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Medicinal Chemistry-I PC-707

# Alkylating Agents As Anticancer Agents

**References:**
Kim, KW., Roh, J.K., Wee, HJ., Kim, C. (2016). Alkylating Anticancer Drugs. In: Cancer Drug Discovery. Springer, Dordrecht. https://doi.org/10.1007/978-94-024-0844-7_4

## 1 INTRODUCTION

**Definition:**
Chemotherapy drugs that damage DNA in cancer cells, stopping their division and causing cell death.

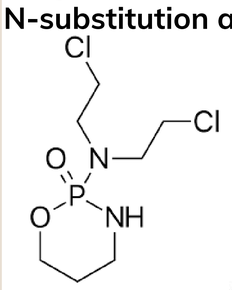
**How They Work:**
- Add alkyl groups to DNA bases.
- Prevent DNA replication and cell division.
- Trigger cell cycle arrest and apoptosis.
- Can act on one strand (monofunctional) or crosslink both strands (bifunctional).

**Common Uses:**
1) Leukemias. 2) Lymphomas
3) Solid tumors: breast, lung, ovarian, prostate
4) Some neuroendocrine tumors

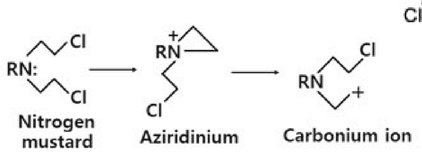
**Notes:**
- Non-specific: affects all rapidly dividing cells → bone marrow, gut, reproductive organs.
- Platinum drugs (cisplatin, carboplatin) act on DNA but not true alkylation.
- Teratogenic: avoid in early pregnancy.

## 2 NITROGEN MUSTARD AND ITS ANALOGUE:

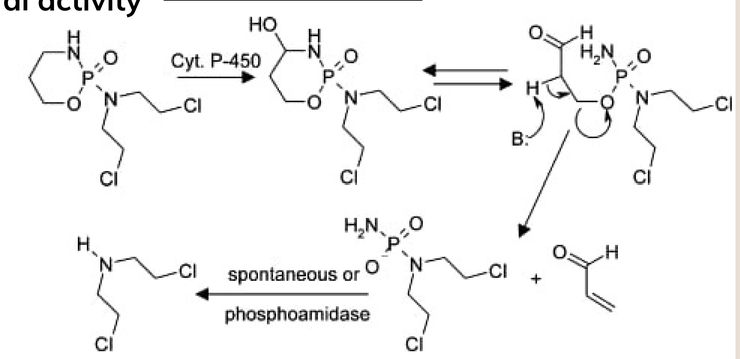
**1-SAR :**
$Cl–CH_2CH_2–$ groups → DNA alkylation
Phosphoramide ring → stability + oral activity
Prodrug (needs CYP450)
Ring controls activation speed
N-substitution affects toxicity

