Cancer Therapy

- Surgery
- Radiation
- Immunologican Therapy (interferons - Incr. prod. T-cells and B cells)
- Chemotherapy
  - Alkylation Agents
  - Antimetabolites / Nucleoside Analogs
  - Antibiotics
  - Antimitotic Agents
  - Micellaneous Antineoplastic Agents
  - Hormonal Therapy

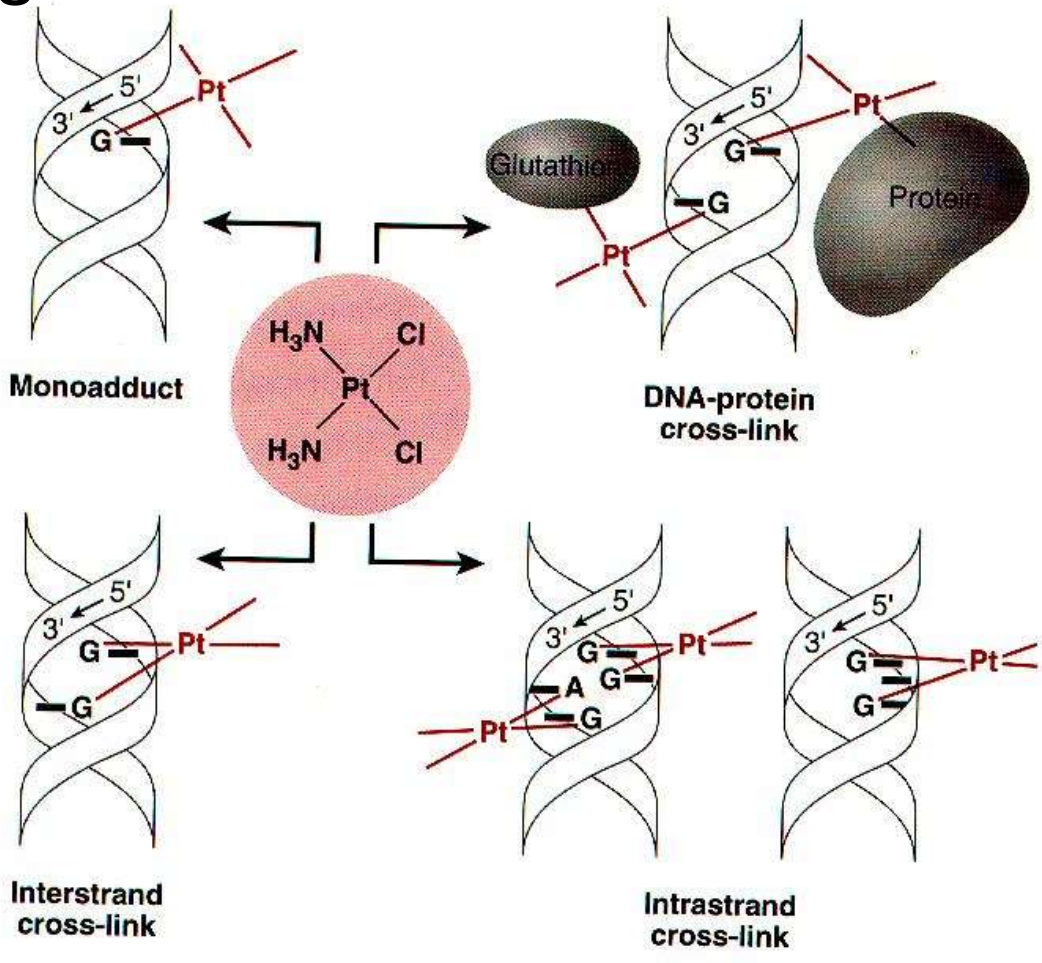
Platinum complexes

Cisplatin

Cisplatin is the cornerstone drug in the modern management of head and neck cancer

Mechanism:

Covalent crosslinks with GG base pairs (bends DNA)



Platinum complexes: Cisplatin

Pharmacology:

IV, not effective orally; most (90%) bound to plasma proteins.

concentrates in liver, kidney, intestine and ovary; excreted in urine.

Toxicity:

N&V, diarrhea, hypersensitivity reactions (rashes), renal damage (reduced with hydration), ototoxicity with high frequency hearing loss and tinnitus, peripheral sensory neuropathy (paresthesia and loss of proprioception), bone marrow depression.

Antimetabolites-

Purines.
Pyrimidines.
Folates.
Related compounds.

The antimetabolite drugs may exert their effects by several individual mechanisms involving:-
enzyme inhibition at active.
enzyme inhibition at allosteric.
enzyme inhibition at related sites.

Antimetabolites (Nucleoside Analogs, Folic acid analogs)

Antimetabolites:

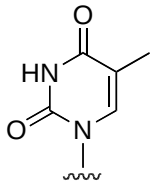
Prevents synthesis of normal cellular metabolites often close structural similarities metabolite and antimetabolite

Nucleoside analogs as antimetabolites

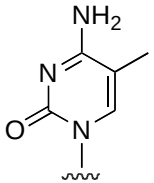
Possible mechanisms:

- Incorporation DNA or RNA; misreading
- Inhibition of DNA polymerase
- Inhibition of Kinases
- Inhib. of enzymes involved in pyrimidine / purine biosynthesis

