Physical And Chemical Mutagen: Mechanism & Examples

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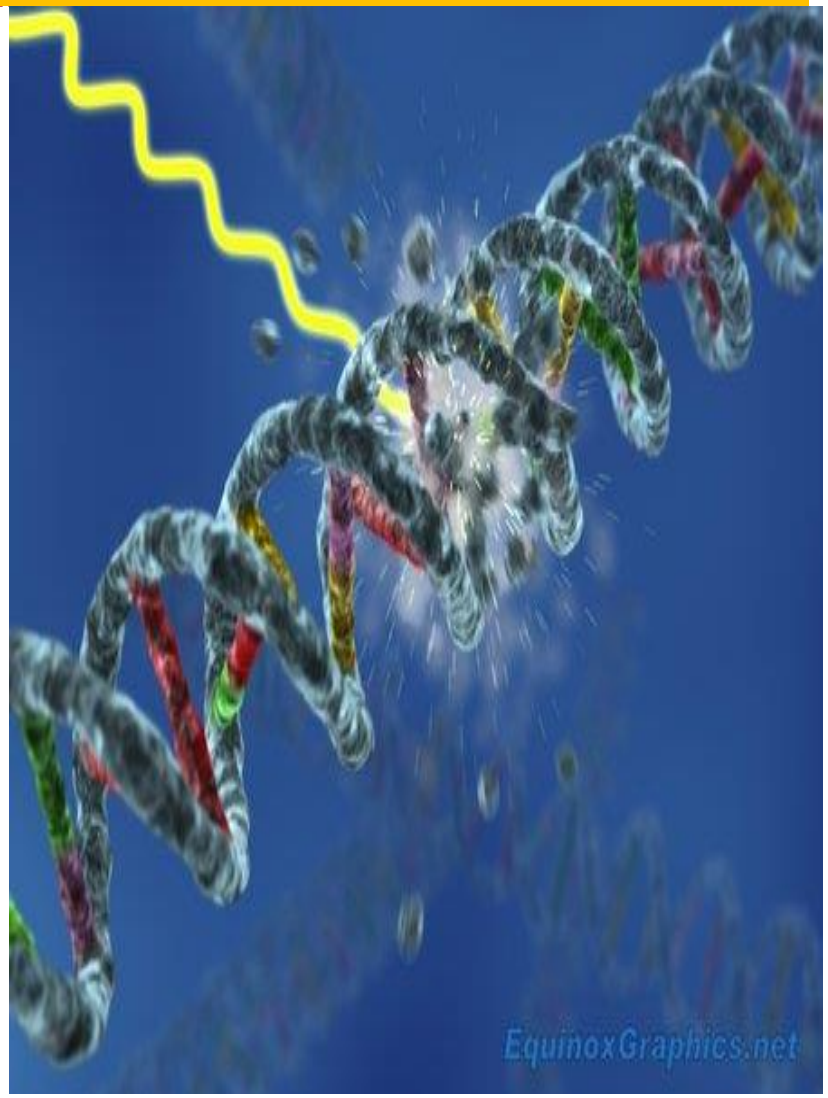
Mutagen

- A mutagen is any substance or agent that can cause a mutation, or change in the sequence or structure of DNA.



Mutation

- A heritable change in the base sequence of DNA
- Point mutation- change in a single base position
  - Additions
  - Deletions
  - Substitutions
    - Transitions
    - Transversions

} Frameshift mutations

- Multiple mutations

Consequences of Mutation

- Silent Mutation---base change, no amino acid change
- Neutral Mutation--- Base change resulting in aa change that does not affect protein function
  - EX. Apartic acid (D) →Glutamic acid (E)
- Missense mutation---altered codon, new aa with different chemical properties. Function affected.
- Nonsense mutation---base pair substitution results in a stop codon (and shorter polypeptide)
- Frameshift mutations—additions or deletions. Peptide may be longer or shorter.
- Sense mutation?

