Name ANSWER KEY

MEDCHEM 562

First Midterm

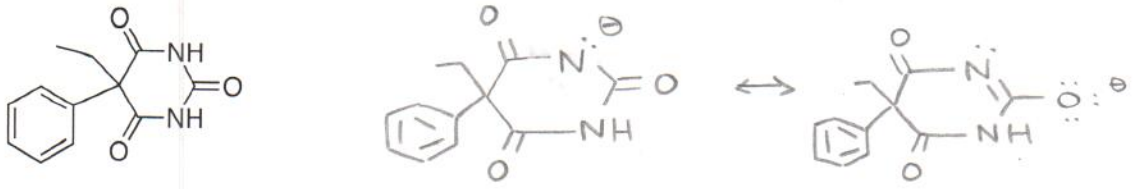
October 22, 2017

Instructions:

- Exam packet totals 9 pages.
- If you need additional space go to the back of that page and tell me you did so.
- Write legibly and in complete sentences when indicated.
- Read the questions carefully and answer the questions you know first.

ADME Question (52 points)

1. (27 points) Phenobarbital is a sedative hypnotic and antiepileptic. It is a weak acid with a pKa of 7.4 (really) and a logP of 1. Approximately 40 percent of the drug is eliminated as a mixture of the para phenol and the corresponding sulphate and glucuronide Phase II metabolites. The other 60% is eliminated via renal clearance of unchanged drug.



a. (5 pts) Above, show <u>one</u> of the reasonance forms of the conjugate base and clearly indicate its charge. (only one needed, just showing two common answers)

wording was confusing for most people

b. (7 pts) Show how you would calculate the **log $D_{5.4}$** (an approximate normal urine pH) for phenobarbital (show work). Approximately what percent of the drug is present in the aqueous phase ~~(octanol/water)~~ as the conjugate base? Compare this estimate to **that found at pH 7.4.**

	HA	A^-
oct	10	— ← no ions in octanol
H_2O	1	0.01

↑ set as 1 first

$\log P = \log \frac{[HA]_{oct}}{[HA]_{H_2O}} = 1$

$10^1 = \frac{[HA]_{oct}}{1} \Rightarrow [HA]_{oct} = 10$

$pH = pKa + \log \frac{[A^-]_{H_2O}}{[HA]_{H_2O}}$

$\log D = \log \frac{[HA]_{oct}}{[A^-]+[HA]_{H_2O}}$

$= \log \frac{10}{1.01}$

$= \boxed{0.996}$

$10^{pH-pKa} = \frac{[A^-]_{H_2O}}{[HA]_{H_2O}}$

$10^{5.4-7.4} = 10^{-2} = \frac{[A^-]_{H_2O}}{1} \Rightarrow [A^-]_{H_2O} = .01$

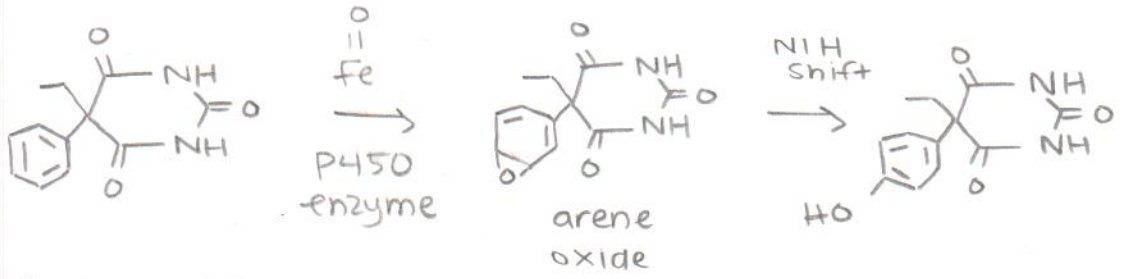
c. (5 pts) The plasma half life of phenobarbital is roughly 120 hours. *In vivo* it has been shown that basification of the urine by oral or iv sodium bicarbonate to a pH of 7.5 to 8 reduces the half-life to approximately 50 hours. Briefly describe how the kidney processes the phenobarbital and explain the mechanism of the pH dependent change in $t_{1/2}$. 1b. continued

