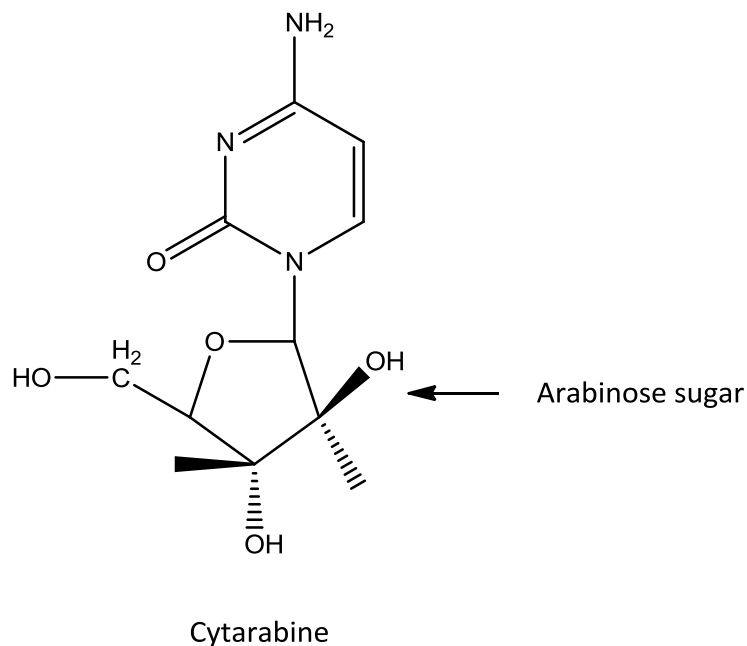


Cancer agents - Problem set #2 (solutions)

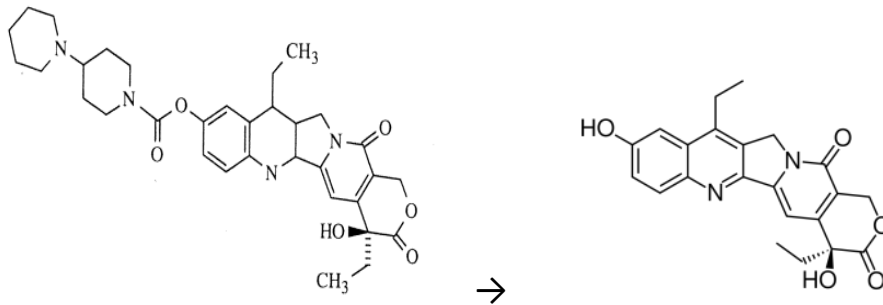
Problem set #2 solutions:

1. MTX is an antimetabolite and specifically an anti-folate type drug. It specifically inhibits the enzyme dihydrofolate reductase (DHFR). Leucovorin can be given as an antidote. MTX is trapped within cells by formation of polyglutamate metabolites.

2. AraC is an antimetabolite and specifically a pyrimidine analog. Its MOA arises from the fact that the sugar moiety is different than the natural form. It is an arabinose sugar instead of a ribose sugar. This interferes with DNA polymerase. AraC can be used for various leukemias including CML, ALL and even meningeal leukemia. It can be administered intrathecally for the latter.



3. The name of the agent is Irinotecan (camptosar). The active metabolite is SN-38 and is shown below at right.



SN-38 is glucuronidated by UGT1A1. This enzyme is expressed polymorphically and some patients have low levels of enzyme. In these people, the AUC can be much higher for a given dose of irinotecan. The higher AUC can lead to greater toxicities in these patients. The homozygous genetic trait is called UGT1A1*28 or UGT1A1 (7/7) which leads to low levels of glucuronidation.

4. The appropriate circle and squares are drawn below. The pathway that involves a polymorphism is the TPMT pathway.