Other Terms

- Conditional Mutation—wild type function except under certain (*permissive*) conditions
  - Ex. Temperature sensitive mutants show mutant phenotype only at certain temperatures
- Leaky mutations— a missense amino acid change that reduces but doesn't eliminate protein function

Effects of mutagens

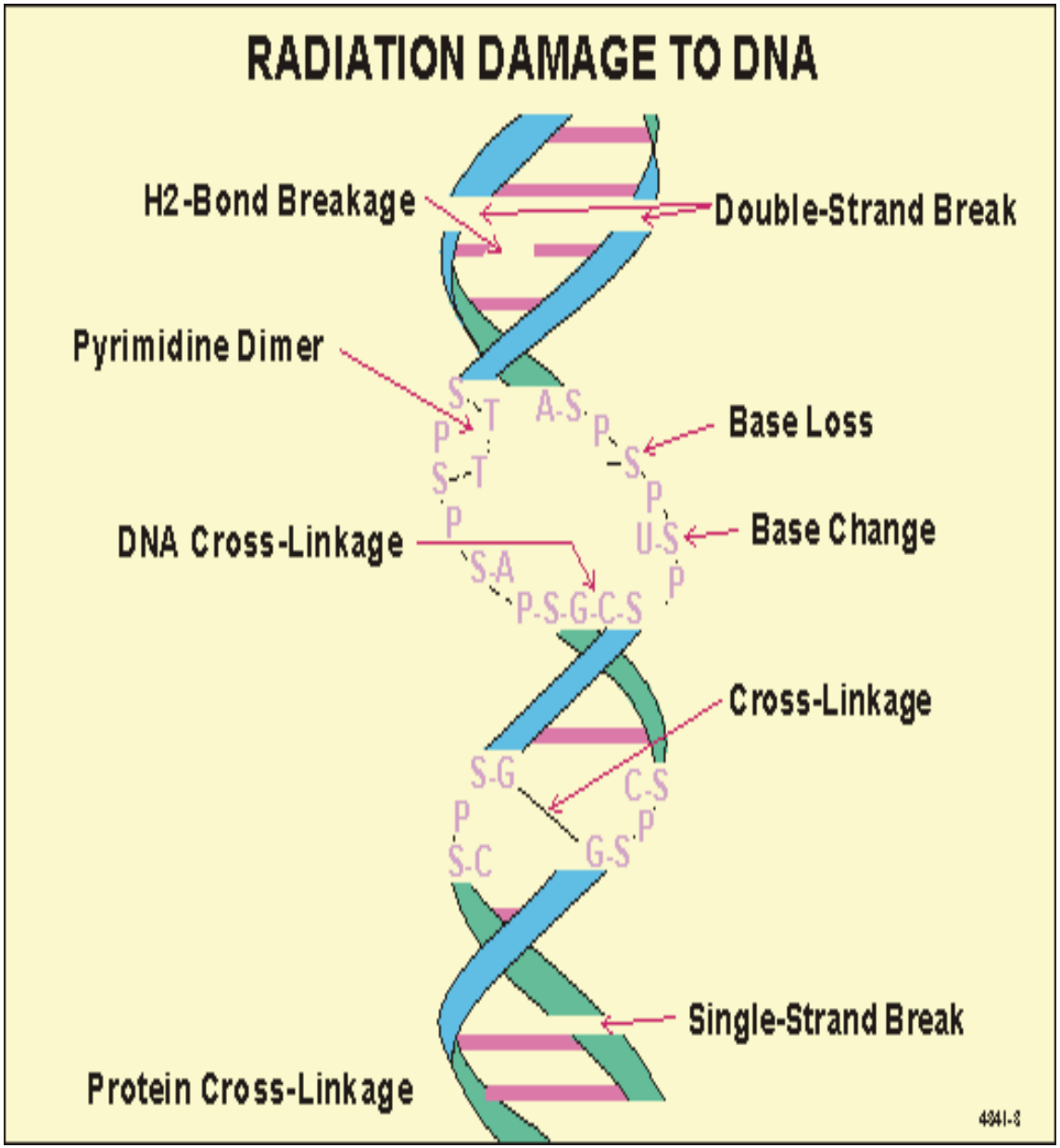
- Mutagens cause changes to the DNA that can affect the transcription and replication of the DNA, which in severe cases can lead to cell death.
- Powerful mutagens may result in chromosomal instability, causing chromosomal breakages and rearrangement of the chromosomes such as translocation, deletion, and inversion. Such mutagens are called clastogens.
- Some mutagens can cause aneuploidy and change the number of chromosomes in the cell.
- Accumulation of mutations may lead to cancer.
- Many mutagens are not mutagenic by themselves, but can form mutagenic metabolites through cellular processes. Such mutagens are called promutagens.

