MEDCH 562P
Fall 2011
Problem Set #3 – ANSWER KEY

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 smokers are not? Make specific reference to each of the factors mentioned above in describing the three stages of the carcinogenic process.

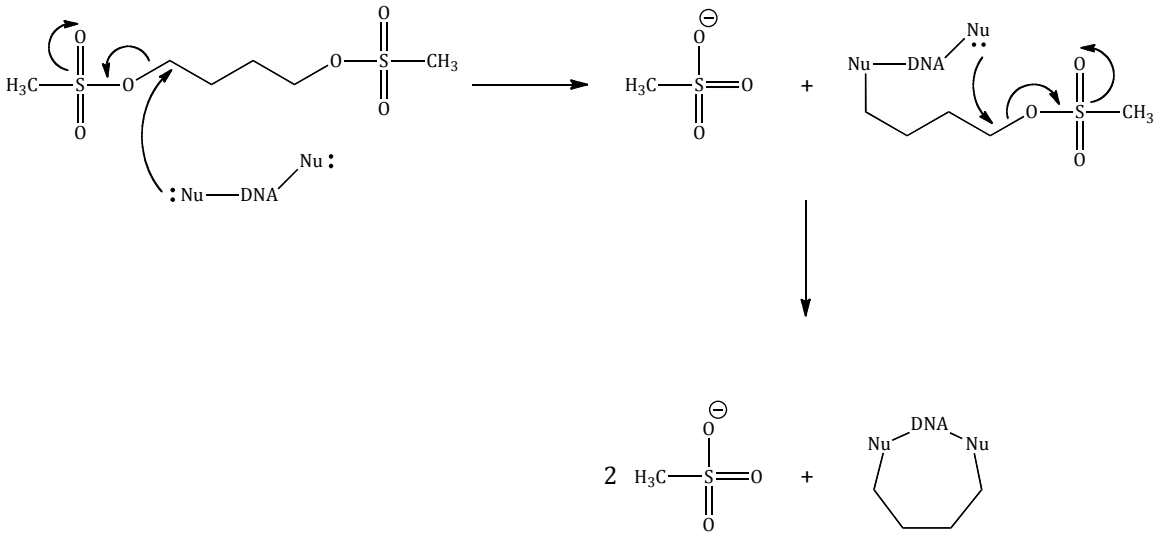
Carcinogenesis is a multi-factorial, multi-step process that usually requires several genetic and epigenetic changes in cells. Initiation can occur via mutations in DNA caused by chemicals (e.g. polycyclic hydrocarbons in tobacco products), viruses, and/or inherited defects, all of which may lead to losses at chromosomal locations such as those at 3p and 6p for genes that encode for a transcription factor and for the tumor suppressor protein $p16^{INK}$. Promotion occurs when an initiated cell is converted to a mutated phenotype with clonal expansion of that mutated phenotype (leading to dysplasia) due to *p53* mutations with loss of the tumor suppressor activity of the p53 protein, plus loss of the mismatch repair gene *hMSH3* as a result of additional mutations that can be caused by continued exposure to polycyclic hydrocarbons in tobacco products, as well as other factors (dietary, radiation, viruses, inherited defects, etc.). Additional mutations in tumor suppressor genes such as *p73*, and mutations in proto-oncogenes such as *k-ras* and *cyclin D*, can lead to their conversion to oncogenes that encode for proteins leading to continued cell growth, loss of cell adhesion, and tumor invasion in the progression of the tumor to a malignant stage that can metastasize. Note that polycyclic hydrocarbons are complete carcinogens that can also be involved in this latter phase of the carcinogenic process, as well as other factors as listed above.

As stated above, carcinogenesis is a multi-factorial, multi-stage process that usually requires several genetic and epigenetic changes in cells. Some chronic smokers may not be stricken with SCLC because they do not have the inherited defects that can allow for initiation, or promotion and progression. Other people who do not smoke, however, may have a genetic predisposition to SCLC (like losses at chromosomal locations 3p and 6p), whereby initiation is triggered by environmental factors such as second hand smoke.

