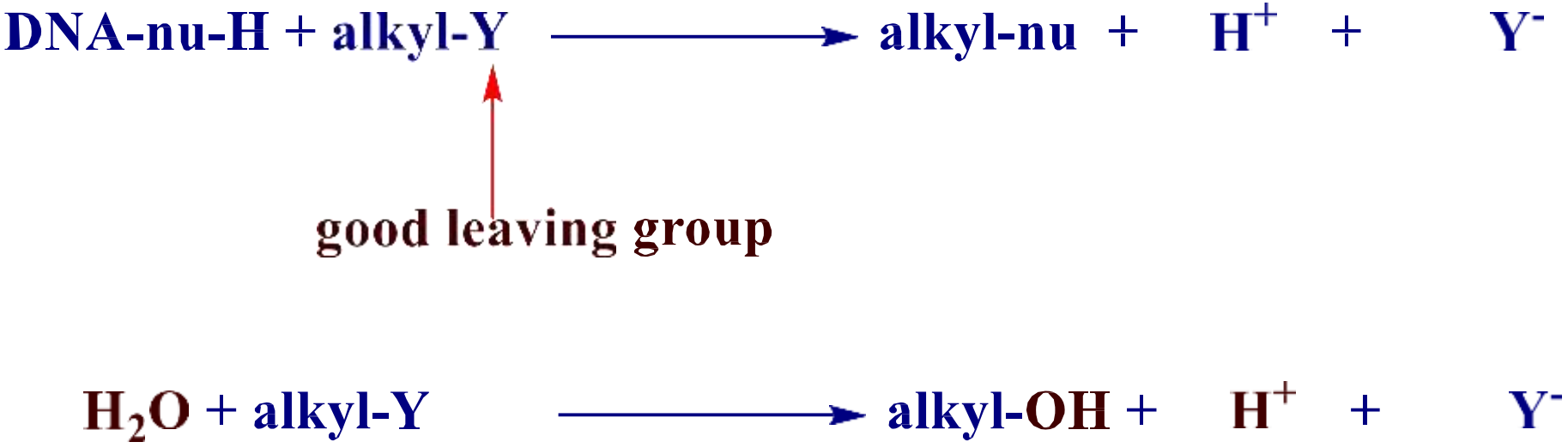
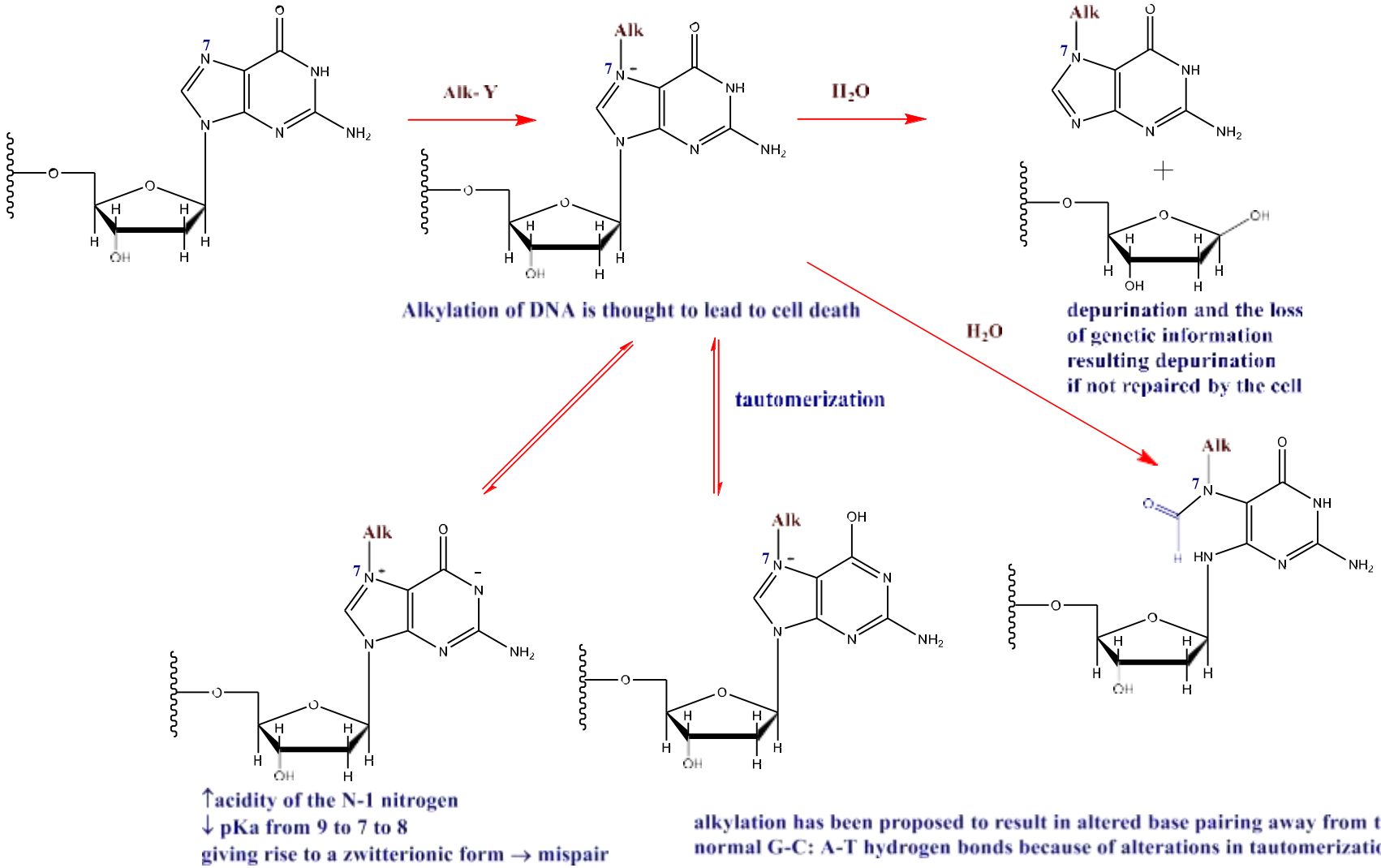
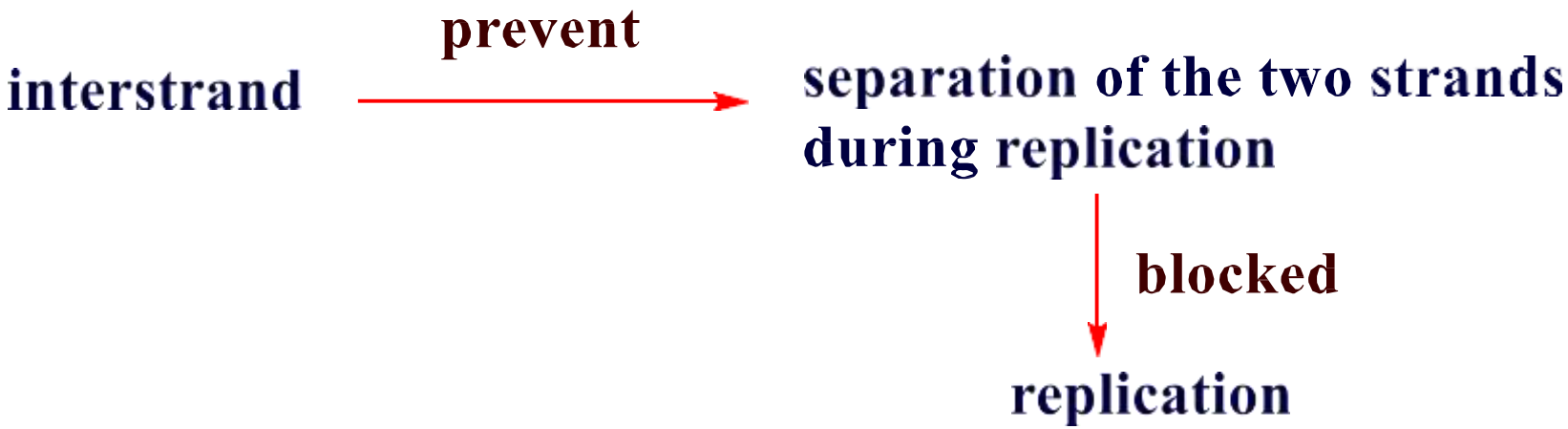
Alkylating agents