Mutagens & Carcinogens

- Carcinogens are agents that cause cancer.
- A mutagen is not the same as a carcinogen.
- While many mutagens are carcinogens as well, many others are not.
- The Ames test is a widely used test to screen chemicals used in foods or medications for mutagenic potential.

Types of mutagens

- Physical mutagen
- Chemical mutagen
- Biological mutagen



Physical Mutagens

Radiation was the first mutagenic agent known; its effects on genes were first reported in the 1920's.

Radiations are of two types.

I. EM radiations

II. Ionizing radiations

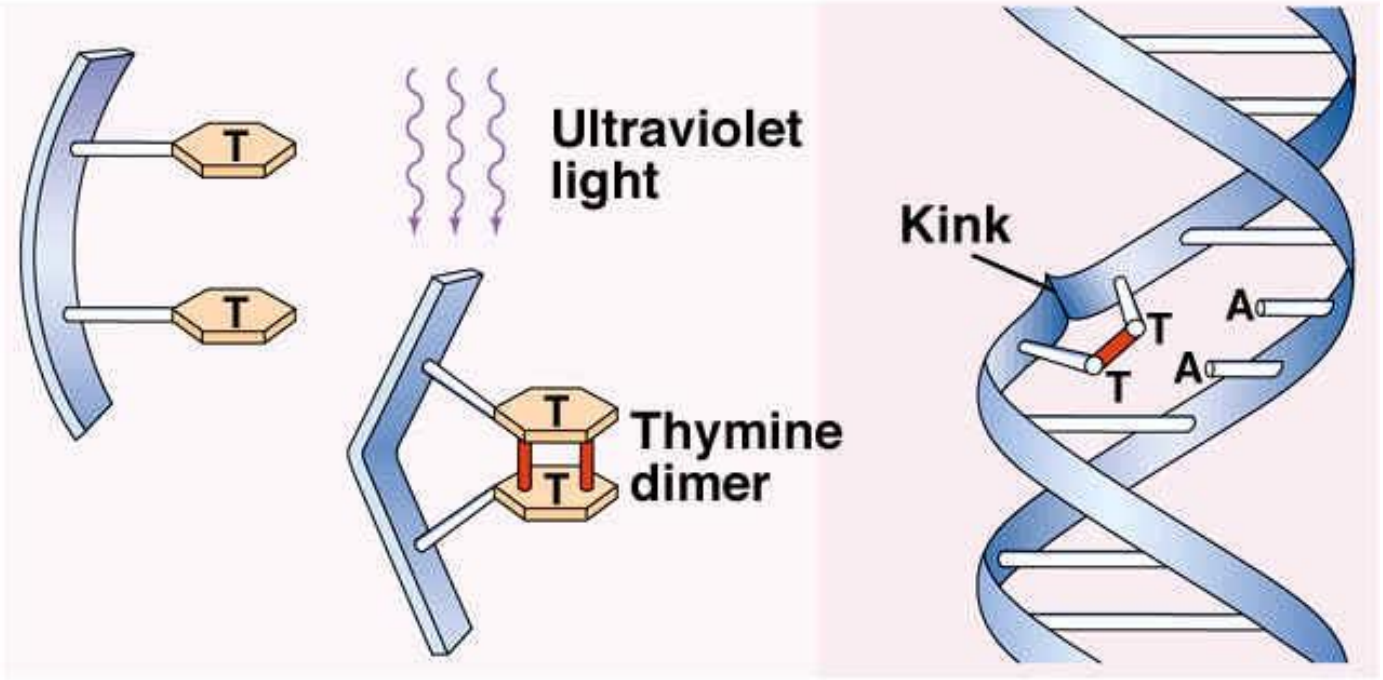
Physical Mutagen

- 1.Electromagnetic Radiations(Non ionizing):

- Visible light and other forms of radiation are all types of electromagnetic radiation (consists of electric and magnetic waves).
- The portion of light which is biologically significant is UV and higher energy radiation.
- UV radiation is not ionizing but can react with DNA and other biological molecules
- UV radiation: Cyclobutane pyrimidine dimers, Thymidine dimers (T-T)

