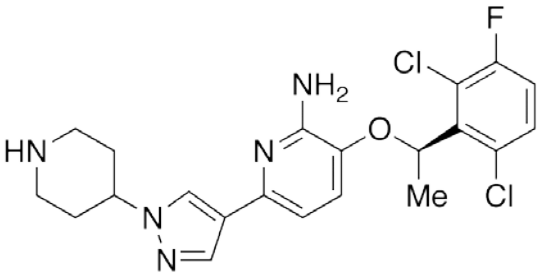
D. Azacitidine (DNA methyltransferase inhibitor; antineoplastic agent; MW 244.2 g/mol)



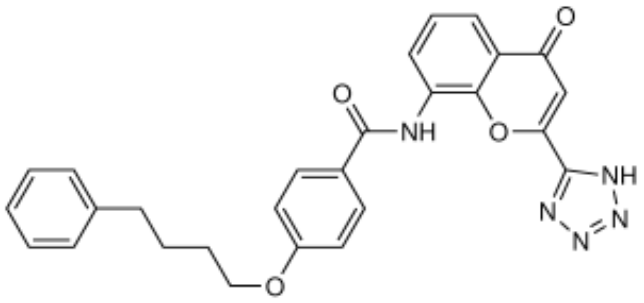
E. Mefloquine (antimalarial agent; MW 378.3 g/mol)



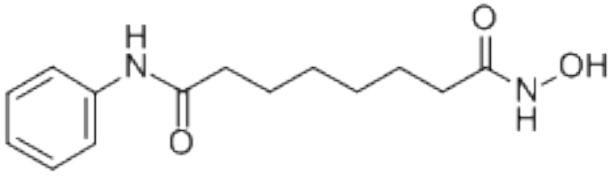
F. Docetaxel (interferes with normal mitotic cellular functions; anti-cancer agent; MW 807.9 g/mol)



G. Crizotinib (kinase inhibitor; anticancer agent; MW 450.3 g/mol)

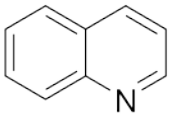


H. Pranlukast (a cysteinyl leukotriene receptor-1 antagonist; anti-asthmatic agent; MW 481.5 g/mol)

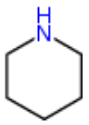


I. Zolinza (histone deacetylase inhibitor; anti-cancer agent; MW 264.3 g/mol)

1. Using drugs **A-I** provided above, please complete this question by matching the letter of the drug to the functional groups indicated below; it is possible that each functional group can be matched to more than one drug. Write **NONE** on the blank if a match cannot be found. **[10 marks, 0.5 mark each; no part marks and no marks for blank spaces]**

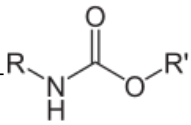


Ester ___A, B, F _____



Quinoline___E_____

Piperidine ___E, G_____

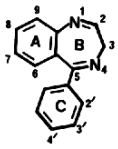


Carbamate____F_____

Pyridine_ B, C, G, may also see E (as part of the quinoline)

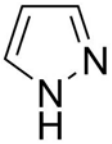
Steroid nucleus___B_____

Benzodiazepine_____None_____



Amide_C, H, I, also accepted was D (as part of ring system), F (as part of carbamate)

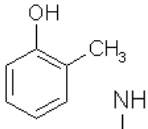
Guanidine__D (as part of ring system)__



Pyrazole___G_____ __

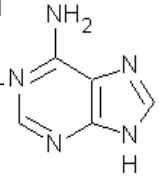
A hydrophobic halogen __A, C, E, G, _____

Lactone __None_____

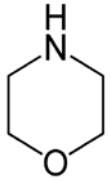


o-cresol ____None_____

Aromatic ether_C, H, also accepted was G (as part of the pyridine rir

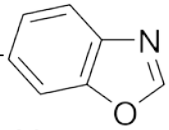


Adenine _____None_____

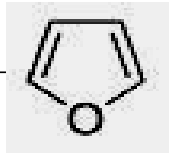


Morpholine _____None_____

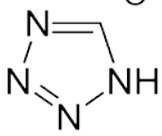
Secondary Alcohol _____D, E, F_____



Benzoxazole ____None _____



Furan ____None_____



Tetrazole_____H_____ _

2. Drugs **A-H** provided above are classified as small drug molecules (MW < 2000g/mol). Calculate the size range (in nm) for Drugs **A-H** and indicate which of these drugs is most likely to enter the body *via* paracellular diffusion in the GIT. Explain your choice(s). **(2 marks; 1 mark for size range, 0.5 marks each for choice(s) and explanation)**