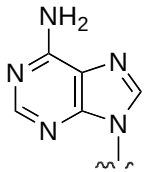
DNA



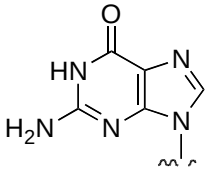
Thymin



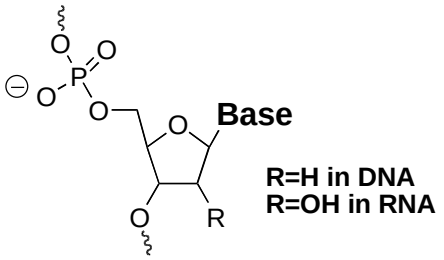
Cytosin



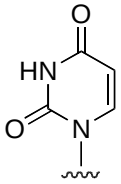
Adenine



Guanine



RNA



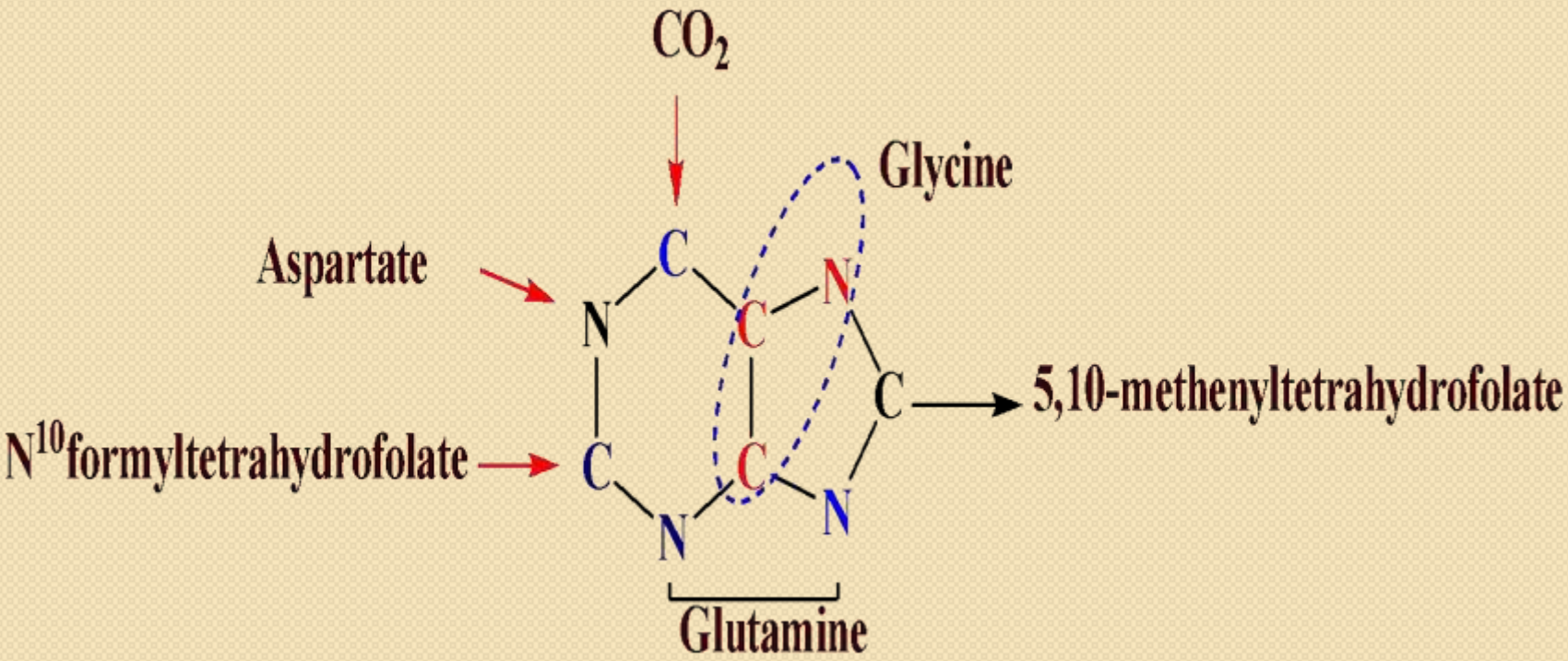
Uracil

Cytosin

Adenine

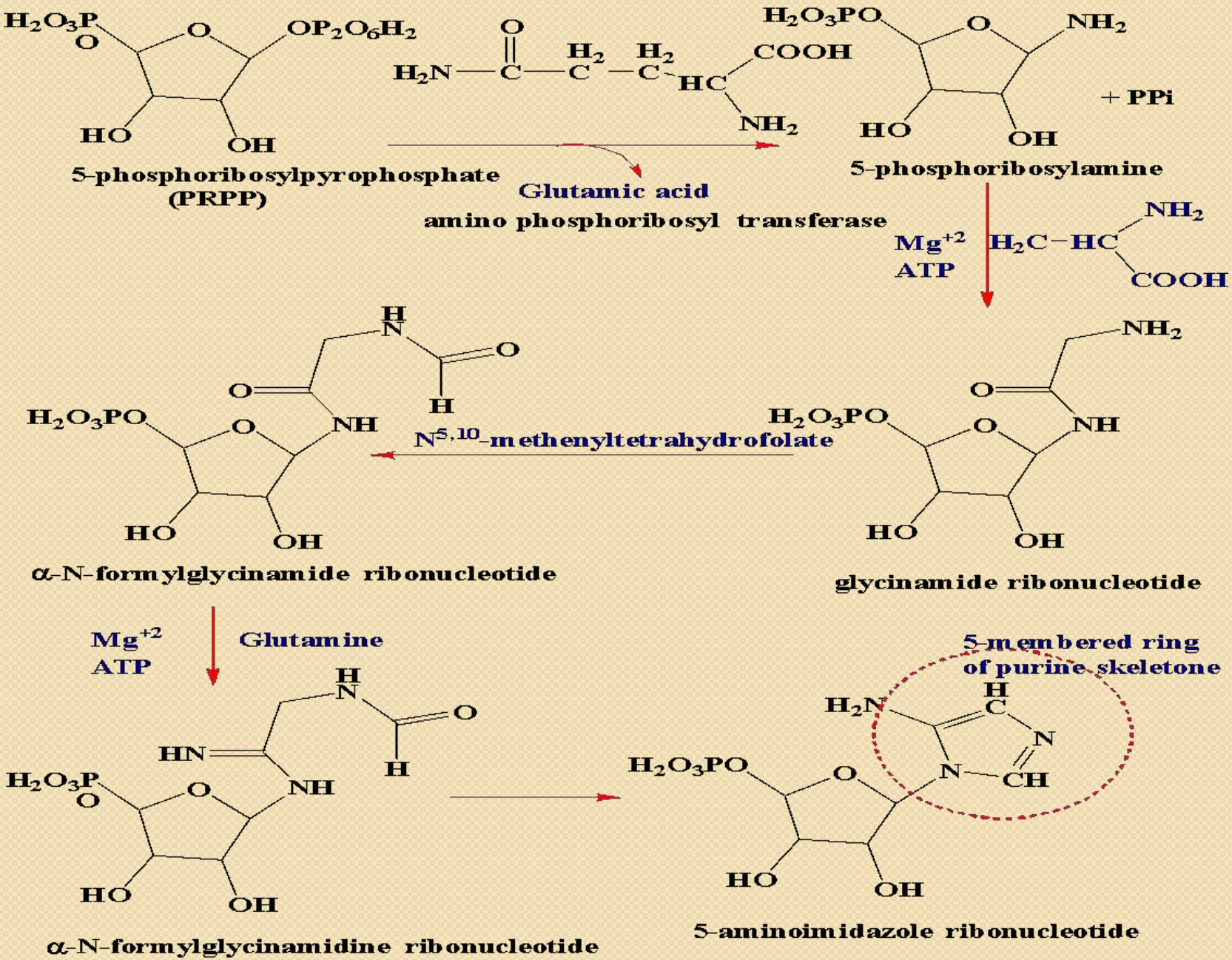
Guanine

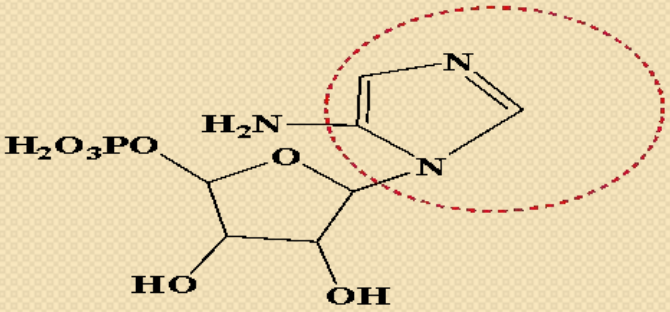
Purine antagonist



Inhibit the synthesis of Purine, inhibit synthesis of AMP (Adenylic) and GMP (guanylic) through the following steps:-

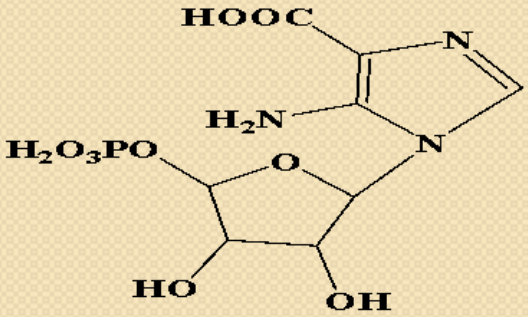
1)Inhibit the conversion of 5-phospho ribosyl pyrophosphate into 5-phosphoribosylamine.
2)Inhibit conversion of inosinic acid to adenylsuccinic acid.