Physical Mutagen

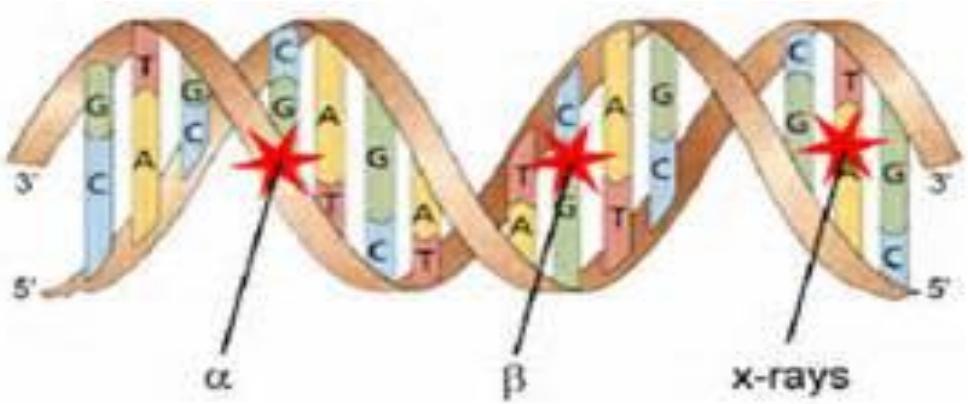
Pyrimidine Dimer



Physical Mutagen

- 2. Ionizing Radiatons:

- X- and gamma-rays.
- Produce reactive ions (charged atoms or molecules) which react with biological molecules.
- Damage base and sugar residues.
- This term also includes corpuscular radiation-
- streams of atomic and subatomic particles emitted by radioactive elements:
- these are of two types, alpha- and beta-particles



Physical Mutagen

- The rapidly dividing cell types (blood cell-forming areas of bone marrow, gastrointestinal tract lining) are the most affected by ionizing radiation.
- The severity of the effects depends upon the dose received.
- **Ionizing** radiation produces a range of effects on DNA both through free radical effects and direct action:
  - -breaks in one or both
  - -damage to/loss of bases (mutations)
  - -crosslinking of DNA to itself or proteins

Chemical Mutagens

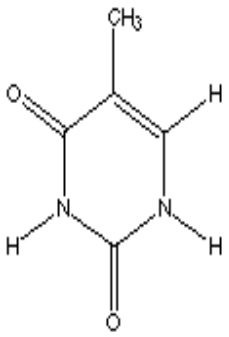
- The first report of mutagenic action of a chemical was in 1942.
- There are many hundreds of known chemical mutagens.
- Chemical mutagens are categorized into four general groups, based on the mechanism by which they interact with DNA.

1. Base analogs
2. Base altering chemicals
3. Intercalating agents
4. Agents altering DNA structures

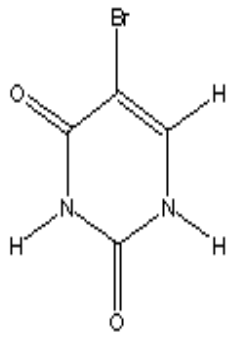
Chemical Mutagens

I.Base analogs:

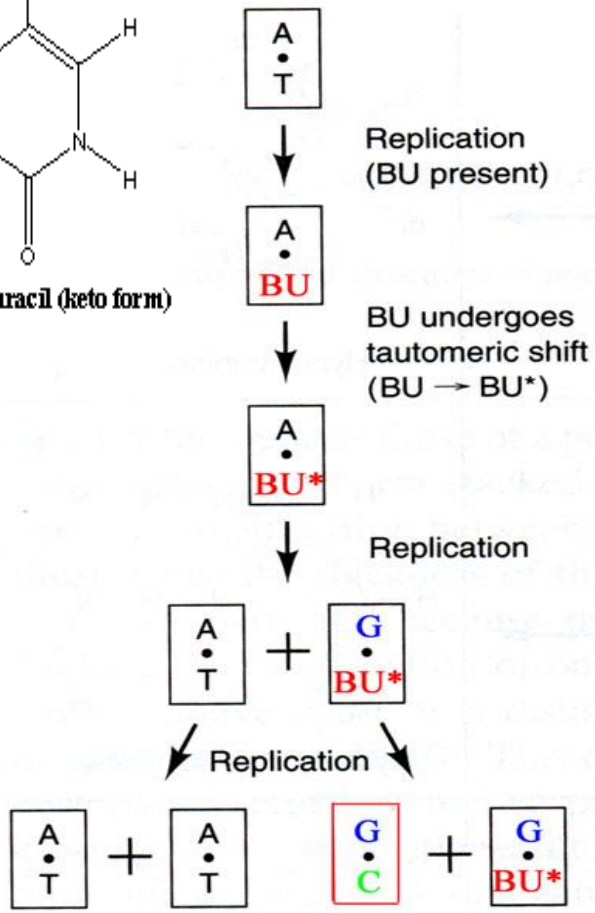
- These chemicals structurally resemble purines and pyrimidines and may be incorporated into DNA in place of the normal bases during DNA replication:
- **bromouracil** (BU)-- artificially created compound extensively used in research.
- Resembles thymine (has Br atom instead of methyl group) and will be incorporated into DNA and pair with A like thymine. It has a higher likelihood for tautomerization to the enol form (BU*)