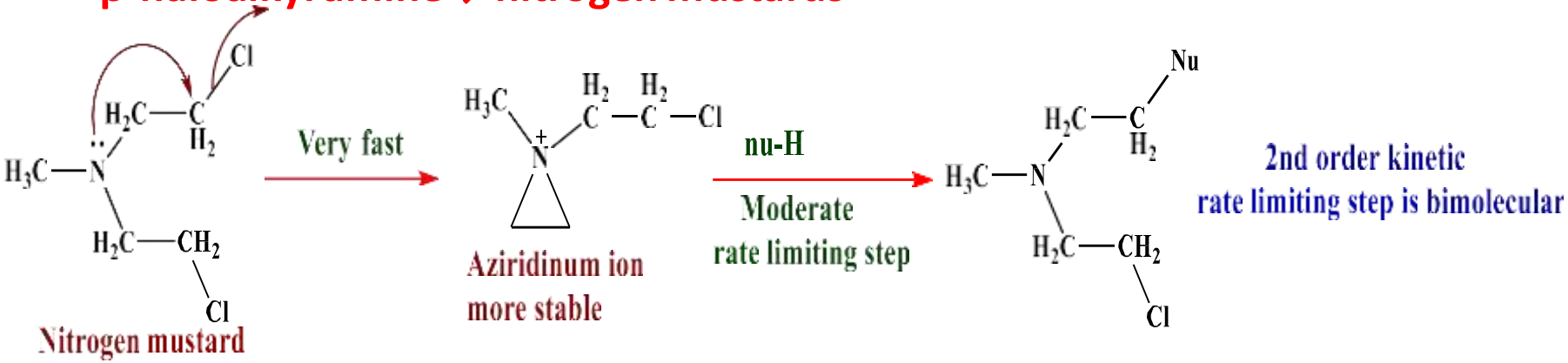
Alkylation of guanine N-7 and subsequent depurination of DNA.