3)Inhibit conversion of adenylsuccinic acid to AMP
4)Inhibit conversion of inosinic acid to xanthylic acid.


5-phosphoribosylpyrophosphate
(PRPP)
Glutamic acid
amino phosphoribosyl transferase
+ PPi
5-phosphoribosylamine
Mg+2
ATP
α-N-formylglycinamide ribonucleotide
N5,10-methenyltetrahydrofolate
glycinamide ribonucleotide
Mg+2
ATP
Glutamine
5-membered ring
of purine skeletone
α-N-formylglycinamidine ribonucleotide
5-aminoimidazole ribonucleotide

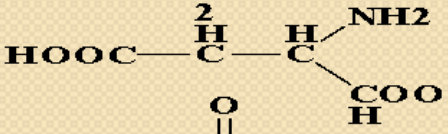


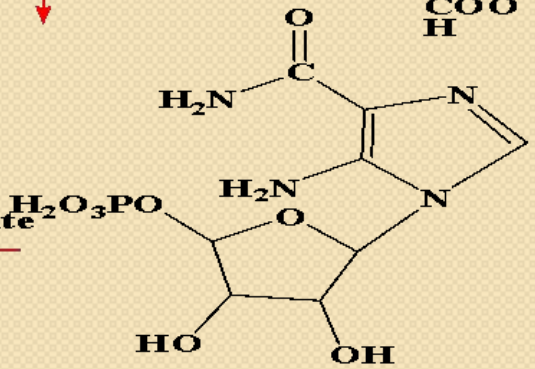
5-aminoimidazole ribonucleotide

CO_2



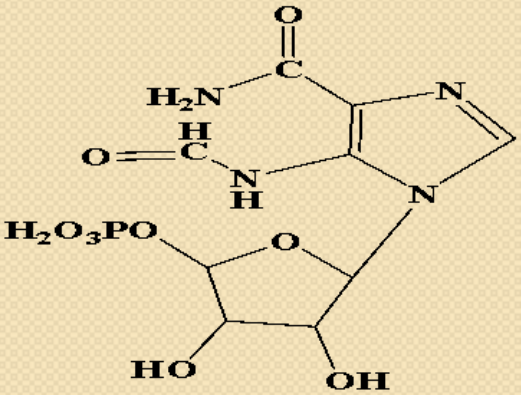
5-aminoimidazole -4-carboxylateribonucleotide



