

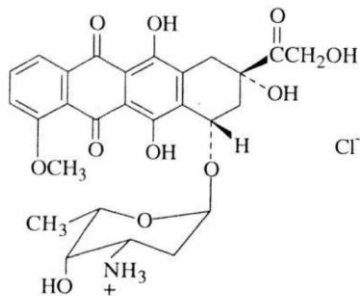
1. Both methotrexate (MTX) and 5-fluorouracil (5-FU) are important anti cancer agents.
 - a. To what specific class or type of anti-cancer agent does MTX belong?
Antimetabolites, specifically: Folate analog
 - b. To what specific class or type of anti-cancer agent does 5-FU belong?
Antimetabolites: Pyrimidine analogs
 - c. Both of the drugs can inhibit thymidylate synthetase (TS). The inhibition of TS by 5-FU is direct. Explain this mechanism.

5-FU inhibits thymidylate synthetase by binding to it and then because of the H → F substitution, is unable to be released, permanently inactivating the enzyme.

- d. The inhibition of TS by MTX is indirect. Explain this mechanism

MTX inhibits DHFR, which is responsible for converting Folate to DHF, which then goes through to make Methenyl tetrahydrofolate. If Methenyl tetrahydrofolate is not available, there is no available carbon donor for thymidylate synthetase.

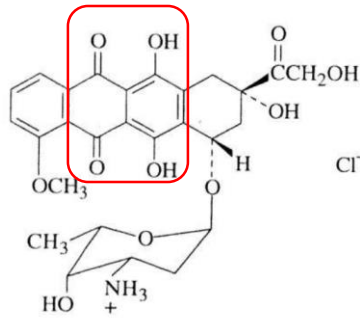
2. The structure below is a member of an important class of anticancer agent.



- a. To what specific class or type of anti-cancer agent does this drug belong?
Topoisomerase Inhibitors (Topo II specifically)
- b. What is its mechanism(s) of anti-cancer activity?
DNA intercalation mostly, but also reactive oxygen species play a role.
- c. Use of the agent is associated with an important toxicity that limits its use. Name this toxicity.

Cardiotoxicity due to generation of reactive oxygen species

- d. Circle the atoms in the molecule that lead to this important toxicity.



- e. Name the drug that can be used to reduce this toxicity

Dexrazoxane can be used to minimize cardiotoxicity

3. A hypothetical new drug called "Onconib" was just approved by the FDA.

- a. To what specific class or type of anti-cancer agent does this drug belong?

Kinase inhibitors

- b. If this drug is useful for Ph⁺ tumors, would this drug likely be useful for liquid tumors or solid tumors?

Most likely Liquid

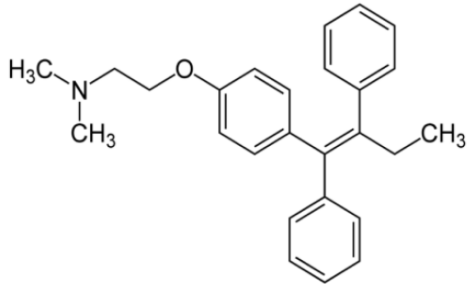
- c. QT prolongation is generally not a common problem with this class or type of cancer drug: True or False?

False

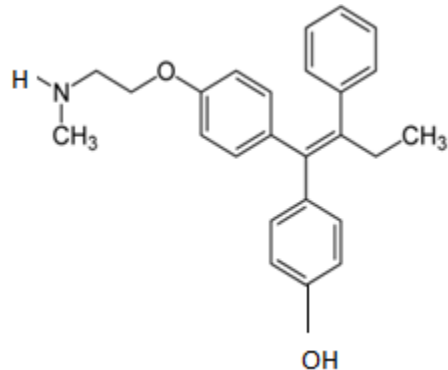
- d. Cytochrome P-450 enzymes (CYP450) generally participate in the metabolism of this class or type of cancer drug. True or False?

True

4. Tamoxifen (Tam) is an older anti-cancer agent and is shown below.



- a. To what specific class or type of anti-cancer agent does this drug belong?
Hormonal Agents - antiestrogens
- b. Tamoxifen is metabolized to a very active metabolite. What is the name of this metabolite?
4-Hydroxy-N-desmethyltamoxifen (endoxifen)
- c. Show the structure of this active metabolite by modifying the structure above. (Hint: There are structural changes involved.)



- d. Which two cytochrome P-450 enzymes participate in the metabolism of Tamoxifen?

CYP2D6 and CYP3A4(or)CYP3A5

- e. Does polymorphic metabolism play a role in the metabolism of Tamoxifen. Yes or no?

Yes