Phenobarbital enters the kidney through glomerulus filtration of blood. Basification of the urine from pH 5.4 to 7.5-8 means there will be more of the drug present as the charged conjugate base (seen to the right) which cannot cross the membrane of the kidney tubules to be reabsorbed (only neutral species can). Thus, more drug is excreted and $t_{1/2}$ is shortened.

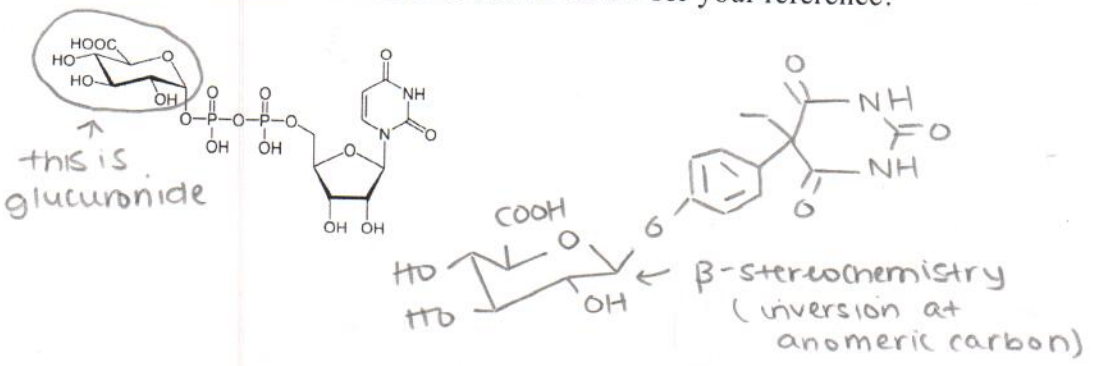
@5.4: % drug in aq phase as A^- = $\frac{.01}{1}$ = $\boxed{1\%}$

@7.4: pKa = pH so $\boxed{50\%}$ of drug in aq. phase is present as A^-

d. (5 pts) What type of enzyme produces the para-phenolic metabolite. Show the metabolite's structure and the structure of the transient intermediate.



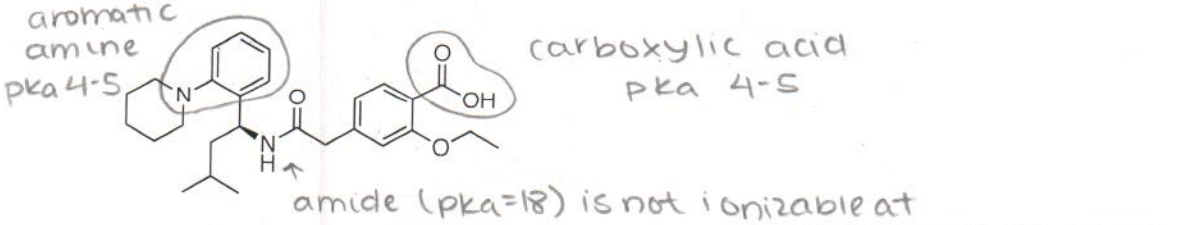
e. (5 pts) Show the structure of the glucuronide metabolite and outline what two properties of a glucuronide conjugate are important in the elimination of drugs and drug metabolites. The structure of co-factor UDGPA is shown below for your reference.