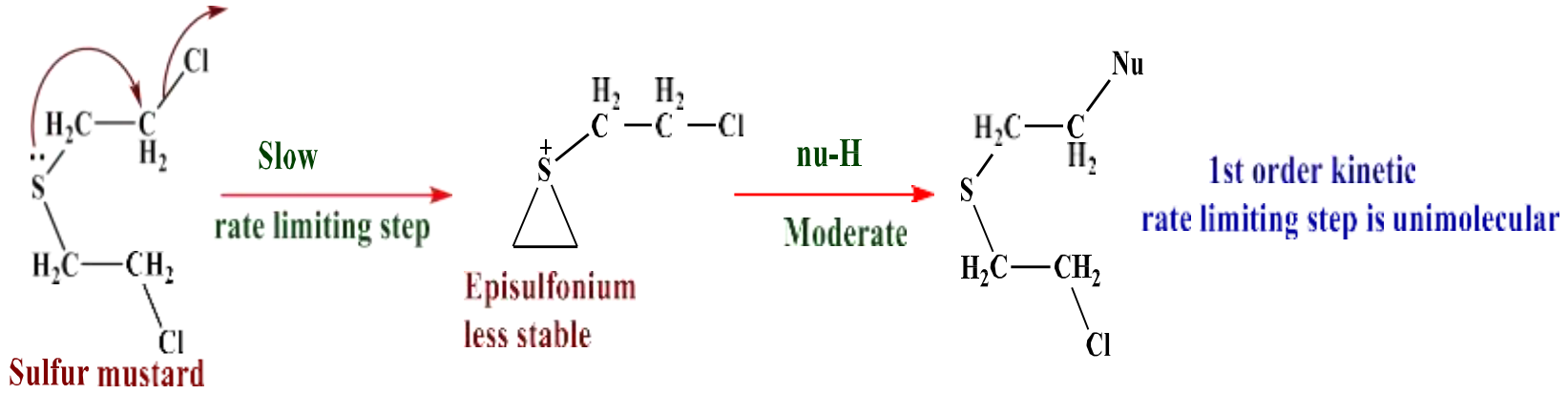
Alkylating agents possess two reactive functionalities, both able to interstrand cross linker



Kinetic of reactions …Order of rx

β-haloalkyl amine→ nitrogen mustards

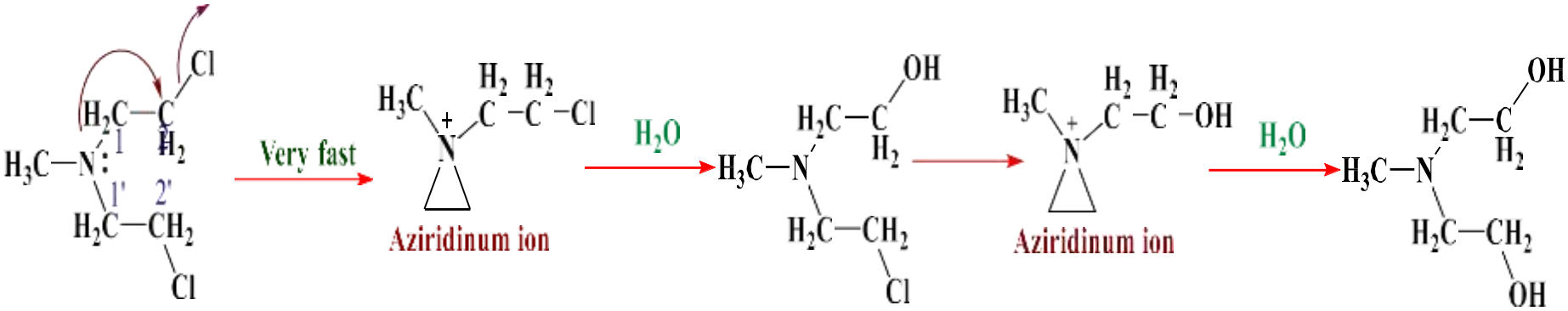




ß-haloalkyl Sulfide→Sulfure mustards

Mechlorethamine

is highly reactive and therefore nonselective, making it unsuitable for oral administration and necessitating direct injection into the tumor