Using the conversion: 200g/mol = 1nm, the size range varies from 1.22-4.04 nm (see below; many students calculated the size of all the drugs):

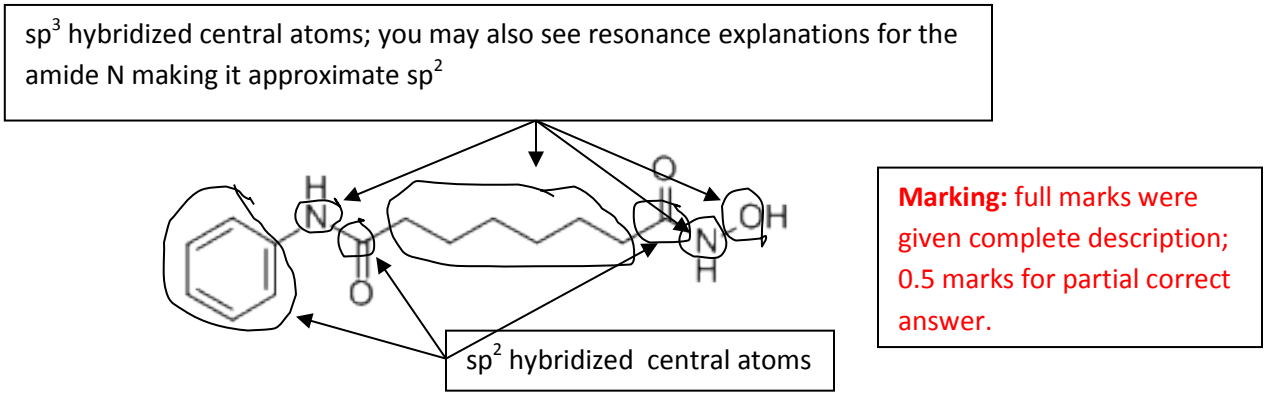
Drug D was the smallest (Azacitidine): 244.2 g/mol/200 g/mol X 1 nm = 1.22 nm **(0.5 marks)**
Drug F was the largest (Docetaxol): 807.9 g/mol/200 g/mol X 1 nm = 4.04 nm **(0.5 marks)**

Choices & reasons: The most likely candidates for paracellular diffusion in the GIT will be the smallest drugs. Since the epithelial junctions in the GIT are on the order of 1-2nm **(0.5 marks)** all except Drug F (Docetaxol) could likely enter the body *via* paracellular diffusion **(0.5 marks)**.

3. As we have discussed throughout the term there are different ways to describe drug structure: **(3 marks total)**

a) List the key aspects you would use to develop an atomic level description of drug structure. **(1.5 marks)**
There are three key components of an atomic level description of a drug: **size** (related to MW), **electronegativity** (including recognition and description of types of electrons & bonds, bond polarity, polar & non-polar functional groups), and **shape** (descriptors might include hybridization & 3D geometry). **Marking: 0.5 marks for each component (some answers provided additional qualifying information as provided above.**

b) For drug **I**, Zolinza, clearly indicate the hybridization around each central atom in the drug molecule. Use the drug structure provided below to show your work. **(1 mark)**



c) Explain why the information about hybridization might be important for understanding what the body might do to this drug. **(0.5 marks)**
Hybridization gives the 3D geometry of the drug molecule which may impact physicochemical properties of drugs such as solubility or how the drug might interact with binding sites in the body (eg., enzyme, receptors etc).

4. Based on your understanding, do you have any concerns about the *in-vitro* chemical stability of **Drugs A-I**? Clearly explain your reasoning and indicate how you would store these drugs. **(3 marks)**
* The two main reactions of concern regarding the *in-vitro* chemical stability of any drugs are **hydrolysis** and **oxidation**. **(Marking: 1 mark each; 2 marks total)**
***** Proper storage of these drugs would be storing them in the dark in a container that minimized exposure to moisture. **(Marking: 1 mark for storage conditions)**

Additional information: While any drug exposed to light can potentially undergo oxidation (via a free radical mechanism), ester-containing drugs are most susceptible to hydrolysis. Of **Drugs A-I,** drugs A,B and F would be susceptible to ester hydrolysis.