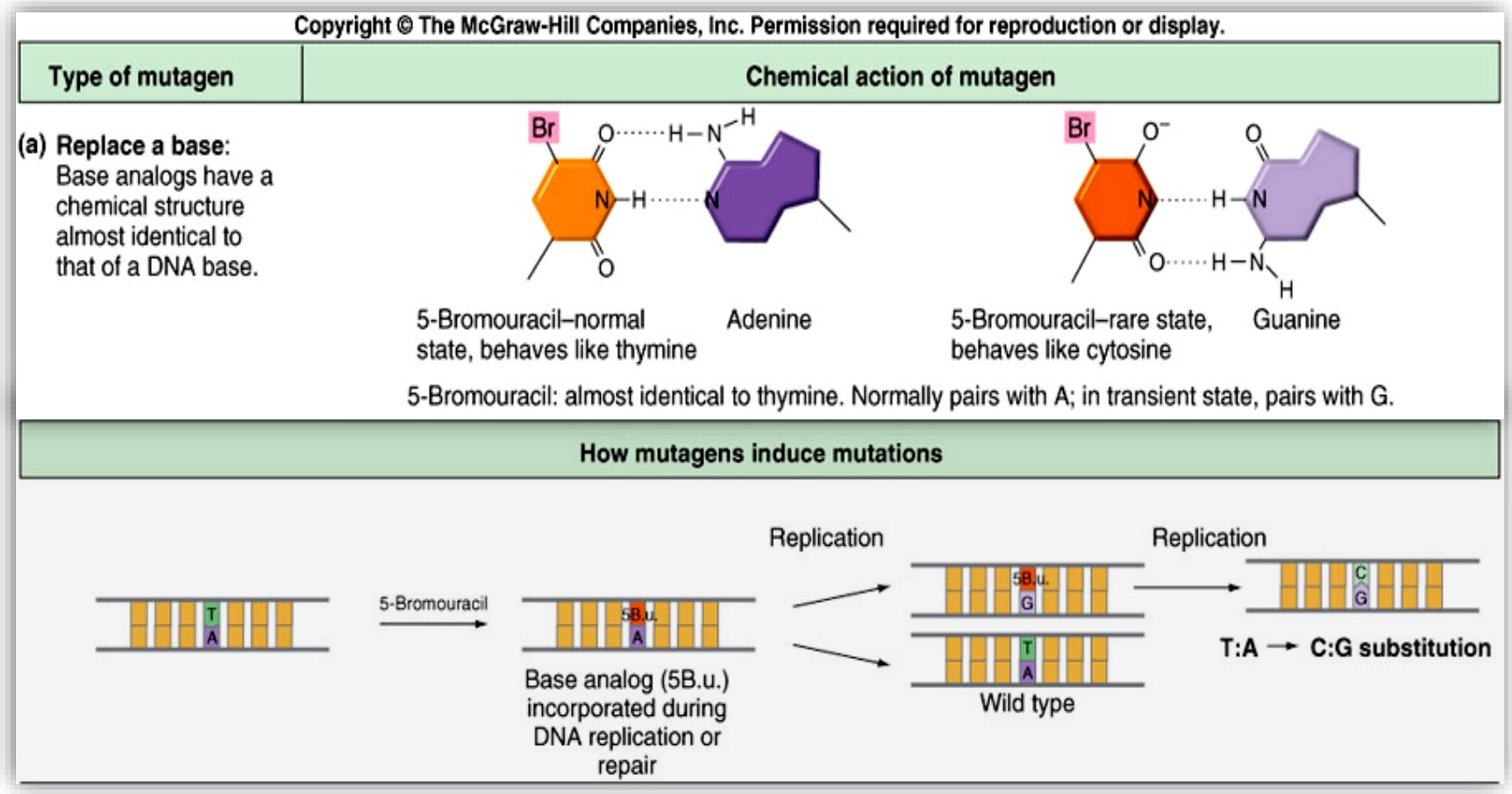
Thymine



5-Bromouracil (keto form)

