Medicinal Chemistry 562

Midterm Examination

November 21, 2016

NAME: Key

Questions 1-15 are multiple choice (3 points each); Select the best answer to each question.
Questions 16-20 are True/False (1 point each); Select A for True and B for False.

1. As discussed in class, clinical trials are important for the development of new drugs. Which are true about clinical trials?

A. They occur in three Phases (Phase 1, Phase 2, and then Phase 3).
B. They are the only mechanism that exists for obtaining accurate and statistically significant information about the safety and efficacy of new drugs.
C. Historically, both women and men have been good enrollers into trials.
D. A and B.
E. A and C.

2. Premedications are often given prior to dosing with cancer chemotherapy drugs. As discussed in class, what types of premedications are commonly used?

A. Antihistamines
B. Corticosteroids
C. Antiemetics
D. A and B.
E. A, B and C.

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

A. It's a tumor suppressor.
B. It is formed by chromosomal rearrangement (a translocation) of chromosomes 9 and 22.
C. It is important in a type of cancer called chronic myelogenous leukemia (CML).
D. A and B.
E. B and C.

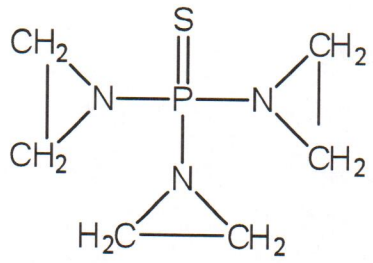
4. As discussed in class, which are true about erythrocytes (RBCs)?

A. They are responsible for transport of oxygen to cells.
B. They live the longest of all blood cells.
C. They never are a concern when giving cancer chemotherapy.
D. A, B, and C.
E. A and B.

5. Alkylating agents are an older class of anticancer drugs. As discussed in class, which of the following are true about them?

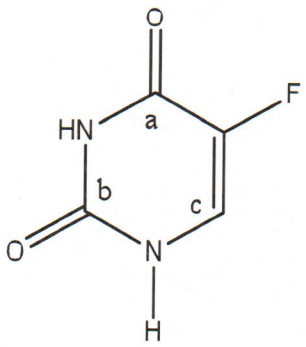
A. They directly react and bind covalently to DNA.
B. They can cause new cancers to form years later.
C. They are not used anymore because better drugs exist.
D. A and B.
E. A, B and C.

6. Thiotepa which is shown below, is an older anticancer drug. Which of the following are true about thiotepa?



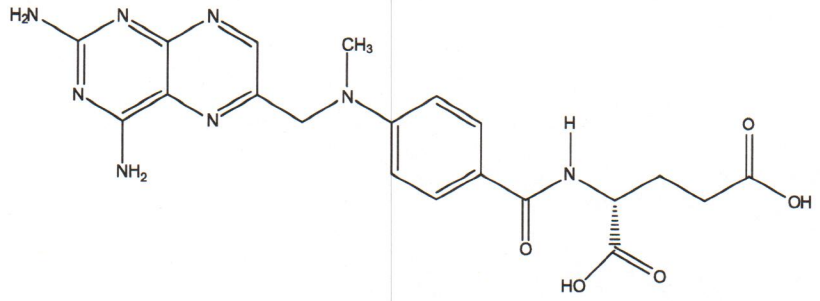
A. It 's a prodrug.
B. It's converted to a diazonium ion.
C. It can be used in bladder cancer by direct instillation into the bladder.
D. A, B, and C.
E. B and C.

7. Shown below is the structure of 5-fluorouracil (5-FU). Which of the following are true about 5-FU?



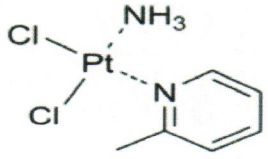
A. The carbon that becomes attached to the enzyme through a thiol (-SH) is labeled with letter c.
B. 5-FU inhibits the enzyme dihydrofolate reducatase (DHFR).
C. A prodrug form of 5-FU exists and is called fludarabine.
D. A, B, and C.
E. A and C.

8. Shown below is the structure of methotrexate (MTX). Which of the following are true about MTX?



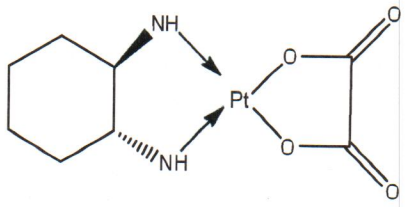
A. The drug mimics folate (or folic acid).
B. The drug inhibits both dihydrofolate reductase (DHFR) and thymidylate synthetase (TS).
C. The drug can be administered IV and PO.
D. A, B, and C.
E. A and C.