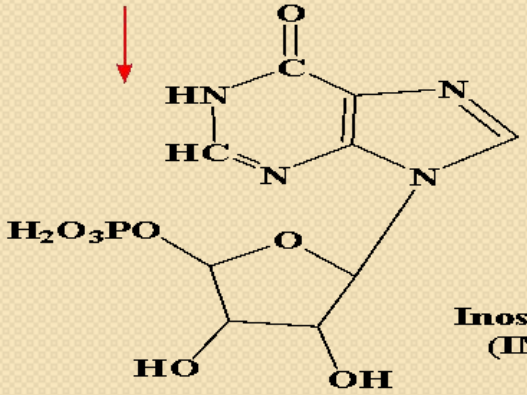


5-aminoimidazole -4-carboxamideribonucleotide

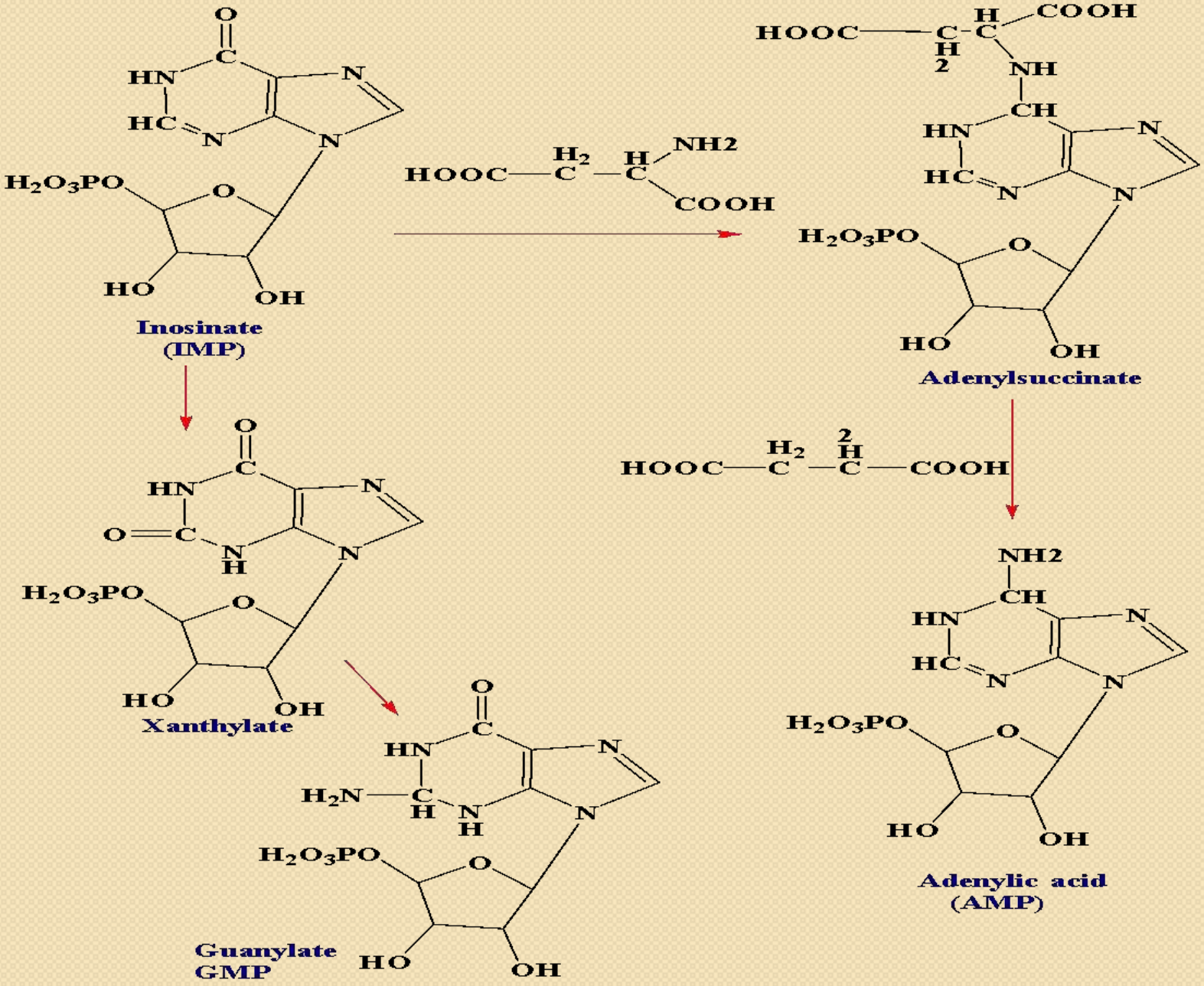
N^{10}-formyltetrahydrofolate



5-formamidoimidazole -4-carboxamideribonucleotide



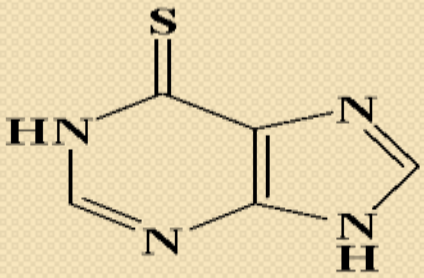
Inosinate (IMP)