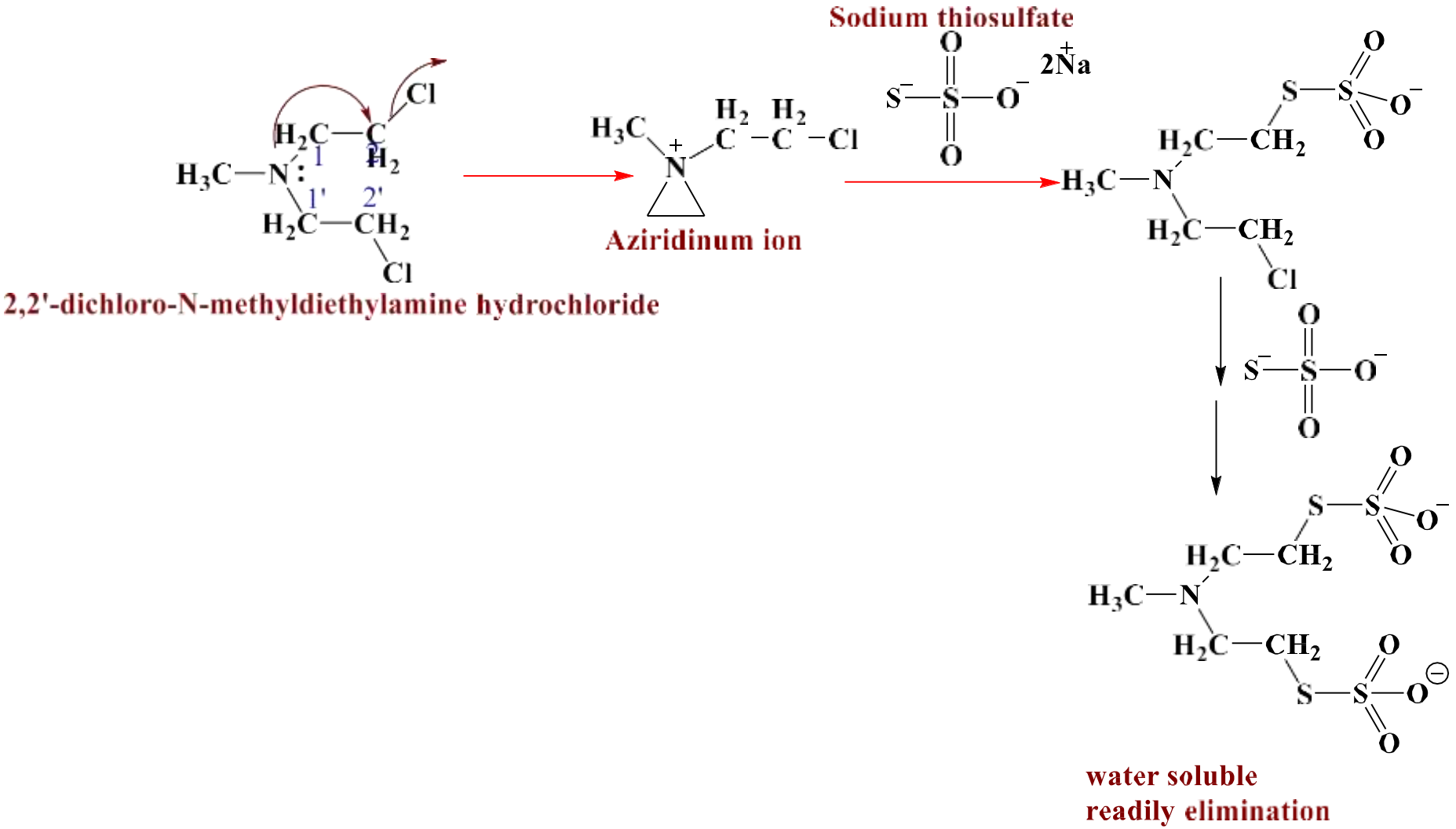
Mechlorethamine is usually used in combination with other antineoplastic agents: M(mechlorethamine), O(oncovin), P(procarbazine), and P(prednisone) and this combination is known as MOPP regimen.

Uses:- Hodgkin, s disease, lymphosarcoma, chronic myelocytic or lymphocytic leukemia, bronchogenic carcinoma, metastatic carcinoma.