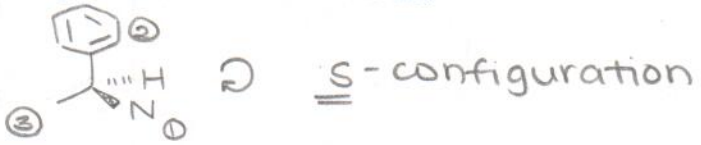
① polar hydroxyl groups

② charged −COOH at physiological pH

2. (15 points) Repaglinide is an oral antidiabetic that promotes insulin release from β-islet cells of the pancreas.



a. (5 pts) What is the configuration at the chiral carbon?



b. (5 pts) Circle the ionizable groups and provide approximate pKa values.

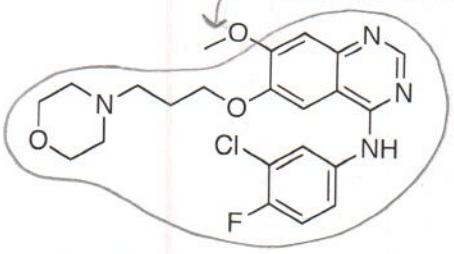
c. (5 pts) The bioavailablity of repaglinide is 60%. Look at your answer to part b and think about the proportion of the molecule that is unionized in the duodenum. Could this molecule move through a membrane without a transporter? Explain your reasoning.

Since the pH of the duodenum is around the pka's of the aromatic amine & carboxylic acid ($pH_{duo} = 5$; $pka_{amine} = 4\text{-}5$; $pka_{carb\ acid} = 4\text{-}5$) there will be ~50% singly charged, ~25% zwitterionic, and ~25% unionized species.

[yes] even if there is only a small % of neutral drug, it will be enough to passively diffuse & move across the membrane w/o a transporter. (also repaglinide is relatively lipophilic logP = 5)

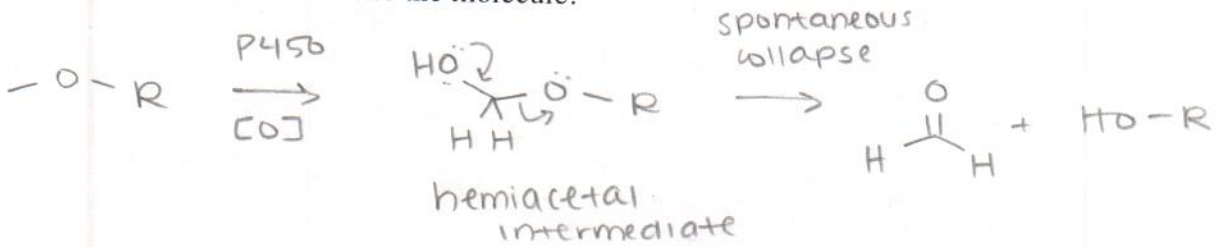
3. (10 points) Gefitinib is an anticancer agent that is metabolized by CYP2D6 via O-demethylation and CYP3A4 by other routes. One of its side effects is rash.

metabolism occurs here



= R

a. (5 pts) Show the structure of the O-demethylated metabolite and the transient intermediate in O-demethylation. Use R for the rest of the molecule.



b. (5 pts) CYP3A4 oxidizes the cloro fluoro phenyl ring to a reactive intermediate that can cause hepatotoxicity. (Mechanism and structure of the reactive intermediate is not important here). Recent research indicates that the incidence of rash in CYP2D6 PMs is significantly lower than for EM's. Tell me what it means to be a CYP2D6 PM and EM. Argue that this finding is consistent with a hypothesis the CYP3A4 metabolism leads to rash.

Since this question was worded poorly, any rationale was given full points.

PM = poor metabolizer, have 2 copies of nonfunctional or defective genes so reduced metabolism

EM = extensive metabolizer, 2 copies of wild-type gene so normal metabolism

① 2D6 rash in PM ↓ 2D6 EM ↑ ② 3A4 met = rash

These two findings are NOT CONSISTENT with one another. We expect 2D6 poor metabolizers to have a higher fraction of drug metabolized by 3A4 (fm) since rerouting metabolism from 2D6 pathway and thus, higher incidence of rash.