9. Below is the structure of a potential anticancer agent that was evaluated in clinical trials but was never actually approved. As discussed in class, what would you expect to be true about this agent?



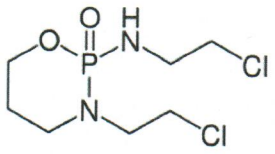
A. It would likely cause myelosuppression.
B. It would likely not cause nephrotoxicity (kidney toxicity).
C. It could be dissolved in saline or D5W.
D. A and B.
E. B and C.

10. Oxaliplatin (Eloxatin) is an important anticancer agent. As discussed in class, which of the following are true about this agent?



A. It is useful in the treatment of colorectal cancer, especially as part of the FOLFOX regimen.
B. It's main toxicity of concern is peripheral neuropathy.
C. It can be dissolved in saline or D5W.
D. A, B, and C.
E. A and B.

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



A. It's not a prodrug.
B. It is a specific enzyme inhibitor.
C. It can be activated to form an aziridine (aziridinium) ring.
D. A and B.
E. A and C.

12. As discussed in class, polypmorphic metabolism is associated with which enzyme(s)?

A. Thymidylate synthetase (TS)
B. Ribonucleotide reductase (RR)
C. Dihydropyrmidine dehydrogenase (DPD)
D. UDP glucuronosyltransferase 1A1 (UGT1A1)
E. C and D.

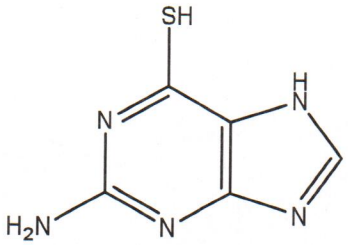
13. Topotecan (Hycamtin) is an approved oncology agent. Which are true about this agent?

A. It inhibits the enzyme topoisomerase 1 (Topo 1).
B. It's a prodrug.
C. It is extensively metabolized by UGT1A1.
D. A and B.
E. A and C.

14. Polymorphic metabolism is an important aspect of the metabolism of Irinotecan (Camptosar). As discussed in class, what enzyme is involved in this polymorphism?

A. Thiopurine methyltransferase (TPMT)
B. Thymidylate synthetase (TS)
C. Uridine glucuronyltransferase (UGT1A1)
D. Dihydropyrmidine dehydrogenase (DPD)
E. C and D.

15. Thioguanine is shown below and is still a useful agent for the treatment of childhood leukemia. What is true about this agent?



A. It's a pyrimidine type of antimetabolite.
B. It's a mimic of hypoxanthine.
C. It 's clearance is mediated by thiopurine methyl transferanse (TPMT) and xanthine oxidase (XO).
D. B and C
E. A and B.

The following are True or False.

16. The package insert is the most reliable source of information for any approved drug.
A. True
B. False

17. Metastatic lesions rarely are the cause of death in cancer patients.
A. True
B. False

18. Busulfan is principally used as a myeloablative agent priot to BMT or SCT.
A. True
B. False

19. T cells are an important type of cells among the white blood cell group that are important for immunological control or elimination of cancer cells.

A. True

B. False

20. The use of biomarkers and surrogate markers are not of any use in the development and use of anticancer agents.

A. True

B. False

2016-Rettie Questions – 50 points

Questions 21- 35 are multiple choice, 2 points per question – use Scantron.
Questions 36 and 37 are short answer.

21. Which of the following is True about the fat-soluble vitamins?
i) a deficiency state is rapidly brought on by poor diet
ii) some can accumulate to toxic levels in the body
iii) they are absorbed via the lymphatic system
Answer **A** if (i) and (ii) are correct
Answer **B** if (i) and (iii) are correct
Answer **C** if (ii) and (iii) are correct
Answer **D** if all are correct

22. Of the four fat-soluble vitamins, how many require some type of interaction with retinoid receptors for their in vivo activity?
i) 1
ii) 2
iii) 3
iv) 4
Answer **A** if (i) is correct
Answer **B** if (ii) is correct
Answer **C** if (iii) is correct
Answer **D** if (iv) is correct