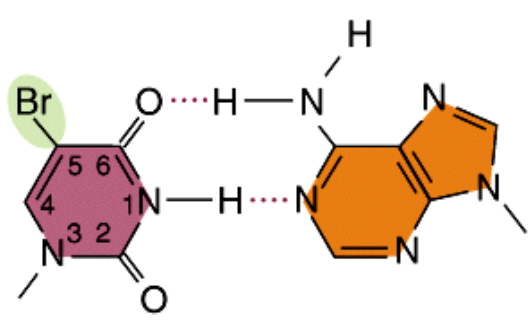


Chemical Mutagens



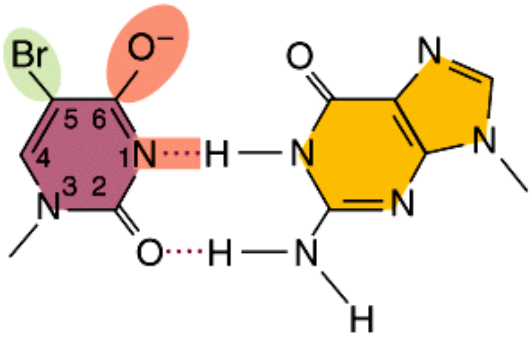
Exposure to Bases Analogs

- Base analogs—substances that are similar to and can substitute for standard bases
- Examples—AZT, 5-bromouracil (5-BU) and 2-aminopurine (2-AP)