Oncology questions (2017): 48 points; 3 points per question

1. (3) Chemotherapy is a major type of therapy for treating cancer patients. As discussed in class, the other major types of therapy for cancer patients are:

A. Surgery
B. Radiation
C. Bone marrow or stem cell transplantation
D. Only A and B
E. A, B, and C

2. (3) Premedications are often given with chemotherapy drugs. As discussed in class, what is a major reason(s) for giving patients premedications?

A. Prevention of allergic reactions
B. Prevention of nausea and vomiting
C. Enhancement of the effect of the other cancer drugs
D. A and B
E. B and C

3. (3) The Philadelphia chromosome (also called bcr-abl chromosome) was discussed in detail in class. What is true about this chromosome?

A. It's an oncogene.
B. It is formed by chromosomal rearrangement (a translocation) of chromosomes 9 and 22
C. It is important in breast cancer
D. A and B
E. B and C

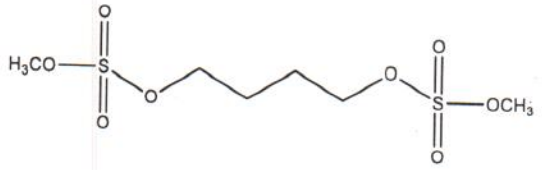
4. (3) Drug resistance is an important issue in the treatment of cancer patients with chemotherapy. As discussed in class, drug resistance arises from:

A. Metastasis
B. Clonal selection
C. Apoptosis
D. A, B, and C

5. (3) Among the different types of blood cells, the following are true about neutrophils:

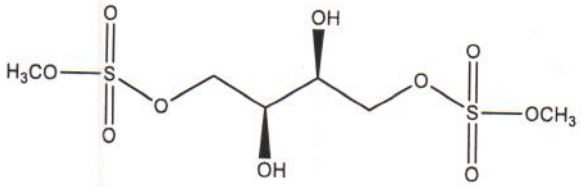
A. They are a subtype of white blood cells
B. They help fight infection
C. They assist with blood clotting
D. They are the most abundant of all blood cells
E. A and B

6. (3) Busulfan (shown below) is an old but useful agent. Which is true about this agent?



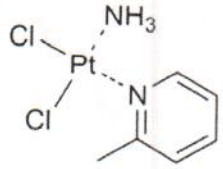
A. It is a bifunctional alkylating agent
B. It is presently used mostly for myeloablation prior to a bone marrow or stem cell transplant
C. It cannot enter the brain
(D.) A and B
E. A, B, and C

7. (3) Below is the structure of Treosulfan which was discussed in class. What is true about this agent?



A. It is a more powerful myelosuppressive agent than busulfan
B. It is more polar than busulfan
C. It appears to cross the blood-brain barrier less than busulfan
D. A and B
(E.) A, B, and C

8. (3) Below is the structure of an anticancer agent that has been evaluated in clinical trials. As discussed in class, what would you expect to be true about this agent?

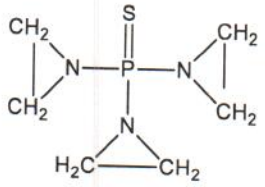


A. It would directly bind to DNA
B. It would likely cause myelosuppression and nephrotoxicity (kidney toxicity)
C. It would certainly not cause ototoxicity (hearing loss) or peripheral neuropathy
(D.) A and B
E. B and C

9. (3) Three platinum agents (cisplatin, carboplatin, and oxaliplatin) were discussed in class. What is true about these agents?

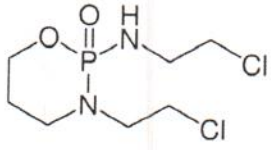
A. All can potentially cause myelosuppression and ototoxicity (hearing loss)
B. All can be diluted with saline
C. Peripheral neuropathy is a major concern for oxaliplatin
D. A and B
E. A and C

10. (3) Thiotepa is shown below and was discussed in class. What is true about this agent?