Inosinate
(IMP)
Adenylsuccinate
Xanthylate
Guanylate
GMP
Adenylic acid
(AMP)

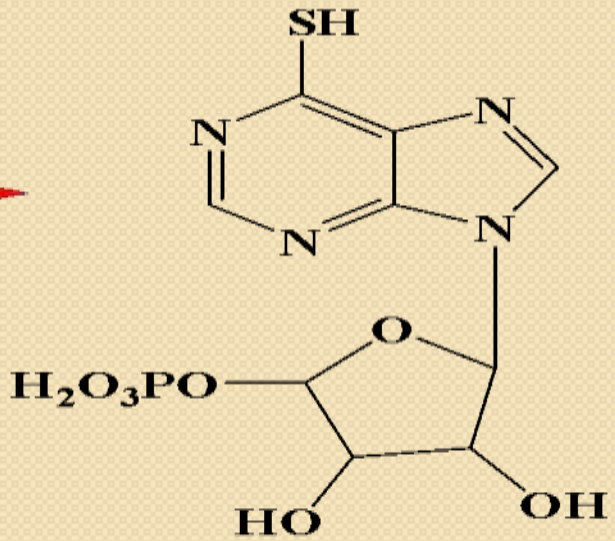
Examples of Purine synthesis inhibitors:-

Mercaotopurine

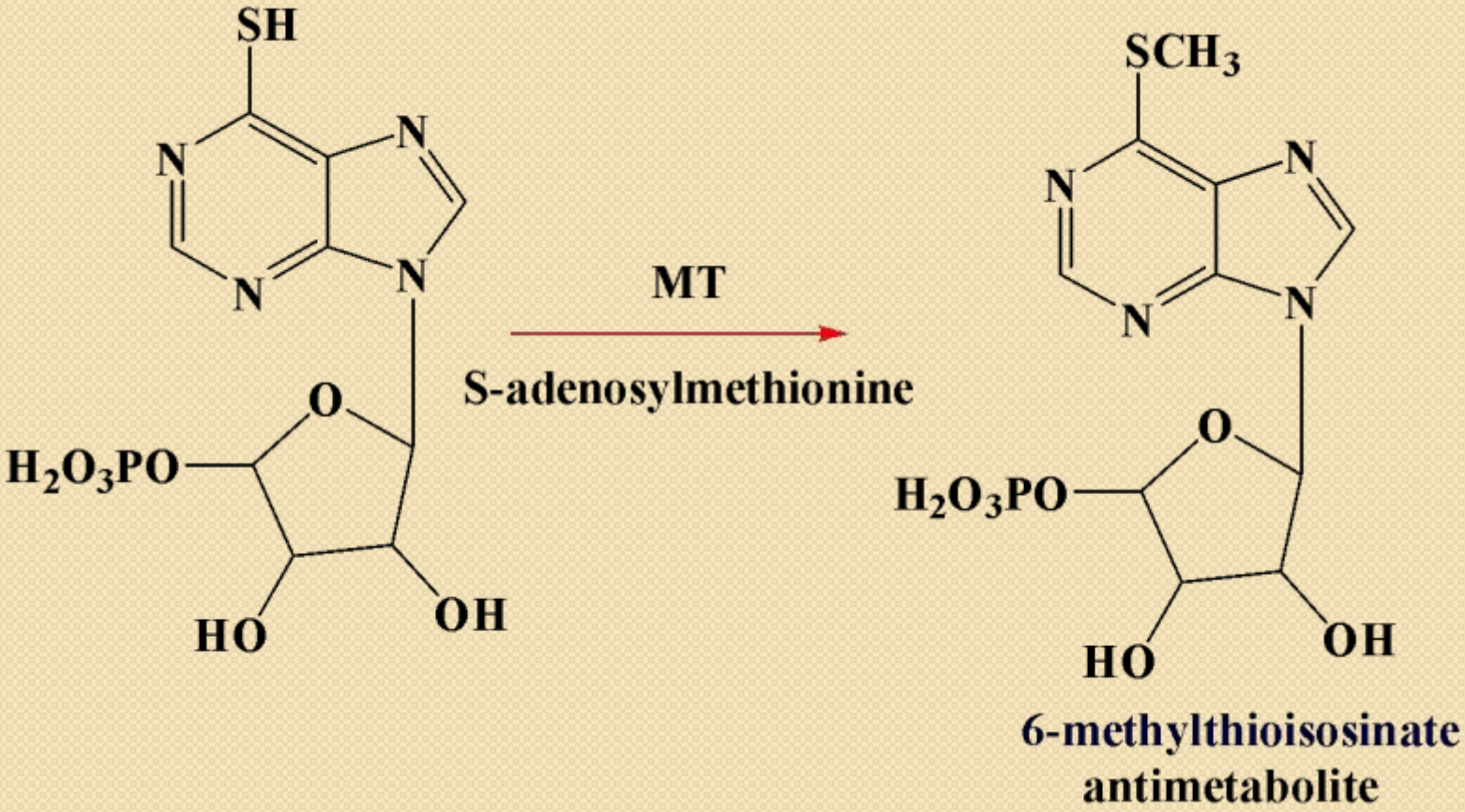
6-mercaptopurine(6-MP)
isosteric thiol/sulfhydryl group
to replace the 6-hydroxyl group
of hypoxanthine and guanine