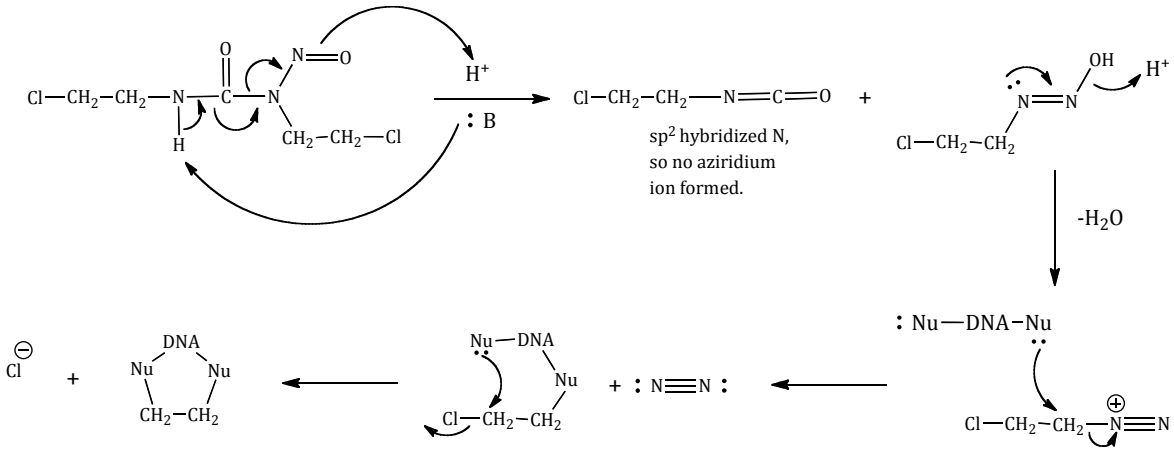
II. ALKYLATION

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.

