Carcinogenesis

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Cancer is a result of a disruption of the normal cellular proliferation.

What are the factors behind this disruption?

Factors are:

1. Biological factors
2. Chemical factors
3. Physical factors

Biological Carcinogens:

1. Viruses

2. Bacteria e.g. *Helicobacter pylori –Stomach Cancer*

3. Parasites e.g. Schistosoma trematodes – Bladder Cancer

Viruses

Groups of viruses: DNA and RNA groups

1.DNA viruses which include

a - Papilloma viruses –Urogenital cancer,Larynx,Cervical 8Kb+10 overlapping genes+E5,E6 are transforming genes.

b – Adeno viruses ???

c - Hepatitis viruses\ Hepatocellular carcinoma-Hepatoma

d - Herpes viruses

– Epstein-Barr \ Burkitts lymphoma(t(8 to 2,22,14) + Nasopharyngeal carcinoma

- Cytomegalovirus\ Kaposis sarcoma, ??Prostate cancer, Colon cancer, Cervical carcinoma

- Herpes 1 &2 ??

2.RNA viruses which include:

a - Complete transforming viruses- v-Oncs, High Oncogenic + induce tumor rapidly at high frequency.

b - Slow transforming viruses- Weak LTR

c - Defective transforming viruses- v-Oncs+ another virus

3. Viral Cycles

a. Virulent or lytic cycle:

New virus particles are made and released-burst- from the host cell.

b. lysogeny cycle or integration cycle

Viral Carcinogenesis Mechanisms

a. DNA viruses

--T-antigens, large, middle and small; LTR and E genes

Functions:

1. Necessary for host cell transformation
2. Stimulates the host cell to replicate its DNA
3. Binds to cellular DNA
4. Binds to p53 protein