6-thioinosinate



6-thioinosinate-5-monophosphate


SH
N
N
N
N
O
H_2O_3PO
HO
OH
MT
S-adenosylmethionine
SCH_3
N
N
N
N
O
H_2O_3PO
HO
OH
6-methylthioisosinate
antimetabolite

Purine antagonist:

6-Mercaptopurine

Mechanism of action:

6-MP inhibit the conversion of **inosine monophosphate** to **adenine and guanine nucleotides** that are building blocks for **RNA and DNA.**

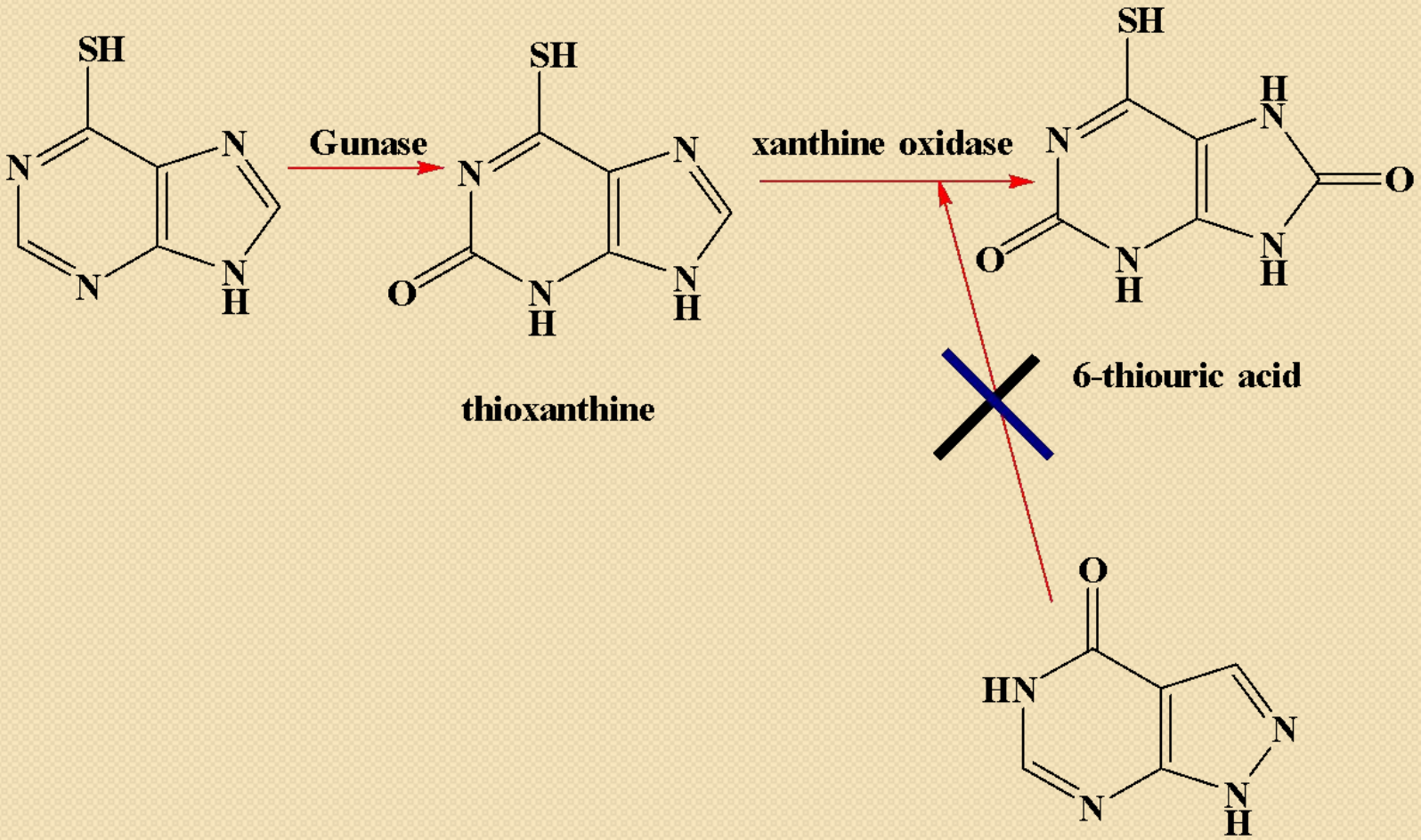
6-MP converted to 6-MPribose phosphate (6-thioinosinic acid, or **TIMP**)

TIMP inhibits the first step of de novo **purine**-ring biosynthesis.

TIMP is converted to thioguanine monophosphate (TGMP), which can be incorporated into RNA. The deoxy-ribonucleotide analogs that are also formed are incorporated into DNA.