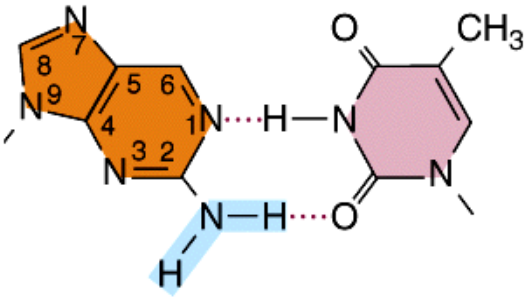
Common keto form of 5-BU

Adenine



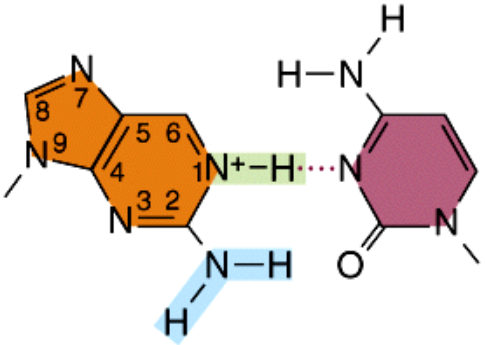
Ionized form of 5-BU

Guanine



2-AP

Thymine



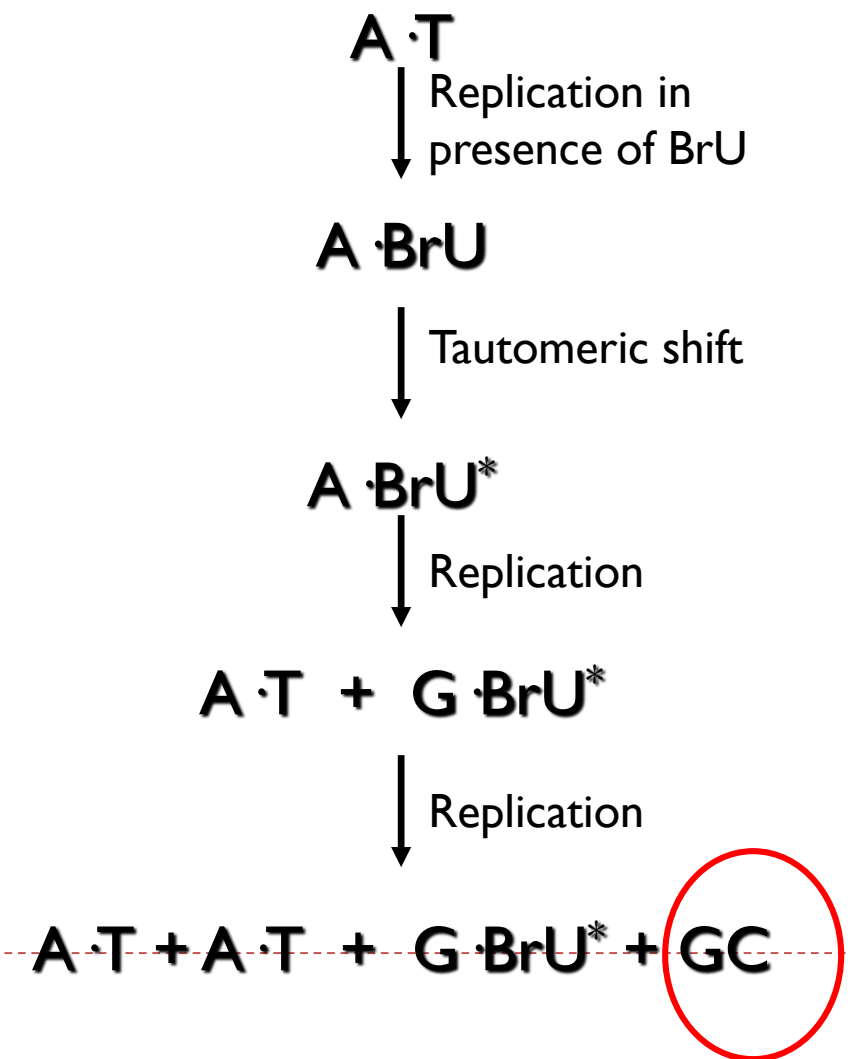
Protonated 2-AP

Cytosine

5 Bromouracil

- The Problem: 5 bromouracil assumes the enol form at a much higher frequency than T
- ∴ if it replaces T, will probably get a mutation due to tautomerization during replication
- Result: A ·T → G ·C

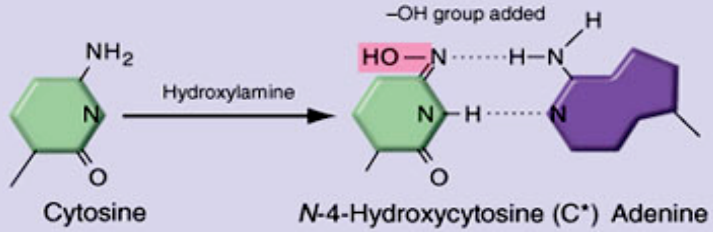
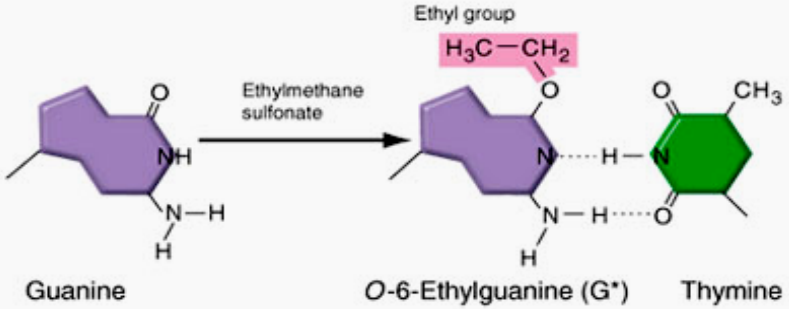
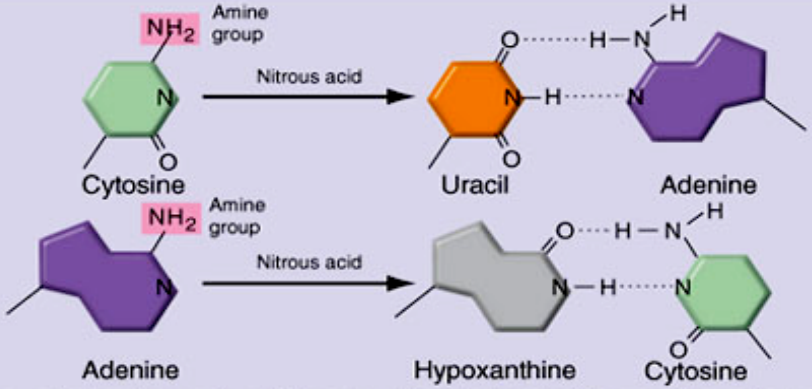
THE PROCESS