5. Using drug structures **B-H** provided above, classify each as acidic, basic, neutral or amphoteric. **(3.5 marks; 0.5 marks each; no part marks)**

Drug **B** (**Abiraterone)** is: ___Basic_____ Drug **C** (**Romfluilast**) is: __Basic_____
Drug **D (Azacitidine)** is: _Basic_____ Drug **E (Mefloquine)** is: __Basic_____
Drug **F (Docetaxel)** is: ___Neutral_____ Drug **G (Crizotinib)** is: __Basic_____
Drug **H (Pranlukast)** is: ___Acidic_____

6. Comparing drugs **D**, **E** and **G** provided above speculate on which drug you would expect to contain the strongest basic site and why? Which drug would contain the weakest basic site and why? **(3 marks; 1.5 marks each; 1 mark each for correct drug selection and 0.5 marks each for correct explanation)**

Structural analysis (pKa estimates are taken from the provided charts; keep in mind here that from a theoretical perspective each functional group acts independently). As shown below drugs D, E & G were dissected according to their basic functional groups, the pKa of each identified with the charts and then the comparisons were made to answer the question):

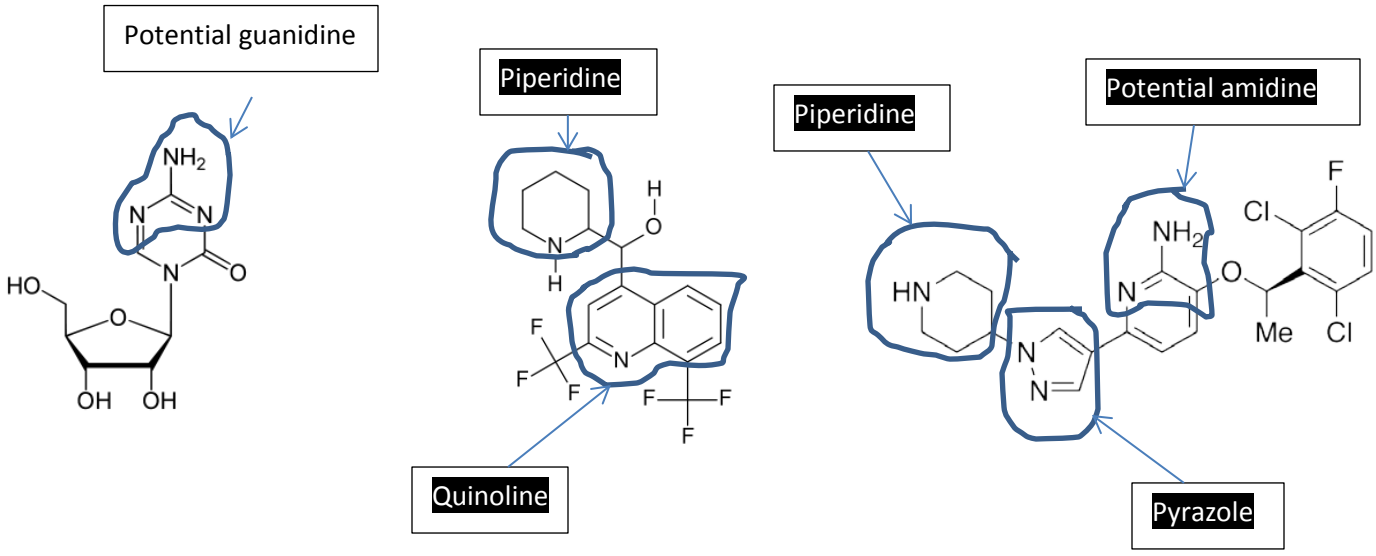
- Drug D (**Azacitidine)** basic sites: guanidine-like structure (pKa ~ 10-13)

- Drug E (**Mefloquine**) basic sites: piperidine (pKa ~ 9-10); quinolone (pKa ~ 4-5)

- Drug G (**Crizotinib)** basic sites: pyrazole (pKa ~ 2-3); piperidine (pKa ~ 9-10); amidine-like structure (pKa ~ 9-10)

Azacitidine (Drug D) would have the strongest basic site (the potential guanidine; from the acids/bases chart the pKas for guanidine are typically 10-13) **(Marking: 1 mark for the drug selection; 0.5 marks for including correct pKa information)**

Crizotinib (Drug G) would have the weakest basic site (the pyrazole group; from the acids/bases chart the pKas for pyrazoles are typically 2-3) **(Marking: 1 mark for the drug selection; 0.5 marks for including correct pKa information)**