b. RNA viruses

- v-Oncogenes--- gag-pol-env-onc or LTR

-Rous sarcoma virus+ src gene

-avian leukemia virus+ LTR

-MC29 virus + Myc oncogene

-Harvey sarcoma virus+ ras genes

-Mouse sarcoma virus + mos gene

-St-Fe SV + fes gene

Chemical Carcinogenesis

-Sources

-Ames test

Group of chemicals

a. Basis analogs

-5-bromouracil , 2-amino purine

b. Nitrous acid group

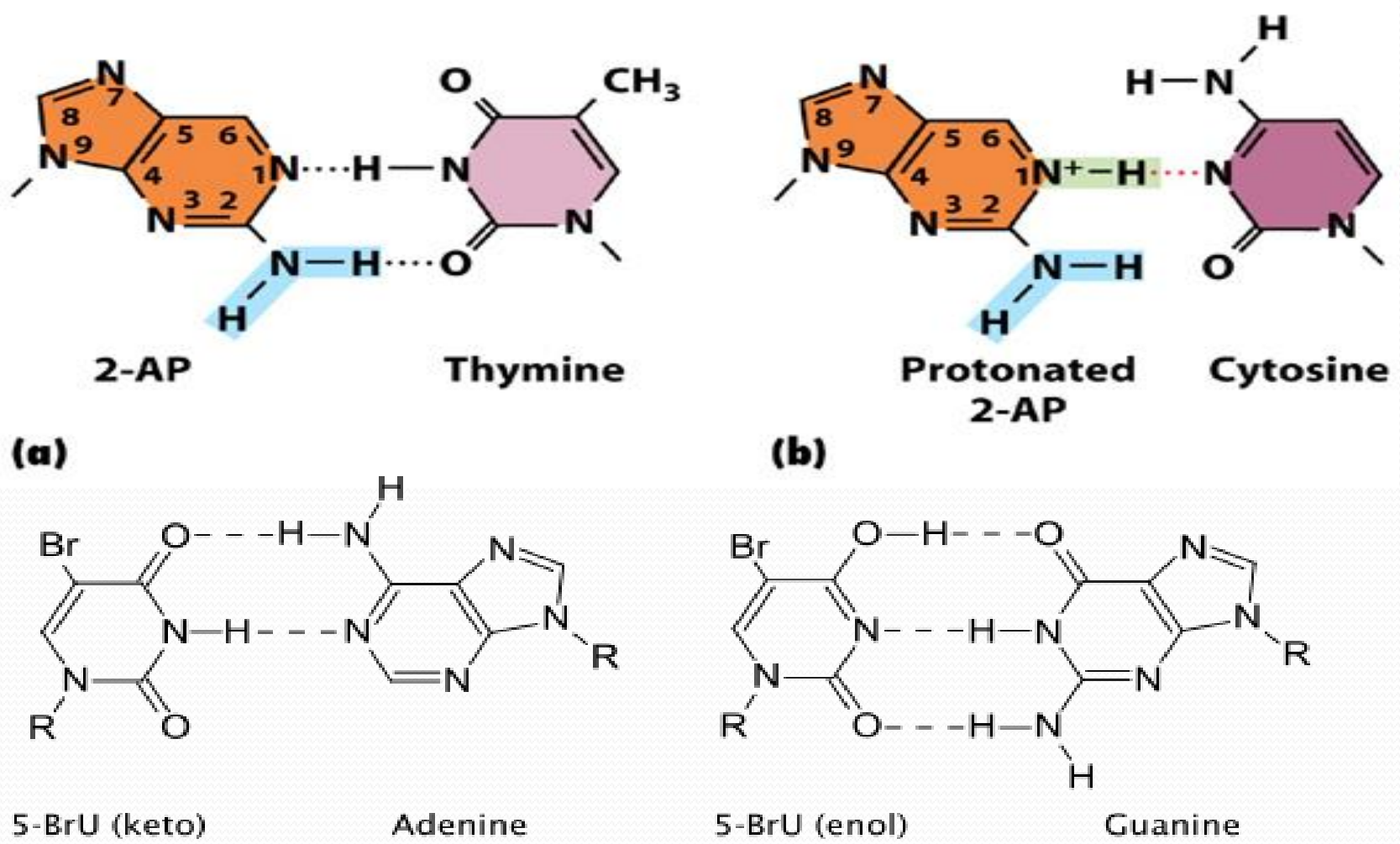
c. Alkylating agents

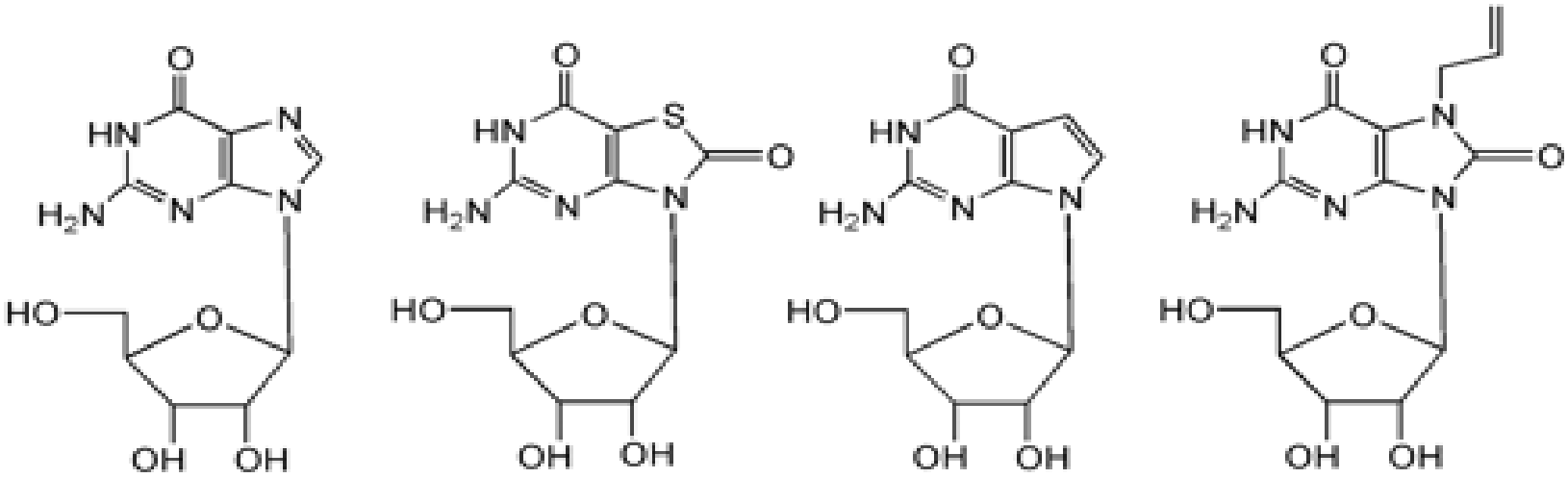