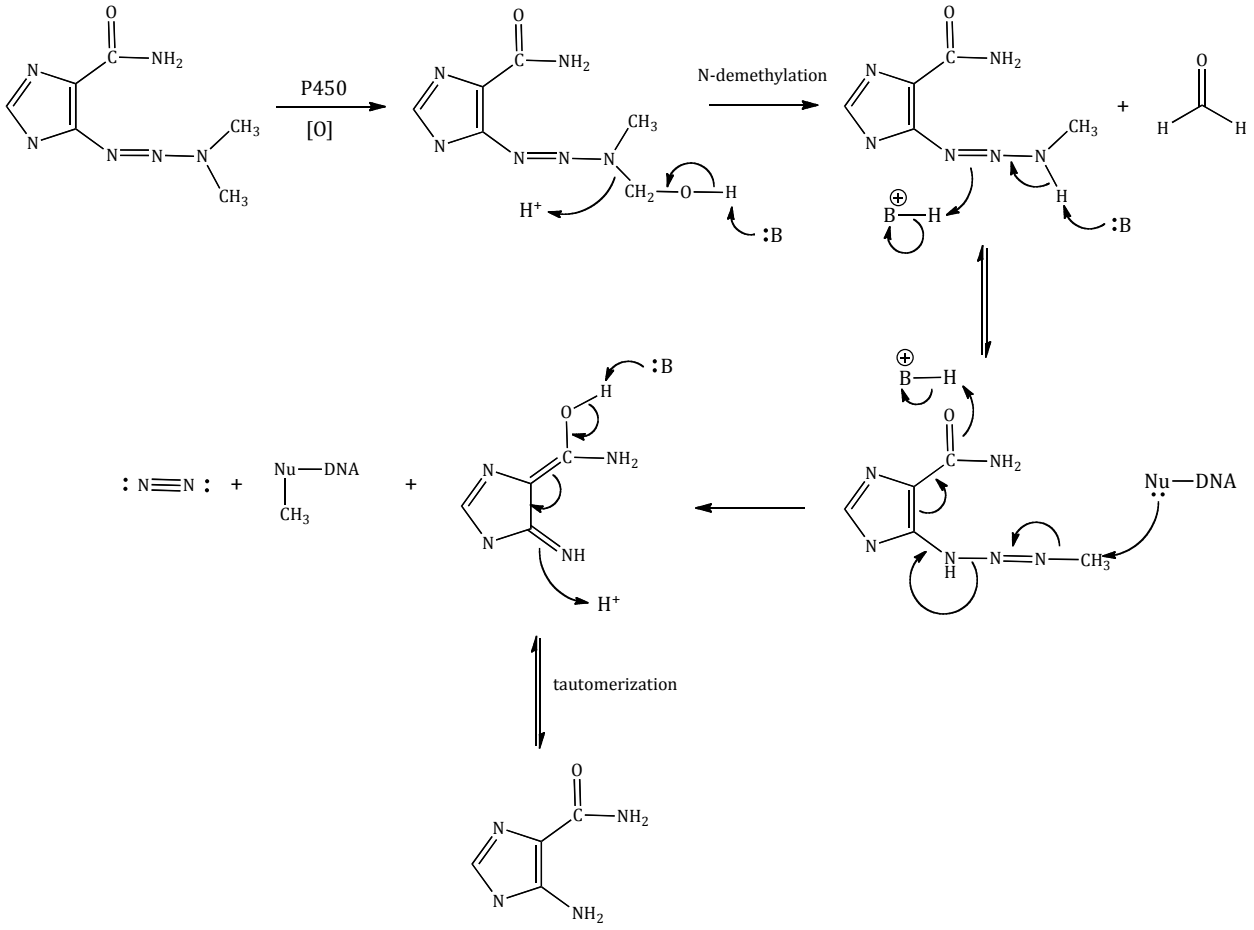
A. Busulfan



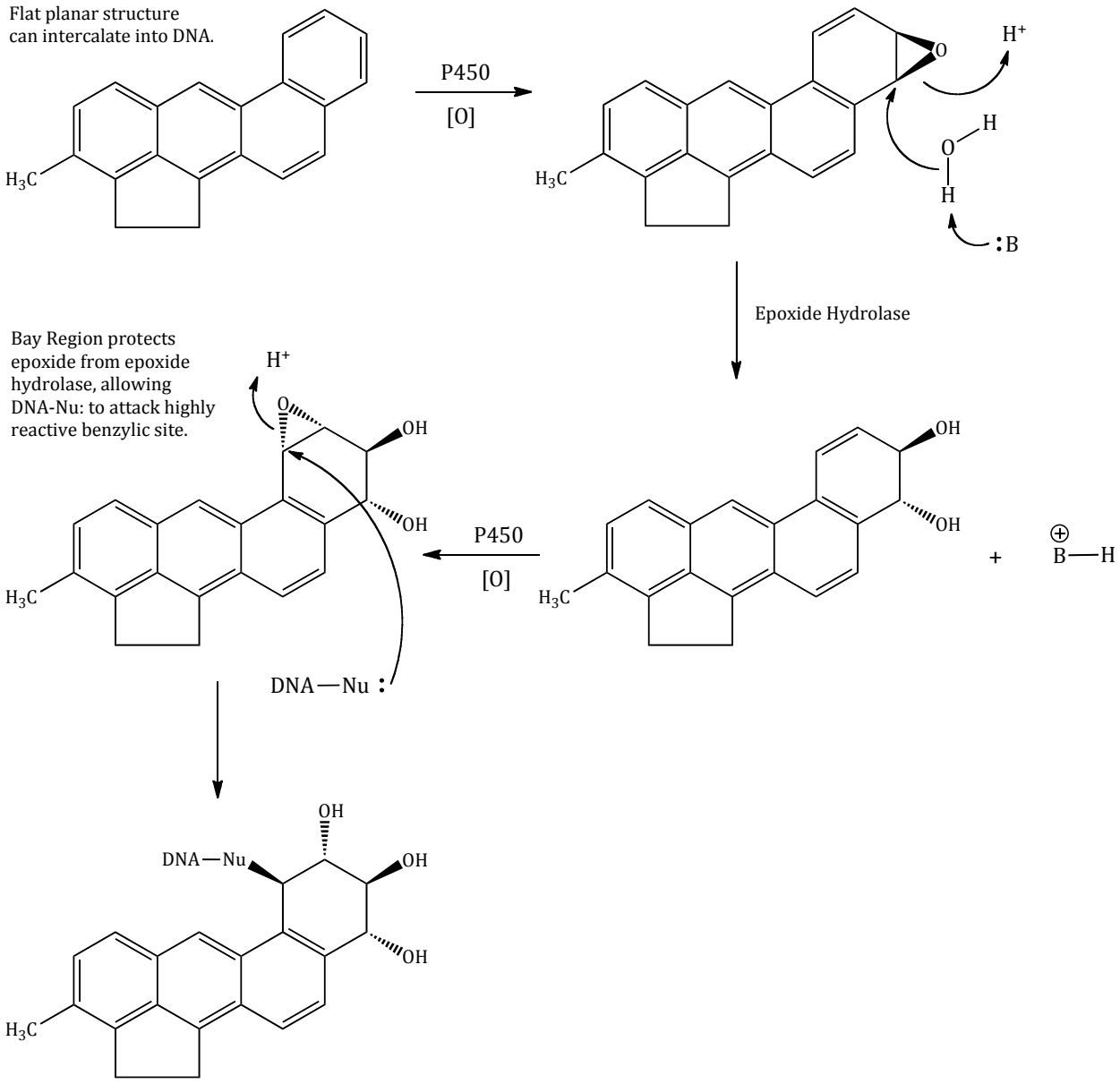
B. Carmustine



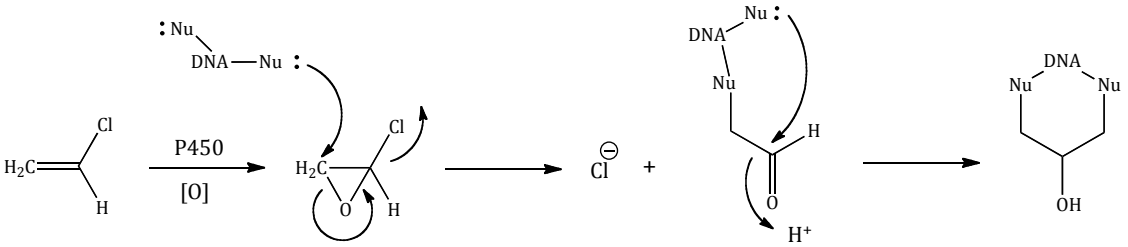
C. Dacarbazine



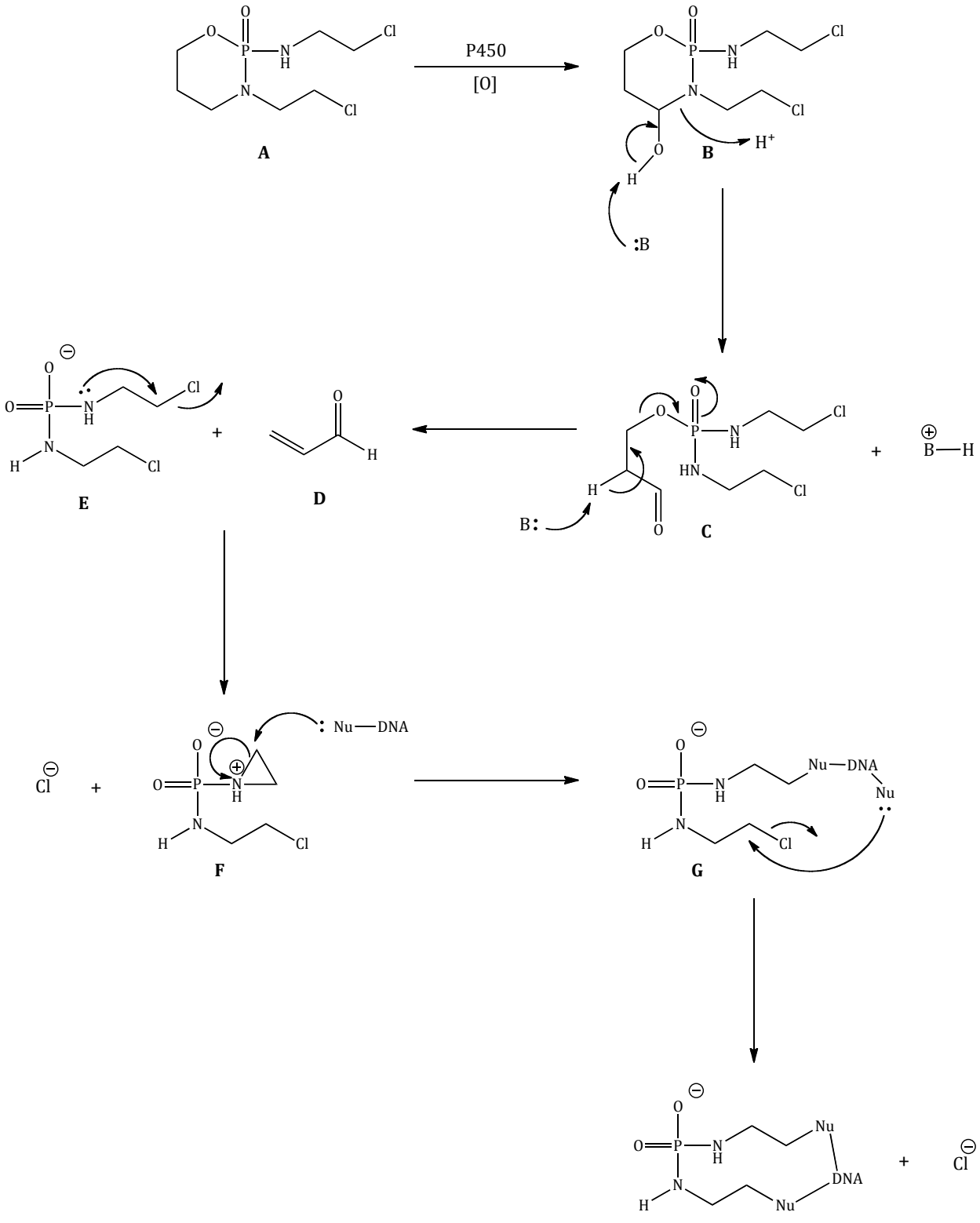
D. 3-Methylcholanthrene (3-MC)



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**.

(see above)

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

(see above)

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

(see above)

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

(see above)

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

G can form an aziridinium ion, which can alkylate DNA by the same mechanism as in part (d). It can also crosslink DNA as shown in product G (see above).