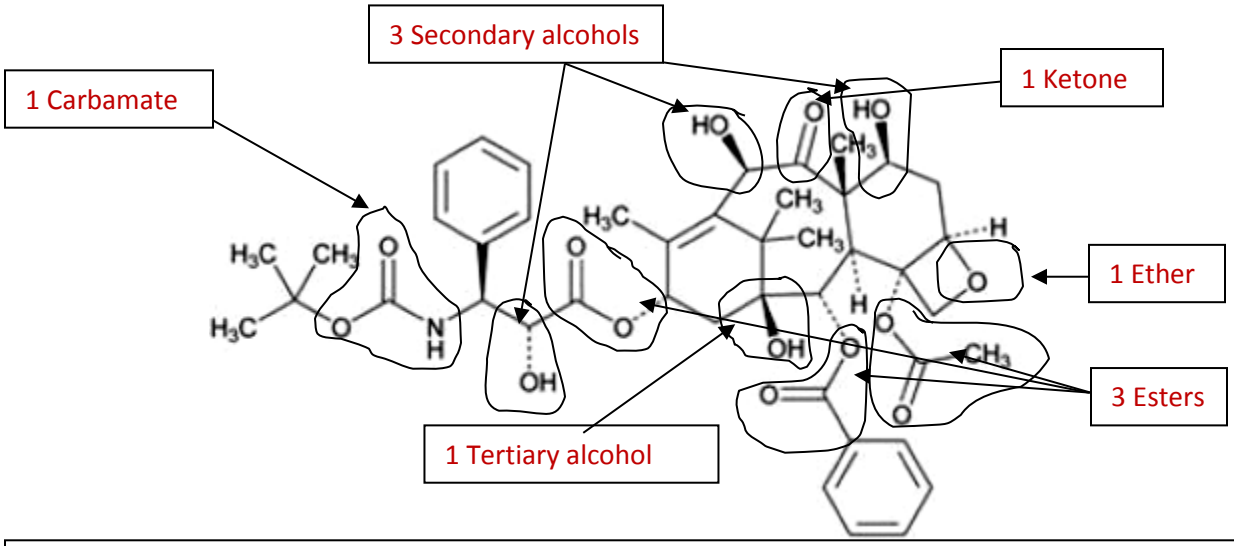
7. Drugs **E**, **G,** and **H** presented in question 1 are formulated and marketed as the salts i)-iii) listed below, respectively. Classify these salts and explain why these drugs might be formulated as salts. **(3 marks; 0.5 marks each for classification; 1.5 marks for your explanation)**

i) **Mefloquine HCl**____inorganic_____ ii) **Crizotinib citrate**_____organic_____
iii) **Pranlukast potassium**_____inorganic_____

Explanation:
There are several reasons why drugs are formulated as salts:
The primary use is for improving water solubility of slightly or poorly soluble drugs molecules in the body.
Additional reasons:
*For improving *in-vitro* chemical stability (salts are less susceptible to hydrolysis and oxidation).
*For improving dissolution rates of oral dosage forms (crystalline, amorphous, polymorphic drug structures - pharmaceutics; P321 & P323).
*For the preparation of parenteral (IV/IM) and opthalmic solutions of slightly or poorly soluble drugs.
*Other uses: increased lipid solubility, increased acid stability, sustained release.

Marking: explanation must include "improving solubility" (0.5 marks), addition of any 2 of the other four areas gets 0.5 marks each)

8. **Docetaxol**, Drug **F** in question 1 above (chemical formula: $C_{43}H_{53}NO_{14}$), is an important therapeutic agent for the treatment of cancer. It is delivered as an IV lipid nanoparticle **(I)** formulation due to poor solubility (0.025 mg/L at physiological conditions). Use the empirical method of intrinsic water solubility to verify or refute this experimental observation. As part of your analysis, use the **Docetaxol** structure provided below to circle and name the functional groups of importance in your solubility estimate. **(5 marks; 3 marks for functional group identification; 1 mark for total of carbons solubilized ; 1 mark for solubility prediction)**



Empirical Solubility:

i) polyfunctional molecule

ii) add up solubilizing power of the polar functional group:

- 1 carbamate = 2 carbons
- 3 secondary alcohols = 3 X 4 carbons = 12 carbons
- 1 tertiary alcohol = 4 carbons
- 3 esters = 3 X 3 carbons = 9 carbons
- 1 ketone = 2 carbons
- 1 ether = 2 carbons

Total = **31 carbons**

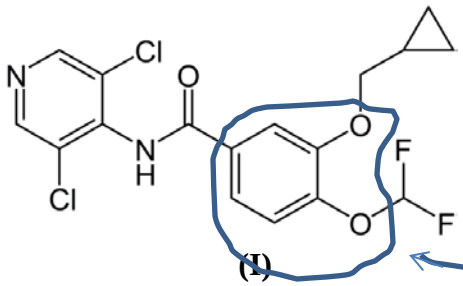
iii) the polar functional group on Docetaxol will solubilize 31 carbons, the drug contains 43 Cs, therefore we would estimate this drug to be insoluble verifying the experimental result.