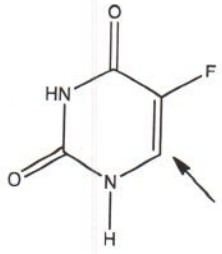
A. It can potentially alkylate DNA three times
B. Its metabolite Tepa is inactive
C. It will not cause myelosuppression
D. A and B
E. A and C

11. (3) Ifosfamide (Ifex), an important anti-cancer drug, is shown below. As discussed in class, what is true about this agent?



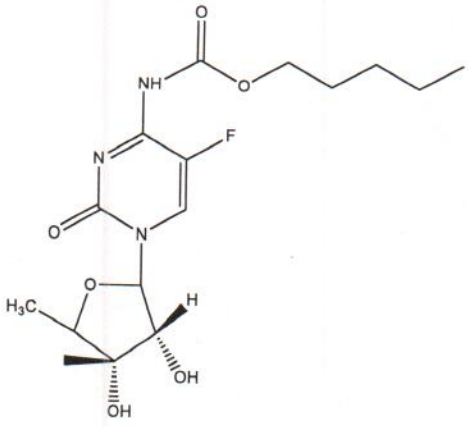
A. It is bioactivated by cytochrome P450
B. It can form an epoxide
C. It can form an azirdine ring
D. A and B
E. A and C

12. (3) 5-Fluorouracil (5-FU) is an old but important oncology agent. As discussed in class, 5-FU inhibits thymidylate synthetase (TS). What else is true about 5FU?



A. It belongs to the class of anticancer drugs called antimetabolites
B. The carbon indicated by the arrow is the carbon that initially reacts with the thiol of TS
C. Before it can inhibit TS, it is ribosylated and phosphorylated
D. A and B
(E.) A, B and C

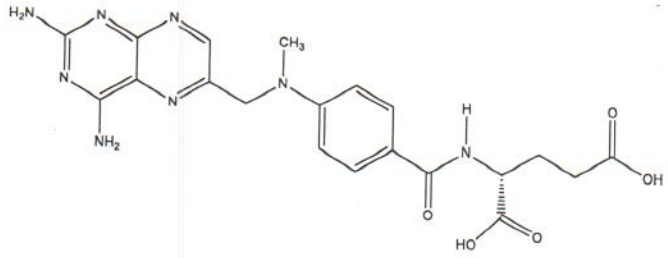
13. (3) Capecitabine (shown below) s a very useful anticancer agent. What is true about capecitabine?



Capecitabine

A. It is a prodrug of 5-fluorouracil (5-FU)
B. It must be administered IV like 5-FU
C. It can cause hand-foot syndrome
D. A and B
(E.) A and C

14. (3) Methotrexate (MTX) is shown below and is an important oncology agent. What is true about MTX?

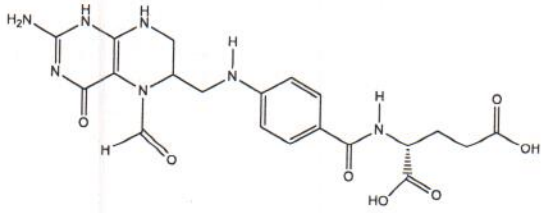


A. It is a mimic of uracil
B. It is a mimic of folate (or folic acid)
C. It is polyglutamated after it enters cells
D. A and C
E. B and C

15. (3) As discussed in class, methotrexate (MTX) directly inhibits this enzyme:

A. Dihydrofolate reductase
B. Thymidylate synthetase
C. Ribonucleotide reductase
D. Dihydropyrimidine dehydrogenase
E. DNA polymerase

16. (3) Leucovorin is shown below. As discussed in class, what is true about Leucovorin?



A. It is often combined with 5-FU to achieve greater killing of cancer cells
B. Like methotrexate, it can inhibit dihydrofolate reductase (or folate reductase)
C. It is used after intentional or accidental overdose of methotrexate
D. A and B
E. A and C