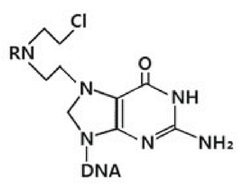


**2-MOA**

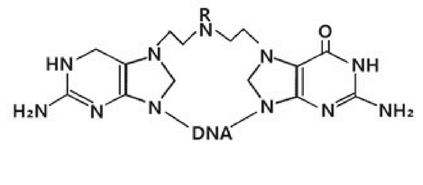



**3-Metabolism:**



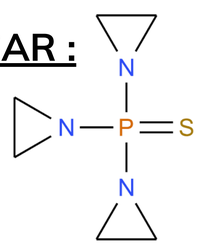

(N7-Gua-DNA) monoadduct




Bis(N7-Guanyl)-DNA interstrand cross-link

## 3 ETHYLENIMINE DERIVATIVES (THIOTEPA)

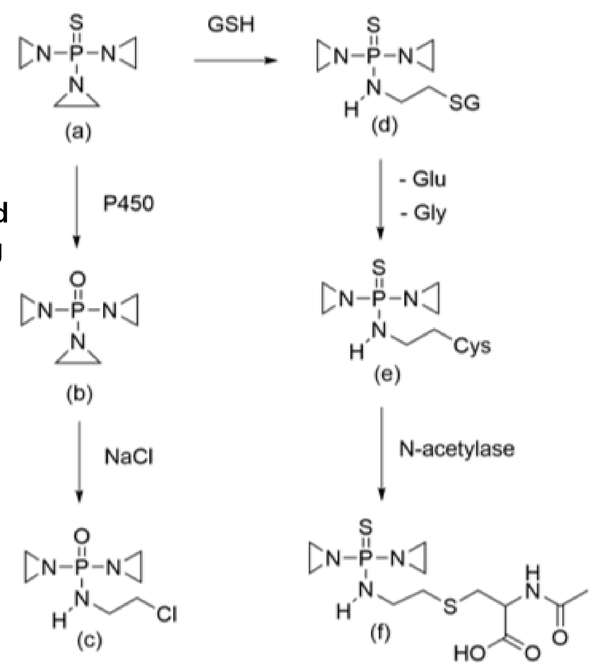
**1-SAR :**



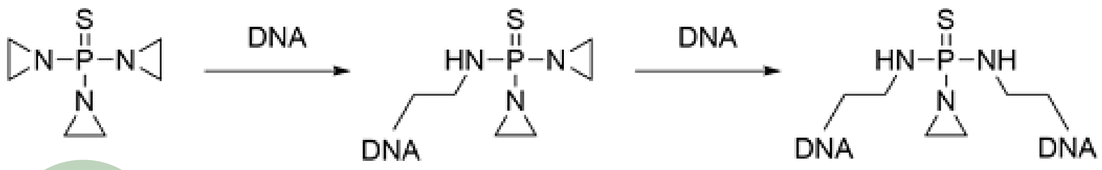
Thiotepa → oxidized by CYP450 to TEPA (more active), Then detoxified via GSH conjugation and N-acetylation, becoming water-soluble.

1. Aziridine ring is essential for activity
2. Electron-withdrawing central atom increases reactivity
3. Substitution on the aziridine ring affects stability and reactivity
4. Lipophilicity affects tissue penetration