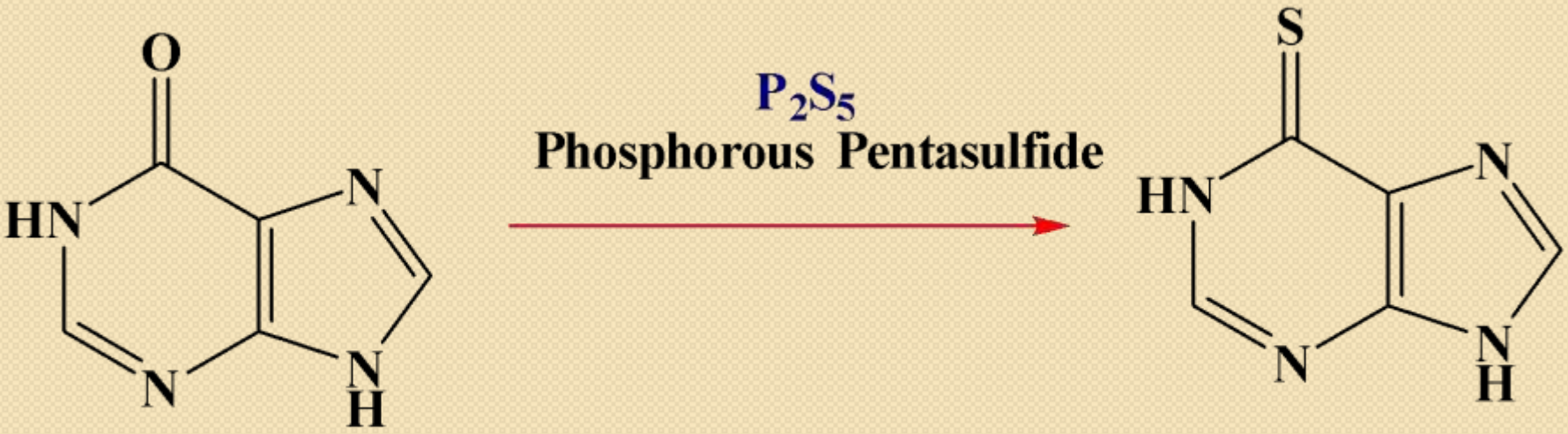
This results in nonfunctional RNA and DNA.

Metabolic degradation (catabolism) of 6-MP



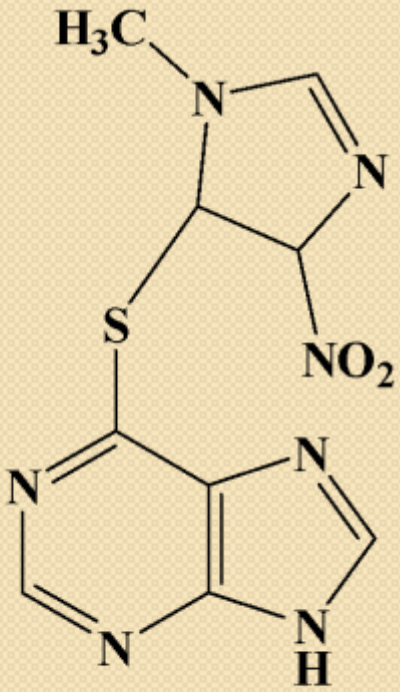
Inhibit xanthine oxidase and Inhibit the formation of thiouric acid so increase the potency of MP

Preparation of 6-MP



Hypoxanthine

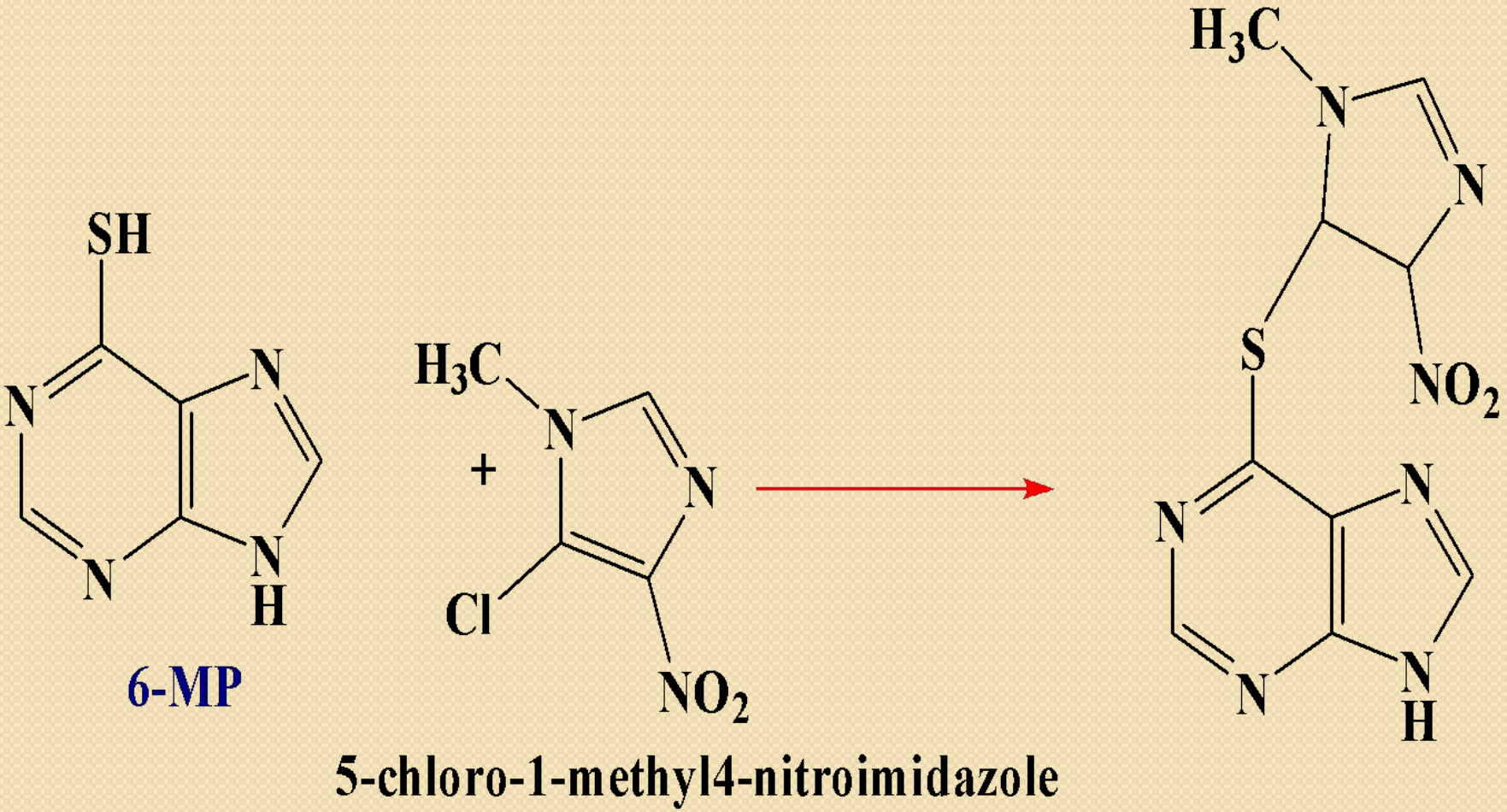
.Azathioprine:- use in treatment acute leukemia