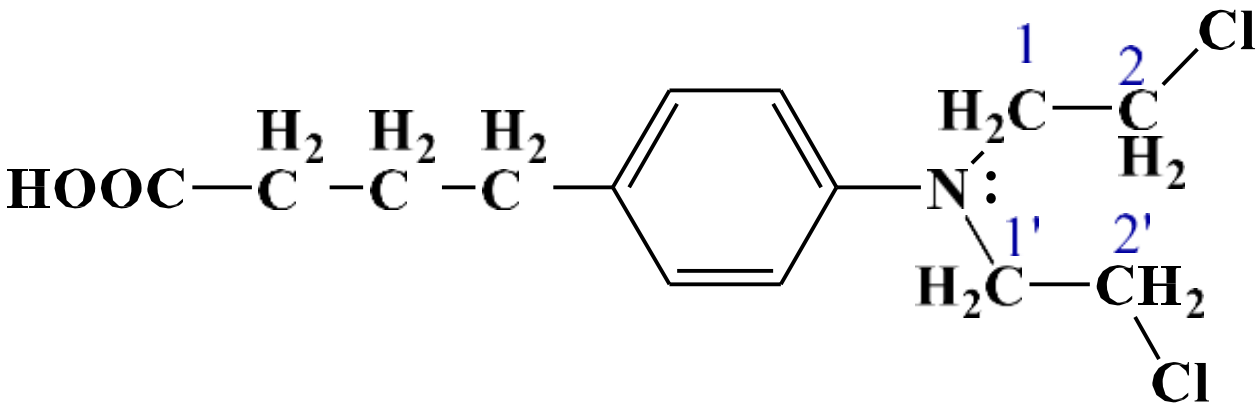
Dosage form: - powder for inj(10mg).

S/E bone marrow depression, nausea and anorexia.

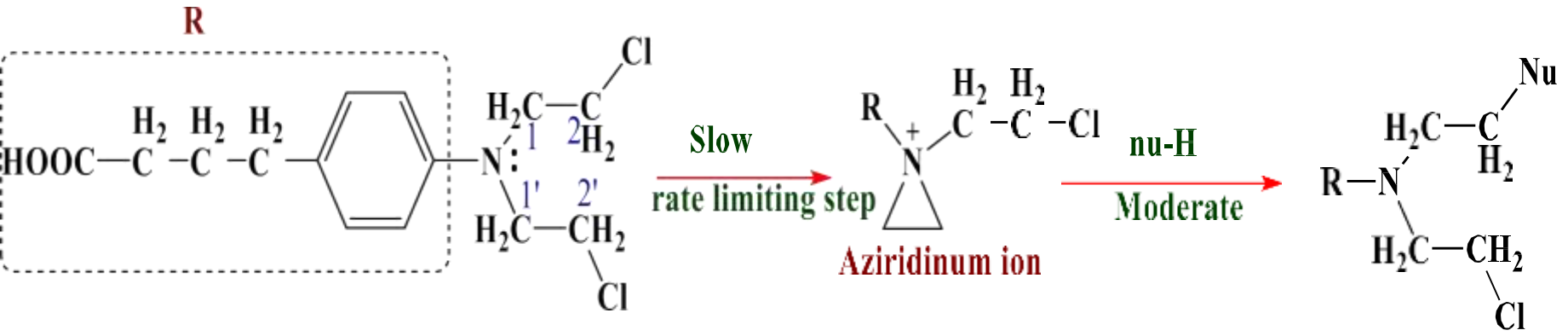
The antidote sodium thiosulfate ($Na_2S_2O_3$), a strong nucleophile, may be administered.