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	Alkylating (DNA damaging) agent	Antimitotic	Alkylating (DNA damaging) agent	Topoisomerase II inhibitor
Chemical Subclass	Nitrogen mustard	Vinca Alkaloid	Triazene	Anthracycline antibiotic
Cell Cycle	CCNS	CCS for M-phase	CCNS	CCNS
Major Toxicity	BMD	Peripheral neuropathy	BMD	BMD, cardiotoxicity, peripheral neuropathy
Mechanism of Action	A prodrug that is metabolized to a phosphoramide mustard that crosslinks DNA via formation of aziridinium ions.	Binds to tubulin dimers, preventing polymerization of microtubules. This leads to blockage of mitosis at the metaphase.	A prodrug that is oxidatively N-demethylated to for a triazene that methylates DNA.	DNA intercalation and inhibition of macromolecular biosynthesis. It stabilizes the topoisomerase II complex after it has cut the DNA chain for replication, preventing resealing of the double helix.

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

In terms of the phases of the cell cycle targeted, this treatment is effective since all phases of the cell cycle are covered, though not selectively (except for the M-phase). Three drugs overlap on the major toxicities, and therefore, the combination would cause severe BMD for people using it. Perhaps one or more agents should be replaced to reduce the potential for BMD and special toxicities associated with them. Thus, based on toxicity profile, this is probably not a very good regimen.