23. Vitamin A deficiency is associated with which of the following symptoms?
i) Xerophthalmia
ii) Measles
iii) Birth defects
Answer **A** if (i) and (ii) are correct
Answer **B** if (i) and (iii) are correct
Answer **C** if (ii) and (iii) are correct
Answer **D** if all are correct

24. Which of the following is/are True;
i) all carotenoids are carotenes
ii) no carotenes contain oxygen
iii) all carotenes have vitamin A activity
Answer **A** if only (i) is correct
Answer **B** if only (ii) is correct
Answer **C** if only (iii) is correct
Answer **D** if none are correct

25. The second isomerization step in the visual cycle generates;
i) all-*trans*-retinal
ii) all-*trans*-retinol
iii) 11-*cis*-retinol
Answer **A** if only (i) is correct
Answer **B** if only (ii) is correct
Answer **C** if only (iii) is correct
Answer **D** if none are correct

26. Vitamin D3 is;
i) derived from ergosterol
ii) has a longer half-life than vitamin D2
iii) circulates in plasma usually at concentrations > 20ng/ml
Answer **A** if (i) and (ii) are correct
Answer **B** if (i) and (iii) are correct
Answer **C** if (ii) and (iii) are correct
Answer **D** if all are correct

27. CYP27B1 carries out the following reaction on the vitamin D nucleus:
i) 27-hydroxylation
ii) 25-hydroxylation
iii) 24-hydroxylation
iv) 1-hydroxylation
Answer **A** if only (i) is correct
Answer **B** if only (ii) is correct
Answer **C** if only (iii) is correct
Answer **D** if only (iv) is correct

28. Parathyroid hormone secretion:
i) increases 25-hydroxylation of vitamin D in the kidney
ii) decreases CYP2R1 in the liver
iii) increases calcium reabsorption in the kidney
Answer **A** if only (i) and (ii) are correct
Answer **B** if only ii) is correct
Answer **C** if only (iii) is correct
Answer **D** if none are correct

29. Vitamin K1 is routinely administered to infants because;
i) breast milk contains only vitamin K2
ii) the gut is sterile at birth
iii) placental transmission of vitamin K is low
Answer **A** if (i) and (ii) are correct
Answer **B** if (i) and (iii) are correct
Answer **C** if (ii) and (iii) are correct
Answer **D** if all are correct

30. Vitamin K's DV and UL are, respectively.
i) 20 mg and 1000mg
ii) 20 mg and no UL
iii) 80 ug and 1000 ug
iv) 80 ug and no UL
Answer **A** if only (i) is correct
Answer **B** if only (ii) is correct
Answer **C** if only (iii) is correct
Answer **D** if only (iv) is correct

31. Which of the following is FALSE about vitamin E?
i) α– β– γ– and δ–tocopherols have equivalent antioxidant potencies
ii) The naphthoquinone ring is critical for antioxidant activity
iii) Tocopherols have 4 chiral centers
Answer **A** if (i) and (ii) are false
Answer **B** if (i) and (iii) are false
Answer **C** if (ii) and (iii) are false
Answer **D** if all are false

32. For vitamin E,
i) bleeding can be an adverse effect
ii) deficiency causes sterility problems in humans.
iii) αTTP selectively transfers 2(R)-tocopherols into VLDL
Answer **A** if (i) and (ii) are correct
Answer **B** if (i) and (iii) are correct
Answer **C** (ii) and (iii) are correct
Answer **D** if all are correct

33. Oxygen is reduced to water in four one-electron steps that involve formation of several ROS (reactive oxygen species according to the scheme below.

$O_2 \rightarrow X \rightarrow Y \rightarrow Z \rightarrow H_2O$

Glutathione peroxidase can scavenge:

i) X

ii) Y

iii) Z

Answer **A** if (i) is correct

Answer **B** if (ii) is correct

Answer **C** if (iii) is correct

Answer **D** if none are correct

34. Superoxide dismutase contains:

i) Copper

ii) Zinc

iii) Manganese

(iv) Iron

Answer **A** if (i) is correct only

Answer **B** if (i) and (ii) are correct only

Answer **C** if (i) (ii) and (iii) are correct

Answer **D** if all are correct

35. Which of the following statements is TRUE about superoxide dismutase?

i) It is the most efficient enzyme in the body

ii) It generates ROS

iii) It is found in mitochondria

Answer **A** if only (i) is correct

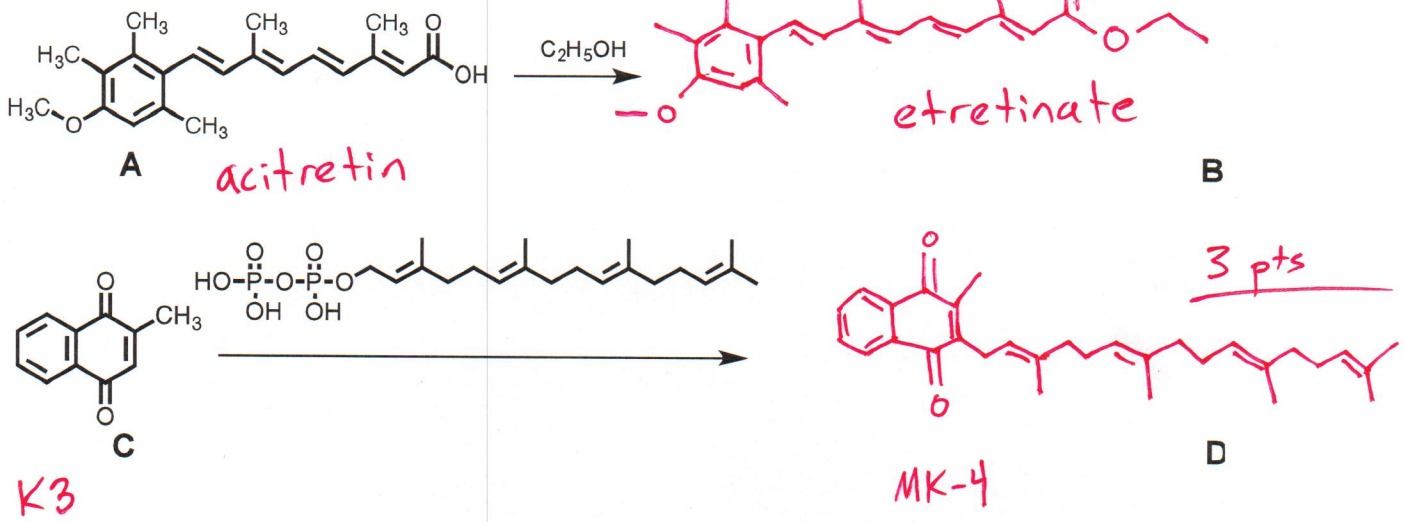
Answer **B** if only (i) and (ii) are correct

Answer **C** if (i) (ii) and (iii) are correct

~~Answer **D** if all are correct~~

36. (9 pts)

a) Draw the products, B and D that are formed in the following reactions from acitretin (A) and menadione(C). [no mechanisms required]. (5)



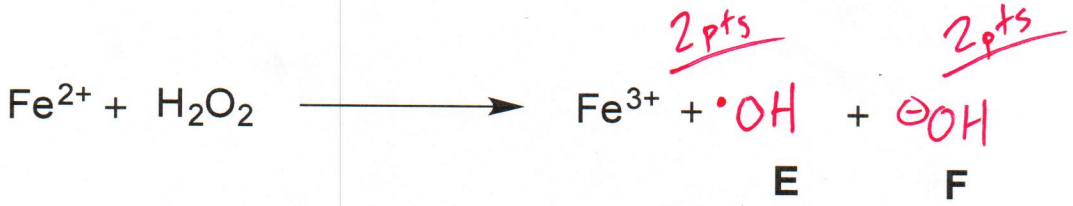
b) Explain how the pharmacological or toxicological effects of B and D differ from the A and C, respectively. (4)

2pts • etretinate has a much longer half-life than acitretin, increased risk of teratogenicity

2pts • MK-4 has Vitamin K activity and K3 does not

37. (11 pts)

a) The reaction below involving ferrous iron is called the Fenton reaction, which generates ferric iron and two other products, E and F. Identify E and F. (4)



b) Explain why the retinol activity of 1 ug of all-trans retinol = 2ug of trans β-carotene in oil = 12 ug food-based all-trans β-carotene. (4)

2 pts
- β-carotene in oil is less active than retinol because BCMO is an inefficient enzyme

2 pts
- β-carotene in food is less active than β-carotene in oil because it is poorly absorbed

c) Identify the enzyme that warfarin inhibits to reduce the formation of clotting factors (1)

1 pt VKOR

d) Circle the important structural elements in warfarin that cause it to be an effective vitamin K antagonist. The structure of warfarin and vitamin K1 are shown below. (2)