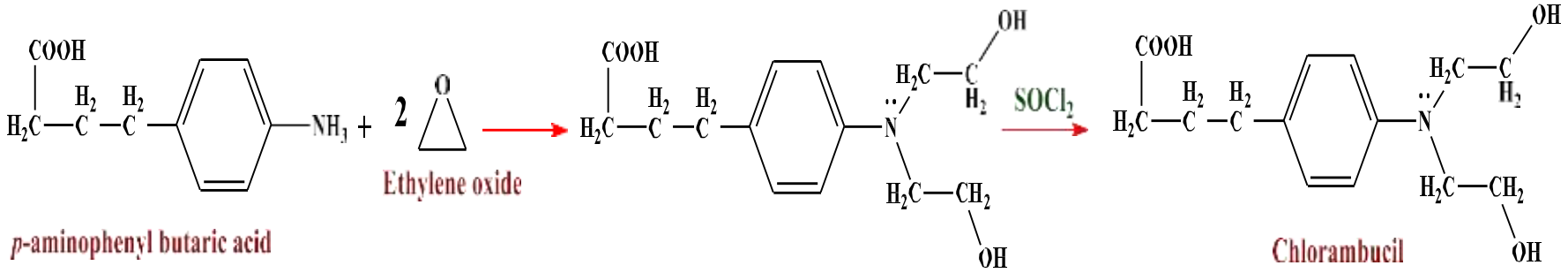
Chlorambucil



4-{bis-(2-chloroethyl)amino}phenylbutaric acid



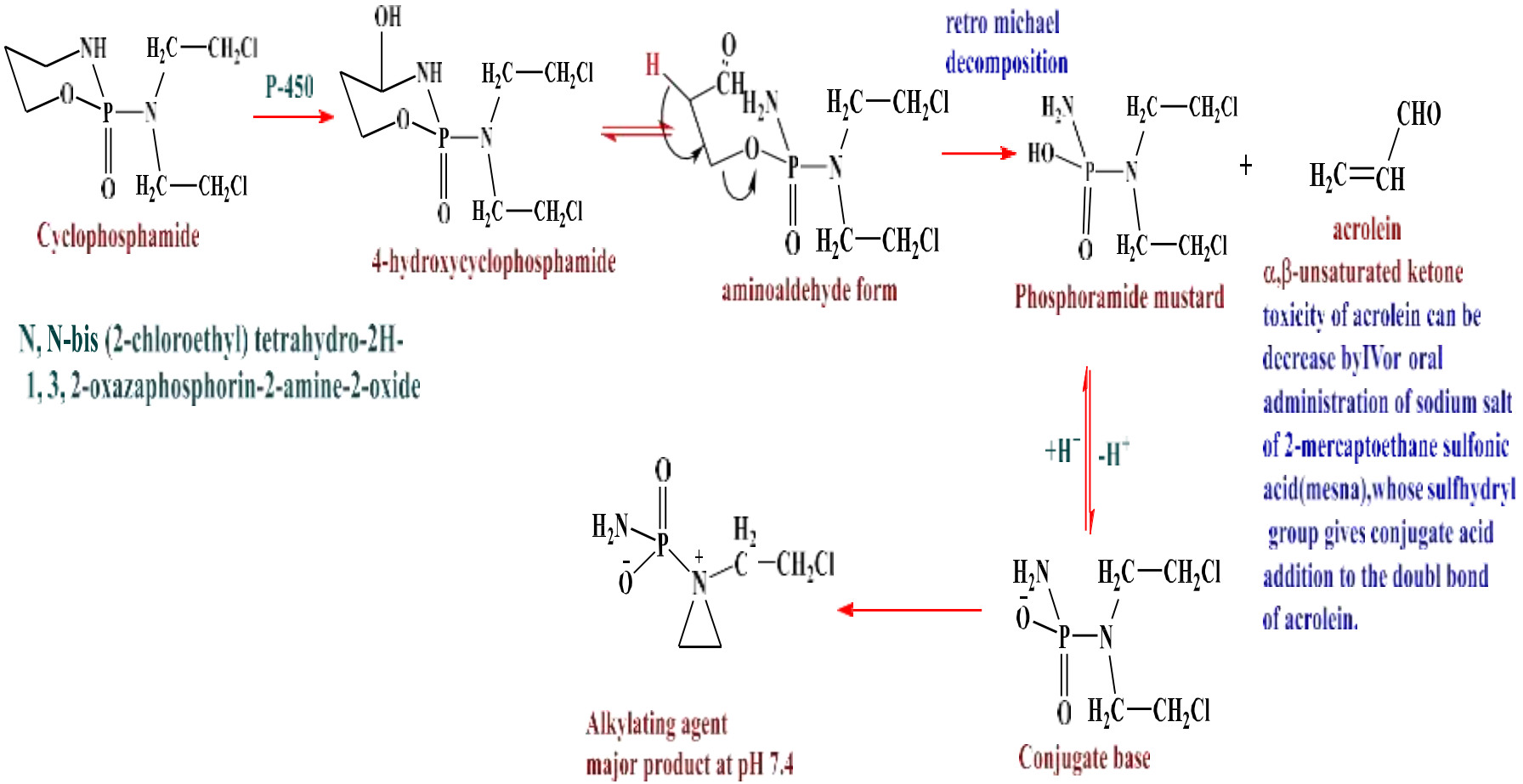
Preparation of chlorambucil



Uses: - Chronic lymphocytic leukemia(CLL), malignant lymphomas carcinoma of breast, lung and ovary ,and Hodgkin, s disease.