Marking: 3 marks for correctly circling and naming polar functional groups (**0.5 marks** only for partial identification); **1 mark** for correct total of carbons solubilised (**0.5 marks** for partial/incorrect answer); **1 mark** for final prediction (no part marks here).

9. Asthma and chronic obstructive pulmonary disease (COPD) are two of the most common diseases worldwide. While inhaled broncodilators and glucocorticosteroids form the mainstay of therapy for these diseases, many patients have problems using inhaler devices and would prefer oral therapies. Newer systemic treatments for these diseases have targeted the phosphodiesterase type 4 (PDE4) family of enzymes, the major cyclic adenosine monophosphate (cAMP) metabolizing enzymes responsible for the pulmonary inflammation associated with asthma and COPD. **Roflumilast (I)**, is a targeted, oral, once-daily PDE4 inhibitor that has recently received Health Canada approval as an anti-inflammatory treatment for COPD. Questions a) to j) below explore the story of **Roflumilast**. **(17.5 marks in total)**

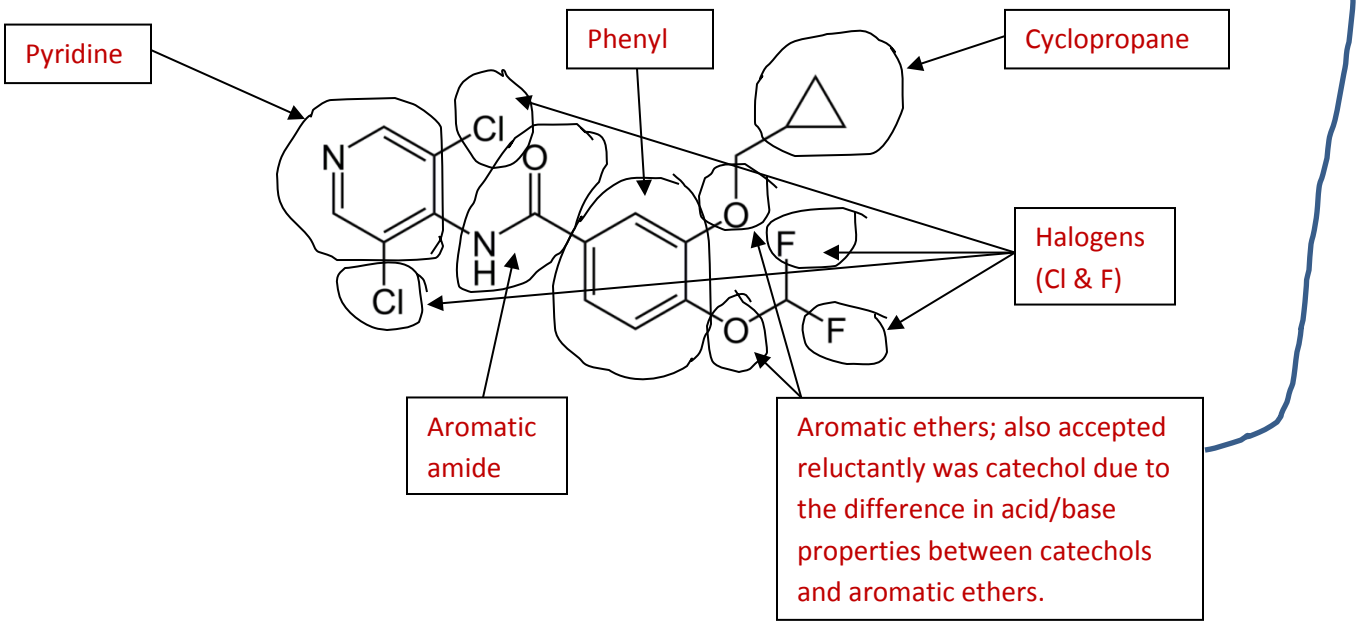
Roflumilast Physicochemical Properties

Chemical Formula	$C_{17}H_{14}Cl_2F_2N_2O_3$
Molar Mass	403.2 g/mol
Water Solubility	0.56 mg/L
LogP	3.99
pKa	5.26