Heterocyclic derivatives of 6-MP

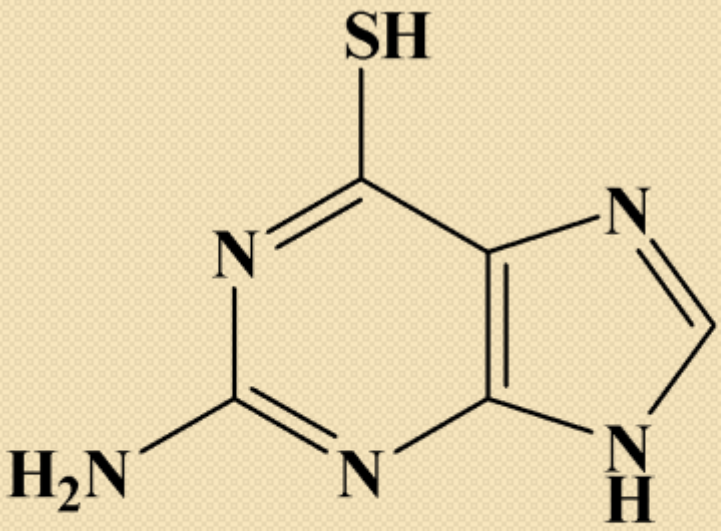
6-{(1-methyl-4-nitroimidazole-5-yl)thio}purine

Preparation of Azathioprine



5-chloro-1-methyl4-nitroimidazole

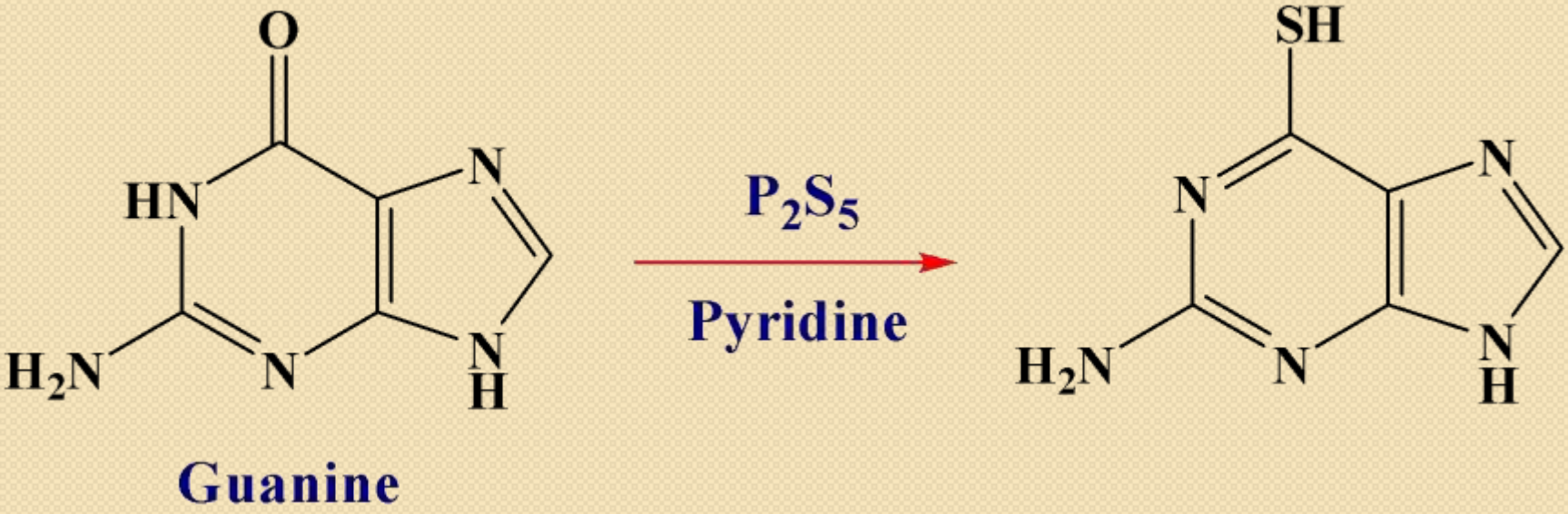
Thioguanine•



2-aminopurine-6-thiol

6-mercaptoanalogeof guanine

Preparation of thioguanine



Guanine