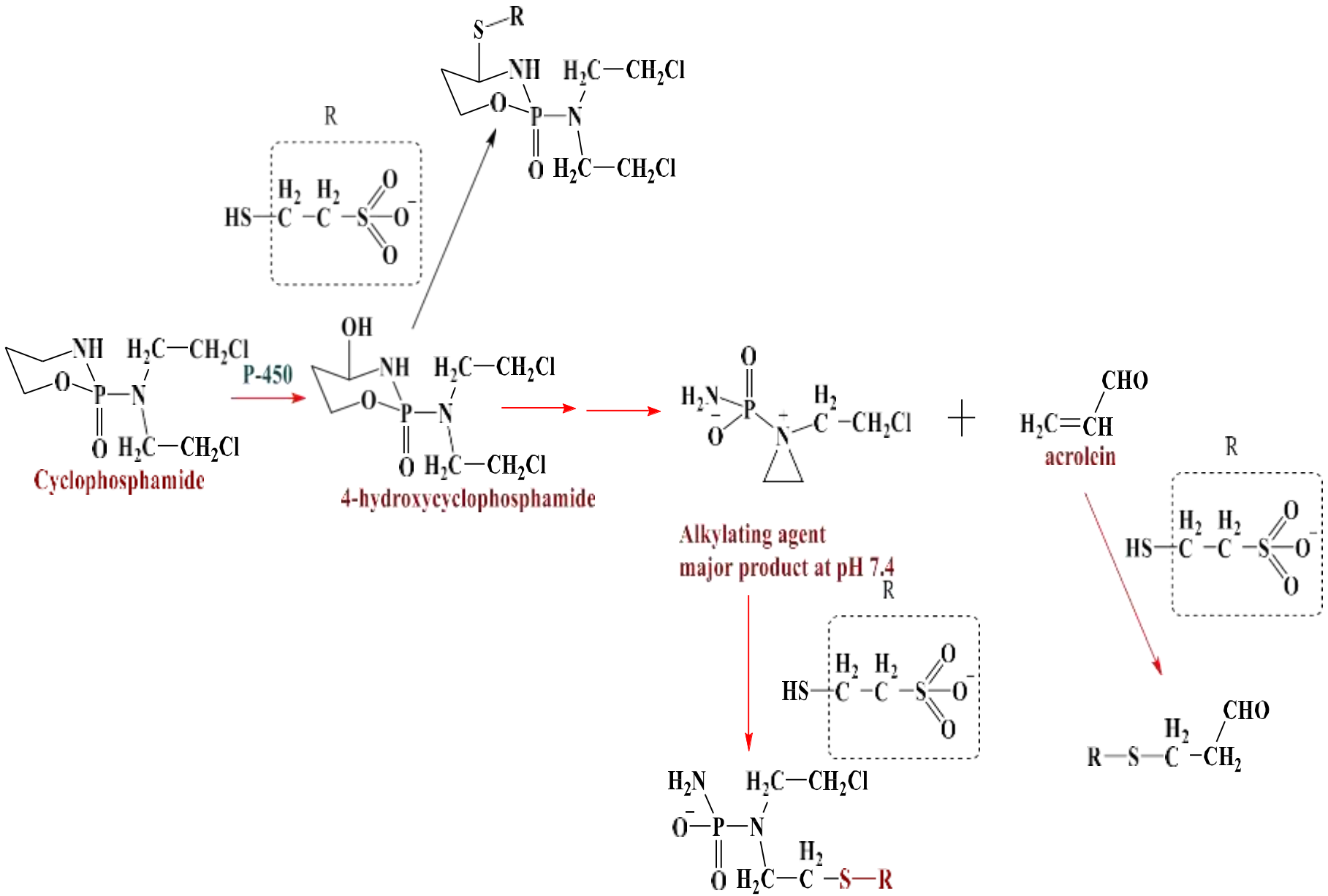
Dosage:-Tablet (2mg). The stability of chlorambucil allows it to be taken orally.

Cyclophosphamide (pordrug)

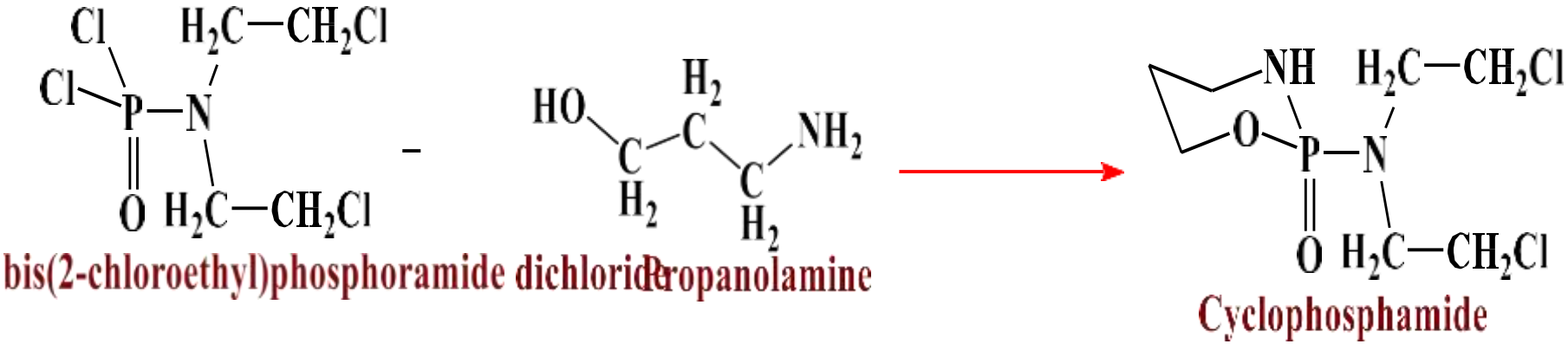


N, N-bis (2-chloroethyl) tetrahydro-2H-
1, 3, 2-oxazaphosphorin-2-amine-2-oxide

α,β-unsaturated ketone toxicity of acrolein can be decrease byIVor oral administration of sodium salt of 2-mercaptoethane sulfonic acid(mesna),whose sulfhydryl group gives conjugate acid addition to the doubl bond of acrolein.