(I)

a) The structure of **Roflumilast** has been provided below. Use it to clearly describe the structure of this drug molecule. **(2 marks)**



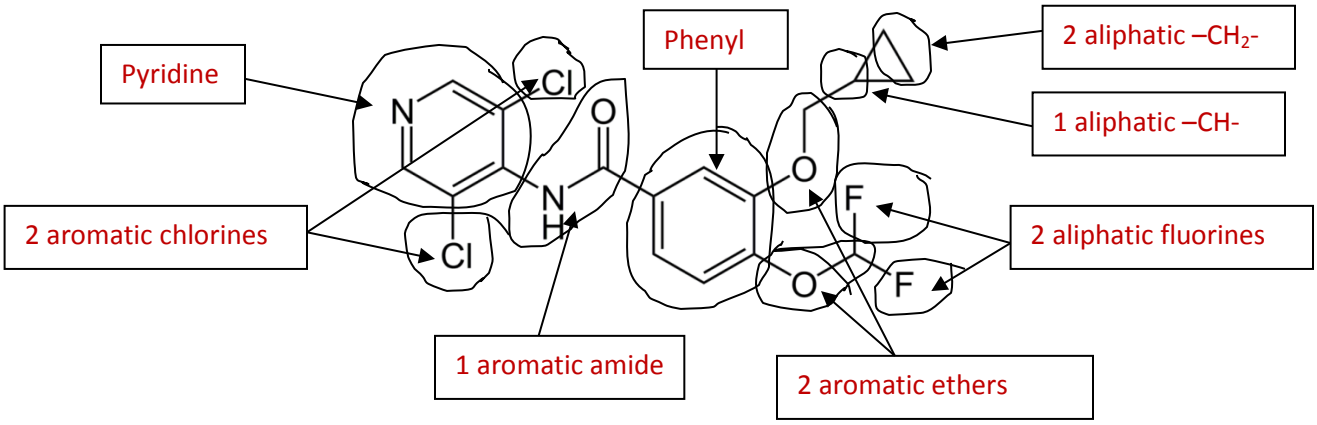
Marking: naming the six groups gets 2 marks; partial naming receives 0.5 marks only.

b) Does the pKa cited in the table above for **Roflumilast** make sense? Explain your answer. **(2 marks)**

Yes the pKa cited in the table above (pKa = 5.26) does make sense for Roflumilast. **(1 mark)**

Explanation: according to the pKa table for basic functional groups pyridine, the basic functional group in Roflumilast, should have a pKa of 4-5. The pKa cited is close to this range. **(1 mark)**

c) According to the table of physicochemical properties shown above, **Roflumilast** is "practically insoluble" in water. Use both the empirical and analytical method of intrinsic water solubility to verify or refute this experimental observation. Use your understanding of the functional groups in **Roflumilast** to decide how to treat those functional groups or molecular fragments that do not appear on the solubility charts. Assume the hydrophobic substituent constant for pyridine is 1.43. Use the structures below to clearly show your work. **(3 marks; 1.5 marks for each solubility method)**



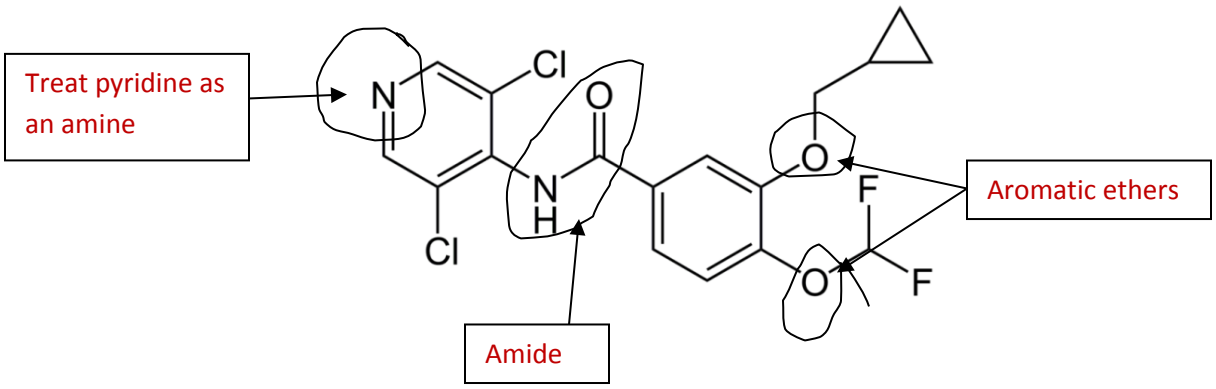
Analytical Solubility:

- 1 pyridine = 1.43
- 2 aromatic -Cl = 2 x 0.76 = 1.52
- -1 aromatic amide = -1.49
- 1 phenyl= 2.13
- 2 aromatic ethers $-OCH_3$ = (2X-0.02) = -0.04
- 2 aliphatic -F = 2 x -0.17 = -0.34
- 2 aliphatic $-CH_2-$ = (2 X 0.50) = 1.00
- 1 aliphatic –CH- = (1 X 0.30) = 0.30

$\log P_{calc}$ = 4.48

Since $\log P_{calc}$ >0.5 we would expect this drug to be insoluble verifying the experimental result.

Marking: make sure that all atoms in the drug have been accounted for. Students may fragment this drug in different ways so the final $\log P_{calc}$ value may vary. This should not change the overall prediction **[1 mark** for clearly showing fragmentation pattern and **0.5 marks** for the process of calculating $\log P_{calc}$ (no marks are given for the $\log P_{calc}$ value)**; 0.5 marks** for solubility prediction based on work-up of molecule**).**



Empirical Solubility:
i) polyfunctional molecule
ii) add up solubilizing power of the polar functional group:
- 1 amine = 3 carbons
- 1 amide = 3 carbons
- 2 ethers = 2 X 2 carbons = 4 carbons

Total = **10 carbons**

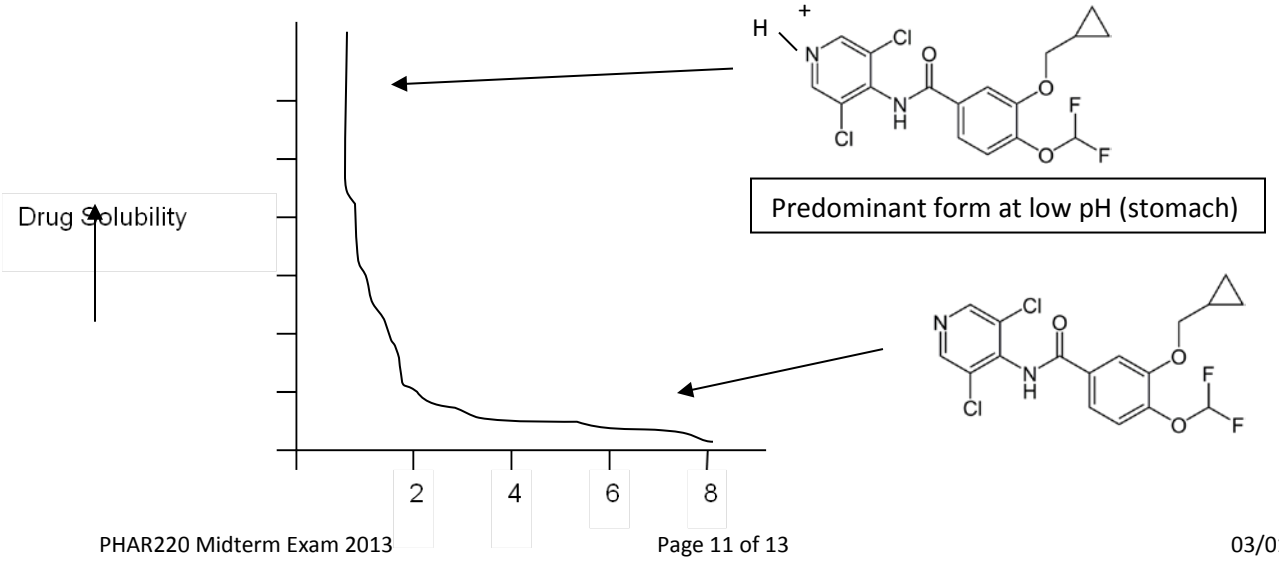
iii) the polar functional group on **Roflumilast** will solubilize 10 carbons, the drug contains 17 Cs, therefore we would estimate this drug to be insoluble verifying the experimental result.