d. Acridine dyes

A.Basis analogs .a

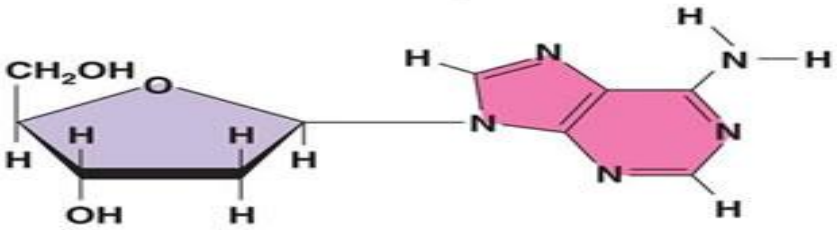
5-bromouracil …analogue to U..T..C

2-amino purine…analogue to G..A .b

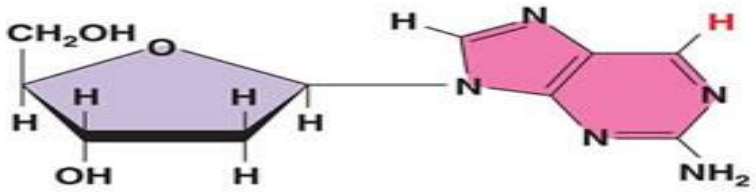




Normal nitrogenous base **Analog**

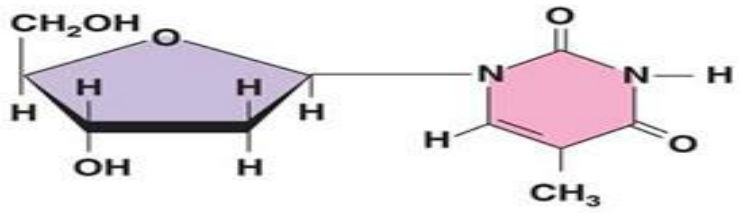


Adenine nucleoside

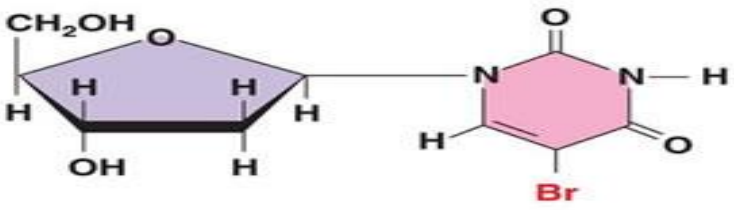


2-Aminopurine nucleoside

(a) The 2-aminopurine is incorporated into DNA in place of adenine but can pair with cytosine, so an AT pair becomes a CG pair.