Cyclophosphamide
P-450
4-hydroxycyclophosphamide
Alkylating agent
major product at pH 7.4
acrolein
R

Preparation of cyclophosphamide



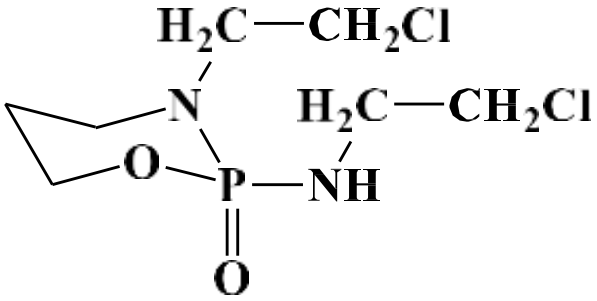
bis(2-chloroethyl)phosphoramide dichloride – Propanolamine → Cyclophosphamide

Uses:- it is active against multiple myeloma, chronic lymphocytic, leukemia, acute leukemia in children's, Burkett's lymphoma, and acute lymphoblastic leukemia in children.

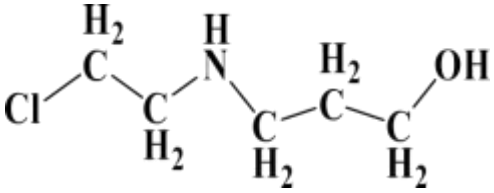
In combination with other chemotherapeutic agents, it has given complete remissions and even cures in Burkett's lymphoma and acute lymphoblastic leukemia (ALL) in children.

Dosage form:- cyclophosphamide has advantages over other alkylating agents in that it is active orally and parentrally and can be given in fractionated doses over prolonged periods.

Ifosfamide

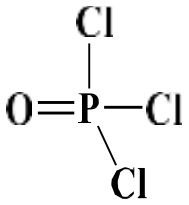


3-(2-chloroethyl)-2{(2-chloroethyl) amino}tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide

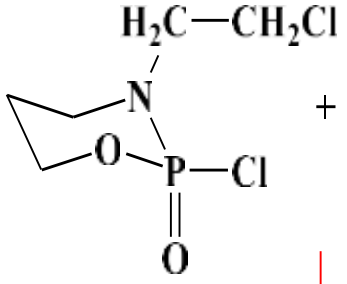


3-((2-chloroethyl)amino)propan-1-ol

+



Phosphorus oxychloride



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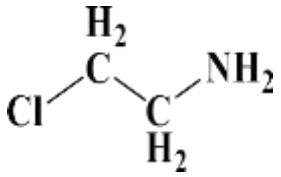
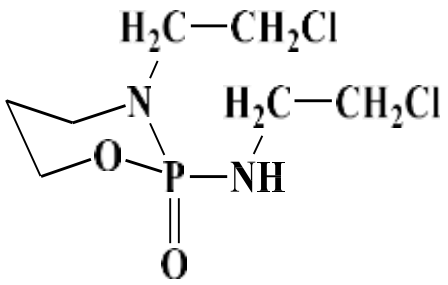


2-chloroethylamine



Ifosfamide

Ifosphamide

longer half life & greater activity than cyclophosphamide

Given IV with **MESNA** (2-mercaptoethane sulfonate).

Converted by liver cytochrome P450 to active & toxic metabolites.

Toxicity: N&V, neurotoxicity (confusion), nephrotoxicity, hemorrhagic cystitis or hematuria (prevented by concurrent MESNA), cardiac toxicity with high dose, bone marrow toxicity

used mainly in testicular tumor

MESNA
(Sodium 2-mercaptoethanesulfonate)

- It is a synthetic sulfur compound and belongs to a class of thiol compounds that produce mucolysis by disrupting disulfide bonds of the mucous polypeptide chains .
- It has been used in a variety of disorders such as mucolytic agent for pulmonary disorders* and protective agent against the toxicity of some chemotherapotic agents.

*Clarke SW, Lopez-Vidriero MT, Pavia D, Thomson D: The effect of sodium 2-mercaptoethane sulphonate and hypertonic saline aerosols on bronchial clearance in chronic bronchitis. Br J Clin Pharmacol 1979; 7: 39–44.

*Berrigan MJ, Marinello AJ, Pavelic Z, Williams CJ, Struck RF, Gurtoo HL: Protective role of thiols in cyclophosphamide-induced urotoxicity and depression of hepatic drug metabolism. Cancer Res 1982; 42: 3688–3695