MEDCH 562P
Fall 2011
Problem Set #3

I. CARCINOGENESIS

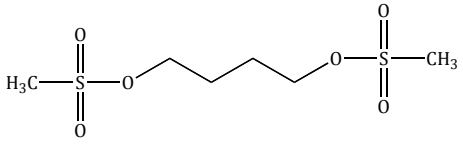
Some observations in sequential cellular changes that occur in small cell lung cancer (SCLC) are losses at chromosomal locations 3p and 6p of genes encoding for a transcription factor and a tumor suppressor protein ($p16^{INK}$). Dysplasia follows and appears to involve p53 mutations and loss of the mismatch repair gene *hMSH3*. Mutations of *k-ras* and *cyclin D*, protooncogenes, as well as in a p73 tumor suppressor gene are associated with tumor invasion.

Based on your knowledge of the carcinogenic process, what would you tell someone who asked you why some non-smokers can be stricken with SCLC while some chronic smokers are not? Make specific reference to each of the factors mentioned above in describing the three stages of the carcinogenic process.

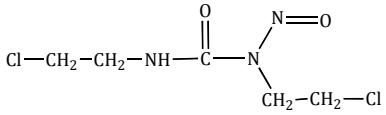
II. ALKYLATION

1. Alkylation is implicated in many carcinogenic reactions and is the underlying principle behind many anticancer agents. Show how the following compounds could alkylate DNA (arrow pushing). Phase I or Phase II metabolism may be required to generate the reactive species.

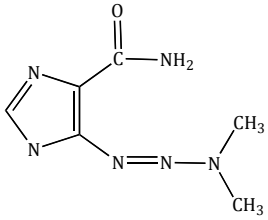
A. Busulfan



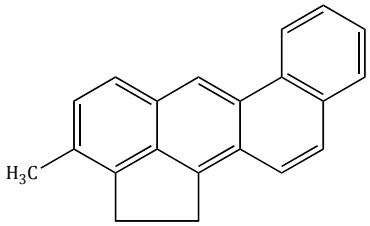
B. Carmustine



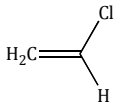
C. Dacarbazine



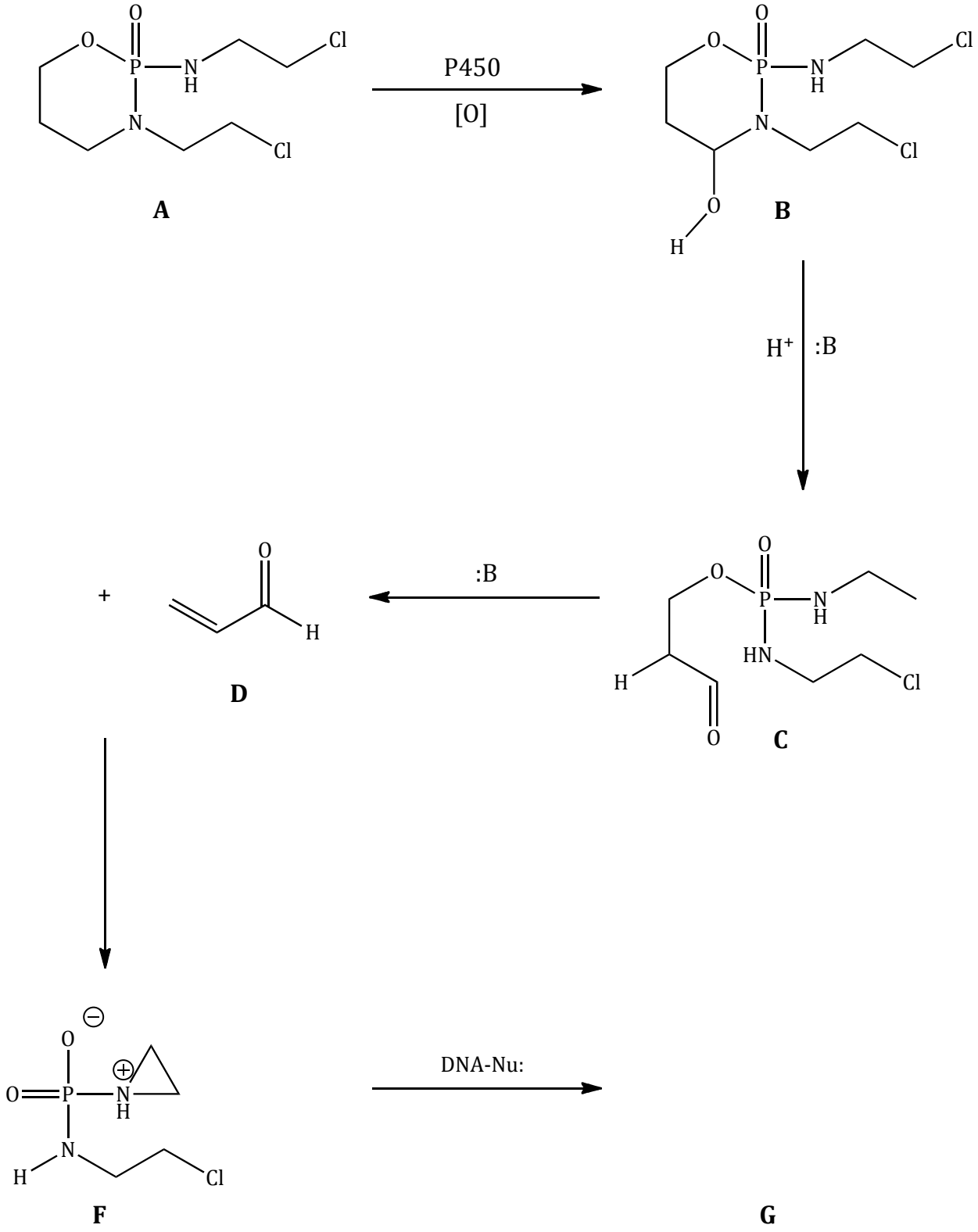
D. 3-Methylcholanthrene (3-MC)



E. Vinyl Chloride



2. Ifex-Mesna is sometimes used in place of Cyclophosphamide. Below is a partial scheme for the conversion of the prodrug Ifosphamide (A) to its active nitrogen mustard alkylating agent.



A. Show (arrow convention) how **B** is converted to **C**.

B. Show the structure of **E**.

C. Show (arrow convention) how **E** forms **F**.

D. Show (arrow convention) how **F** reacts with DNA and give the structure of the alkylated product **G**.

E. Briefly explain how **G** reacts to further damage DNA.

III. THERAPEUTIC REGIMENS

Neuroblastoma is a cancer of embryonic nerve cells, usually in the peritoneal region, and often associated with adrenal glands. It occurs most commonly in young children. One regimen (CODD) consists of Cyclophosphamide (Cytoxan), Oncovin (Vincristine), Dacarbazine (DTIC), and Doxorubicin (Adriamycin). Use the table below to describe each agent with regards to therapeutic class, chemical subclass, cell cycle selectivity, major toxicity and mechanism of action.

	Cyclophosphamide	**Oncovin**	**Dacarbazine**	**Doxorubicin**
Therapeutic Class				
Chemical Subclass				
Cell Cycle				
Major Toxicity				
Mechanism of Action				

Based on your answers above, is this a good regimen? Why or why not?