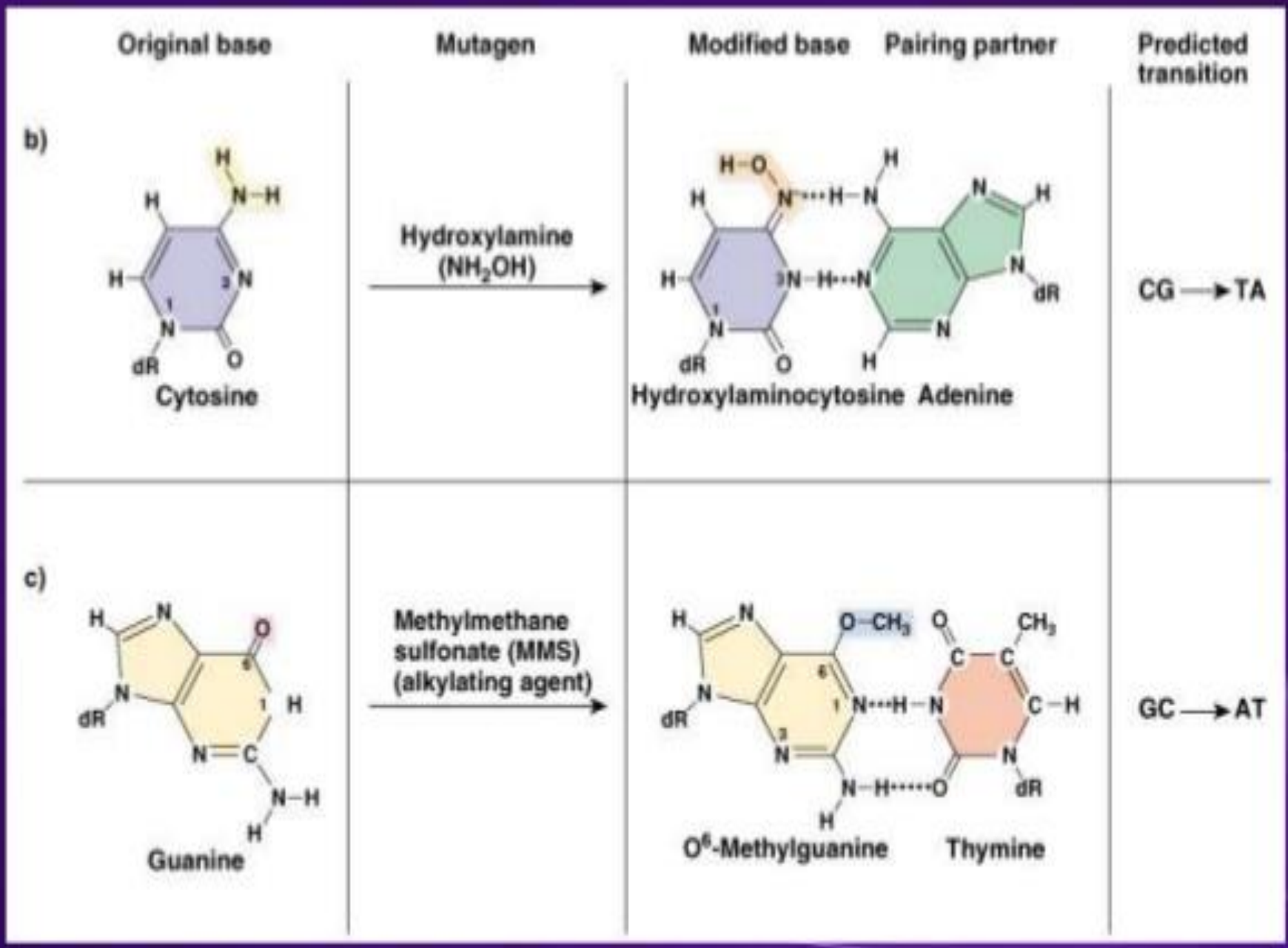


Thymine nucleoside



5-Bromouracil nucleoside

(b) The 5-bromouracil is used as an anticancer drug because it is mistaken for thymine by cellular enzymes but pairs with cytosine. In the next DNA replication, an AT pair becomes a GC pair.


Original base
Mutagen
Modified base
Pairing partner
Predicted transition
b)
Cytosine
Hydroxylamine (NH_2OH)
Hydroxylaminocytosine
Adenine
CG → TA
c)
Guanine
Methylmethane sulfonate (MMS) (alkylating agent)
O^6-Methylguanine
Thymine
GC → AT