Marking: 1 mark for correctly circling and naming polar functional groups; **0.5 marks** for correct total of carbons solubilised; **0.5 marks** for final prediction **(no part marks for this question)**.

d) Pharmacokinetic studies of **Roflumilast** indicate that it is soluble in the stomach but becomes increasingly insoluble in the small intestine and colon. Complete the table by including the % of ionized and unionized drug in column 3 and a brief comment about the solubility characteristics of the predominant form of the drug in each body compartment in column 4. **(3marks; 0.5 marks for each correct table entry; no part marks)**

Body Compartment	pH	pH-pKa Ionization Estimate	Solubility of Predominant Form
Stomach	1.5	1.5 - 5.26 = -3.76 >99.9% ionized	Roflumilast should be completely soluble in the stomach based on the solubilising power of putting 1 charge on a molecule
Small Intestine	6.4	6.4 - 5.26 = 1.14 < 9% ionized; ~91% of the drug is unionized	Roflumilast should be insoluble since most of the drug will be unionized
Colon	7.8	7.8 - 5.26 = 2.54 < 1% ionized; ~99% of the drug is unionized	Roflumilast should be insoluble since most of the drug will be unionized

e) Use your analysis in d) above and the axes provided below to draw a line or curve to represent the solubility profile of **Roflumilast** throughout the GIT. Draw the structure of the predominant form of the drug at the pH extremes in the GIT. **(2 marks; 1 mark for the graph, 1 mark for your structures)**



Predominant form at high pH (colon)

Note: Since the solubility sca **pH** not specified a range of graphs were accepted here that indicated high solubility at low pHs and low solubility at high pHs.

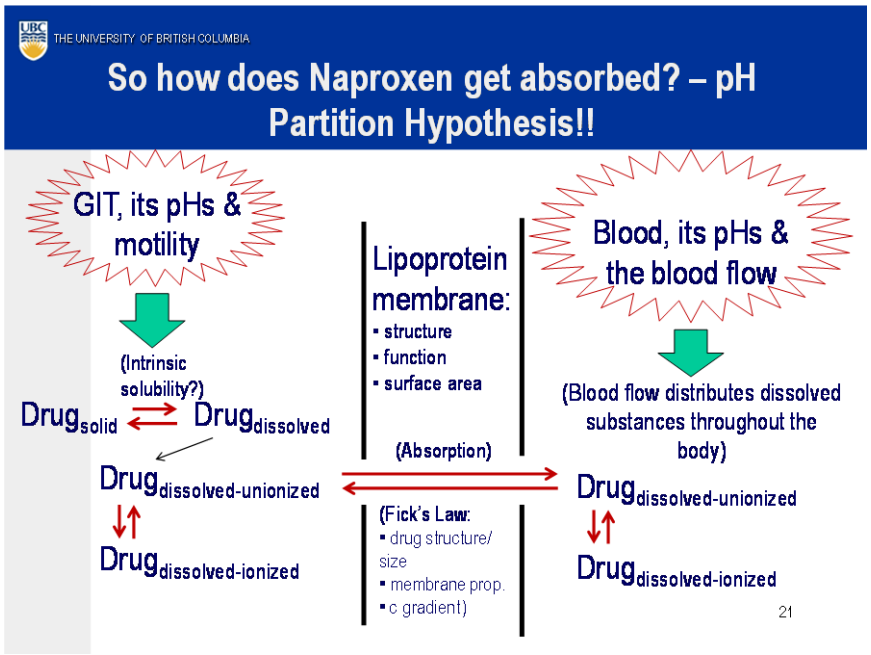
f) Despite the solubility profile explored in f) above, pharmacokinetic studies of **Roflumilast** indicate that it is "very well-absorbed" in the lower GIT. Explain how a drug that is known to be predominantly insoluble in the lower GIT can be well-absorbed. Use a diagram to support your explanation. **(4.5 marks)**

Marking of this question focused on overall understanding of the pH-partition hypothesis theory. While a variation of answers was accepted, particularly important was the interplay between unionized drug, ionized drug, solubility and absorption in the answers. In addition to overall understanding of the theory many explanations made reference to:

pH-partition hypothesis: which states that drug absorption is due to a series of equilibria which are always shifting. As long as there is a small amount of drug solubilised then the rest of the drug will eventually get absorbed by the shifting equilibria. Schematic diagrams that captured elements of the one shown in class (see below) were particularly helpful.

Fick's Law: which among other things says that drugs will passively diffuse through epithelial cells if there is a concentration gradient set up between the inside and outside of the epithelial cell. Fick's Law also indicates the importance of drug structure (P & D in the equation) as well as characteristics of the epithelial cells in the GIT (A & h in the equation).

Possible Diagram:



THE END