**3-Metabolism:**

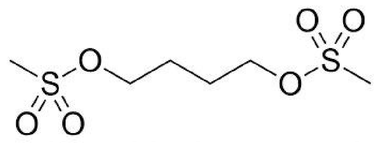



**2-MOA :**



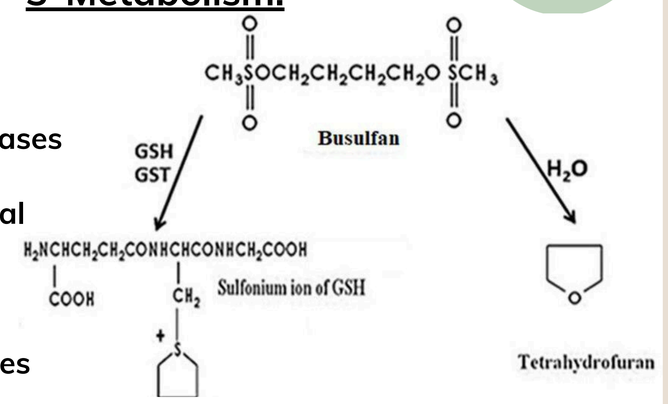

## 4 ALKYL SULFONATES (BUSULFAN)

**1-SAR :**

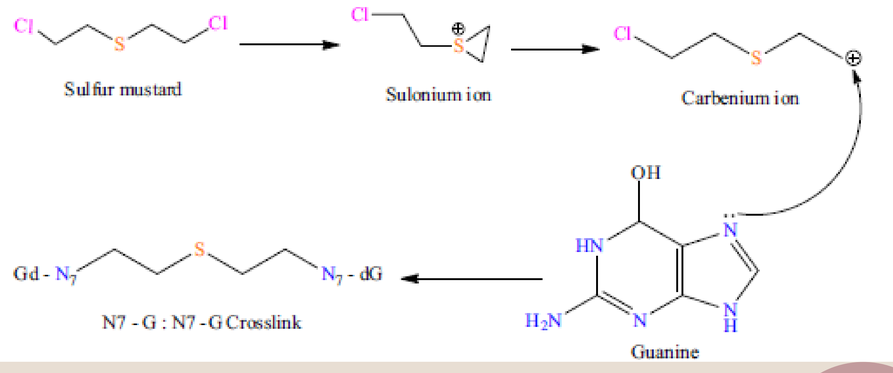


- Replacing sulfur with nitrogen → decreases toxicity.
- Adding an amino group → increases oral bioavailability.
- Adding a substituted phenyl group → increases oral bioavailability
- Introducing an aromatic ring → increases chemical stability.

**3-Metabolism:**




**2-MOA**

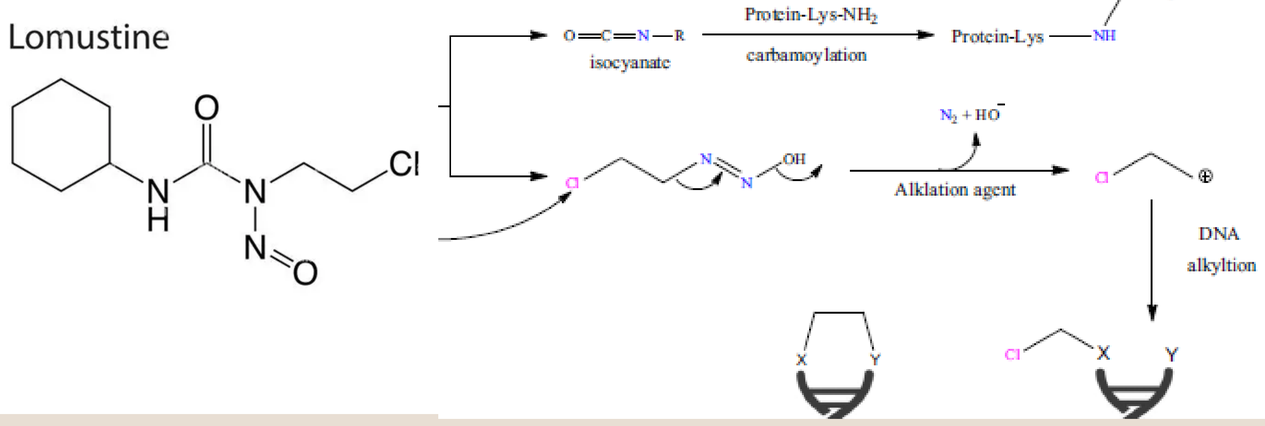



## 5 NITROSOUREA ( LOMUSTINE )

**1-SAR :**
- Core structure: Nitrosourea moiety (–N–NO–CO–) essential for alkylating activity.
- Alkylating group: Chloroethyl chain responsible for DNA cross-linking.
- Lipophilic part: Cyclohexyl ring increases membrane permeability and CNS penetration.

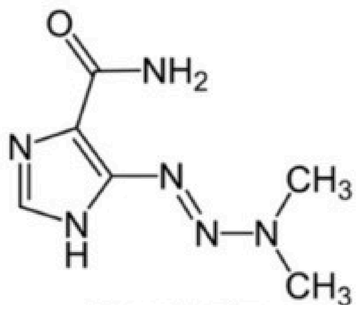
**3-Metabolism:**
Lomustine is rapidly absorbed orally. Undergoes complete first-pass metabolism in the liver, Converted to active metabolites: trans-4-hydroxy-CCNU and cis-4-hydroxy-CCNU, These metabolites have alkylating (cytotoxic) activity.

**2-MOA :**




## 6 TRIAZINES:

**1-SAR :**
- Triazine ring → essential core
- Dimethylamino group → source of methyl (activity)
- Carboxamide → solubility
- Prodrug → forms MTIC (active)
- Methylates O6-guanine



**2-Metabolism:**


**3-MOA :**