b. Nitrous acid group

Oxidation the bases to remove amine group of Carbone atom 6

…..Adenine change to hypoxanthine to bind to cytosine instead of thymine

…..Cytosine change to uracile to bind to adenine instead of guanine

…..Guanine change to xanthine to bind to cytosine

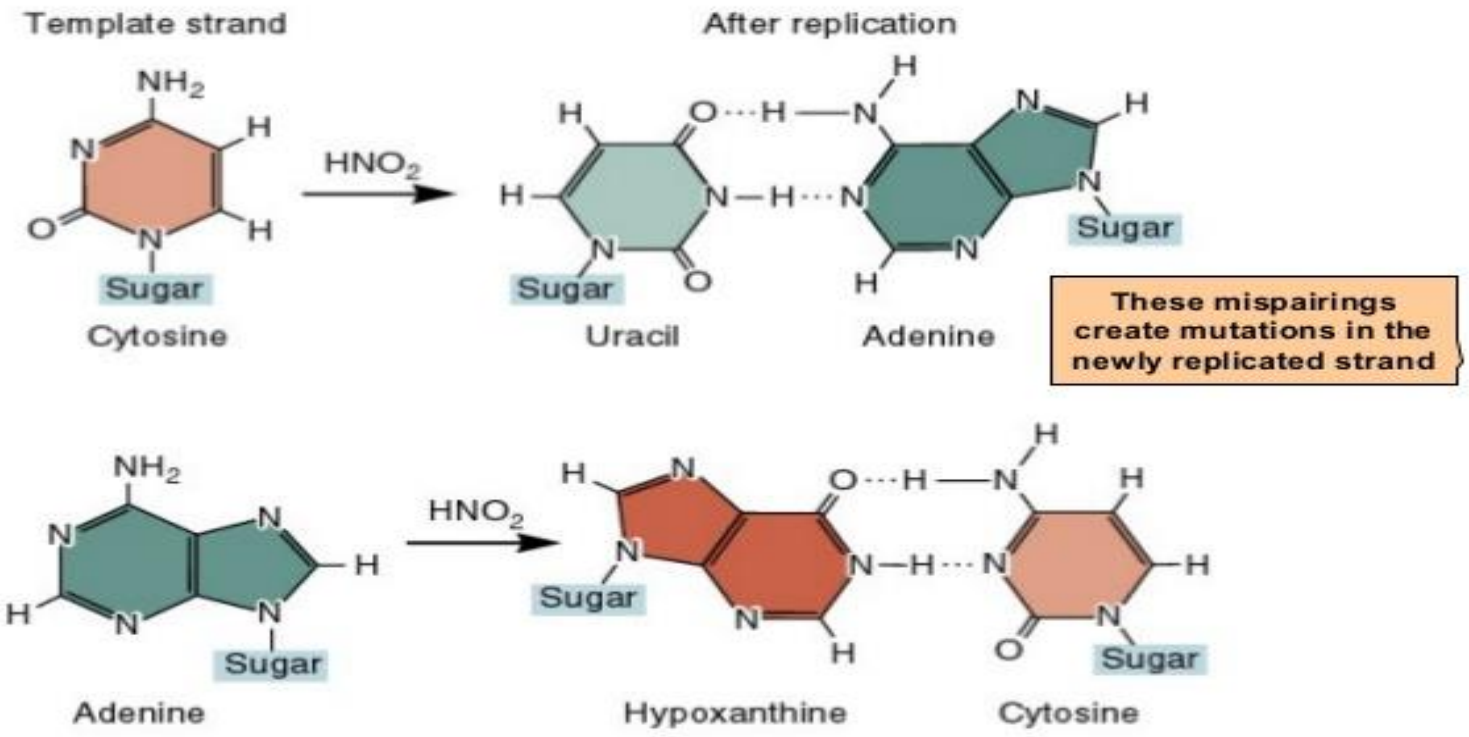
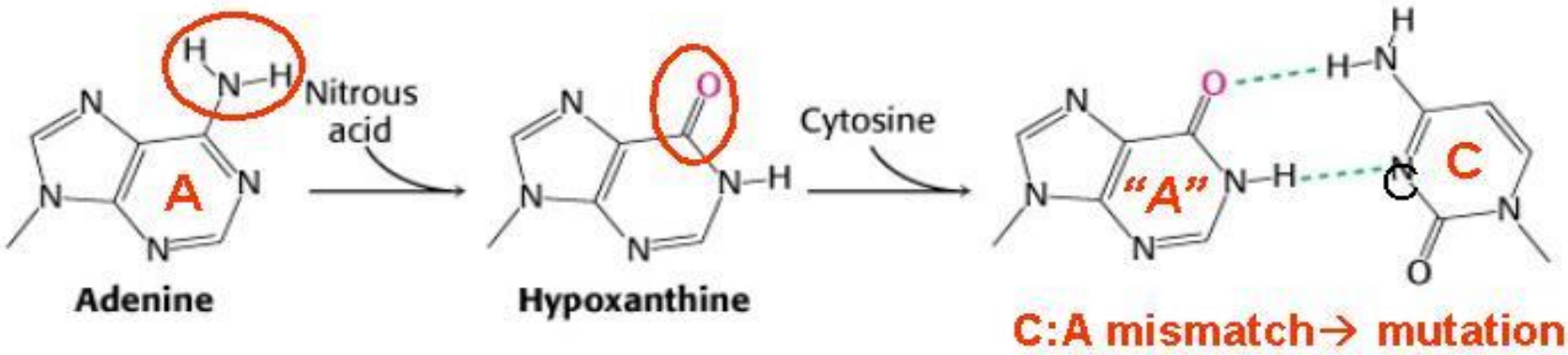


Figure 16.13 Mispairing of modified bases

Chemical Mutagen : Nitrous acid (HNO_2)

Deamination causes A:T to G:C transitions

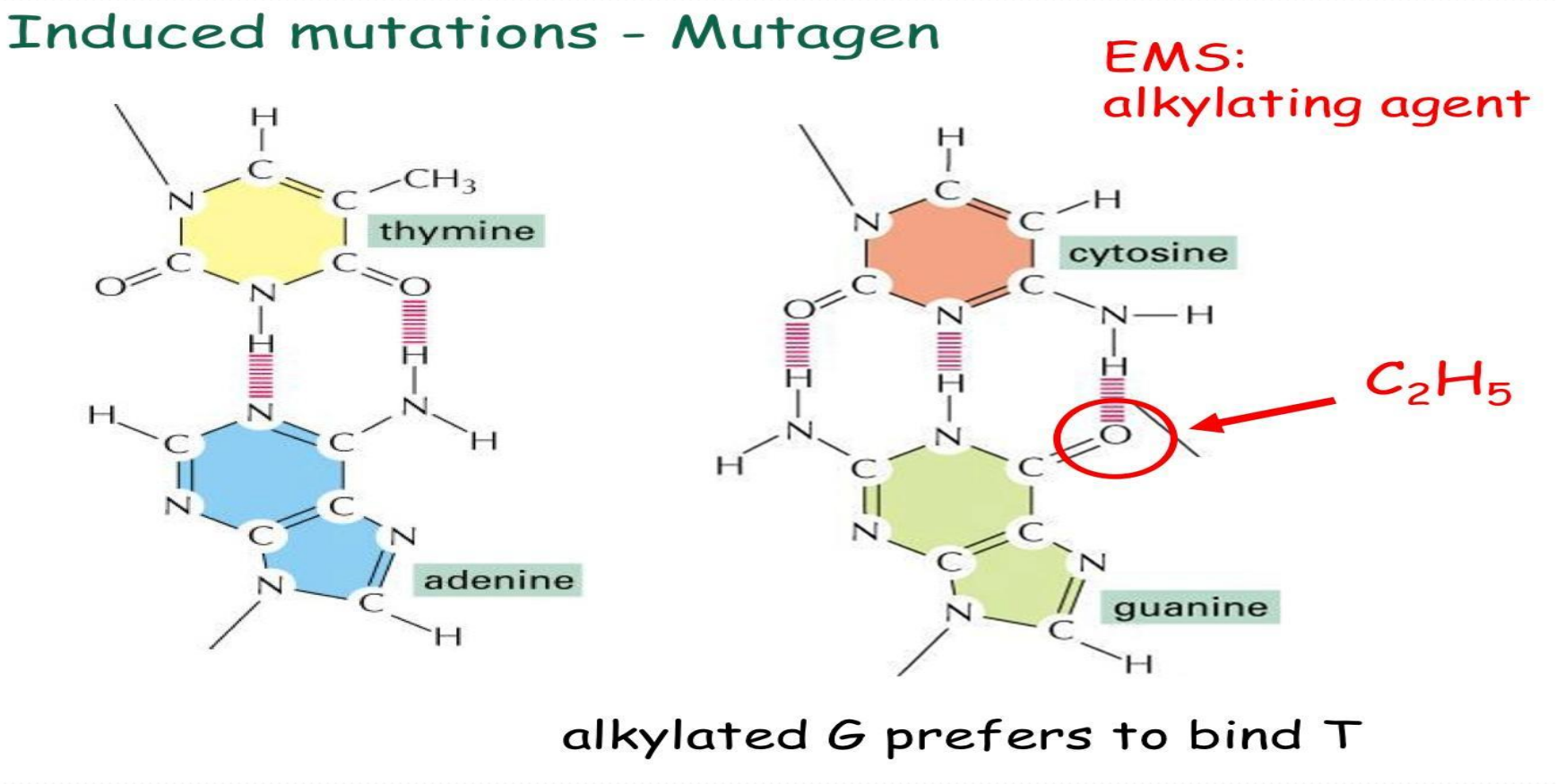


* HNO_2 also deaminates C to U: causes G:C to A:T transitions

c. Alkylating agents

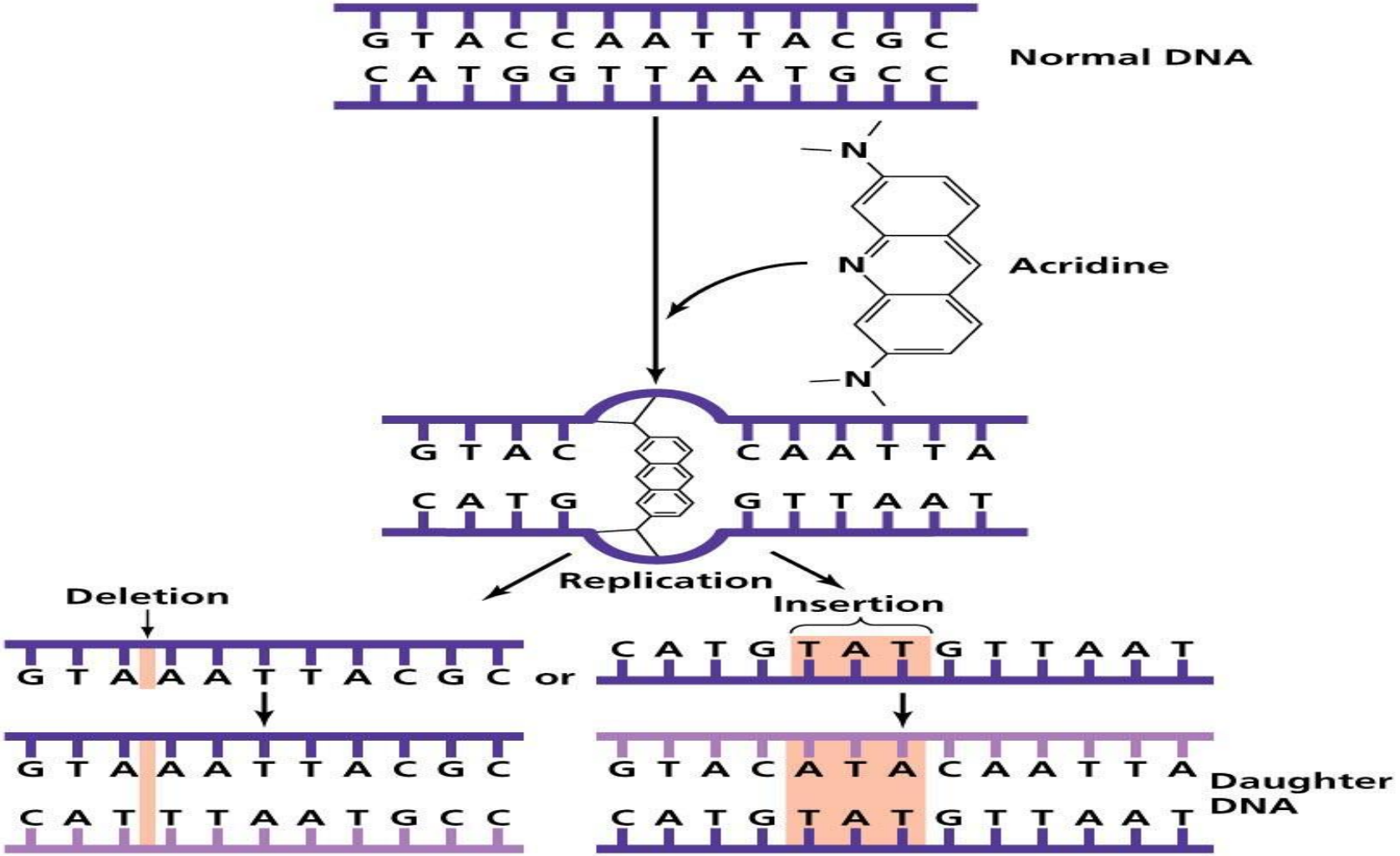
Mustard gas, nitrogen gas, ethyl ethan sulfonate-EES, ethyl methan sulfonate-EMS

Adding ethyl or methyl groups –CH3,CH2- to DNA base



d. Acridine dyes

Cause DNA instability, Framshift mutation



Chemical agents (III)

- **Intercalating agents or acridine dyes**

  * Proflavin, acridine orange, ICR-170, ICR-191
  * Ethidium bromide
  * แทรกระหว่างโครงสร้าง DNA → interfere DNA replication
  * Frameshift mutation