Chemical Mutagens

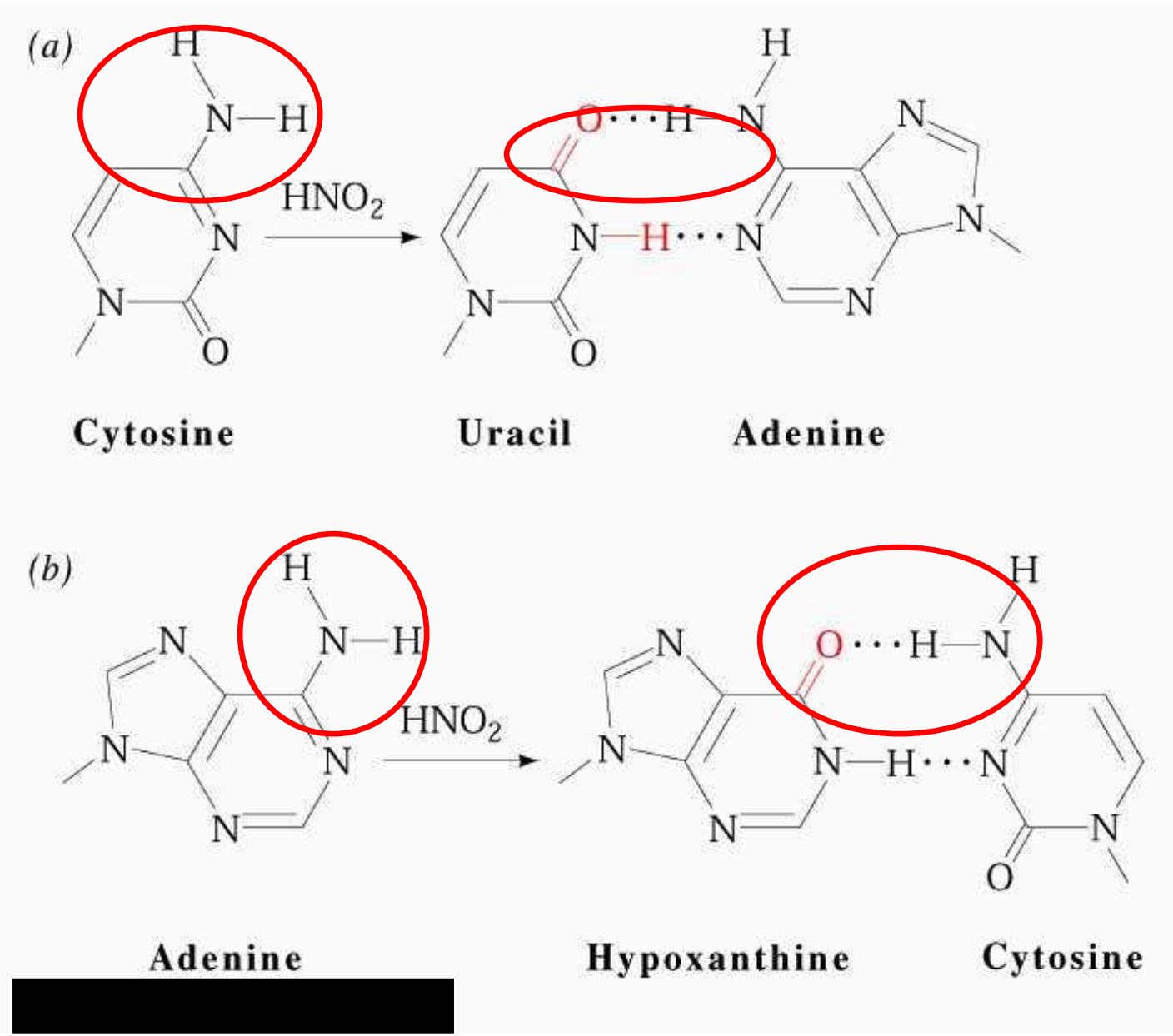
2.Chemicals which alter structure and pairing properties of bases:

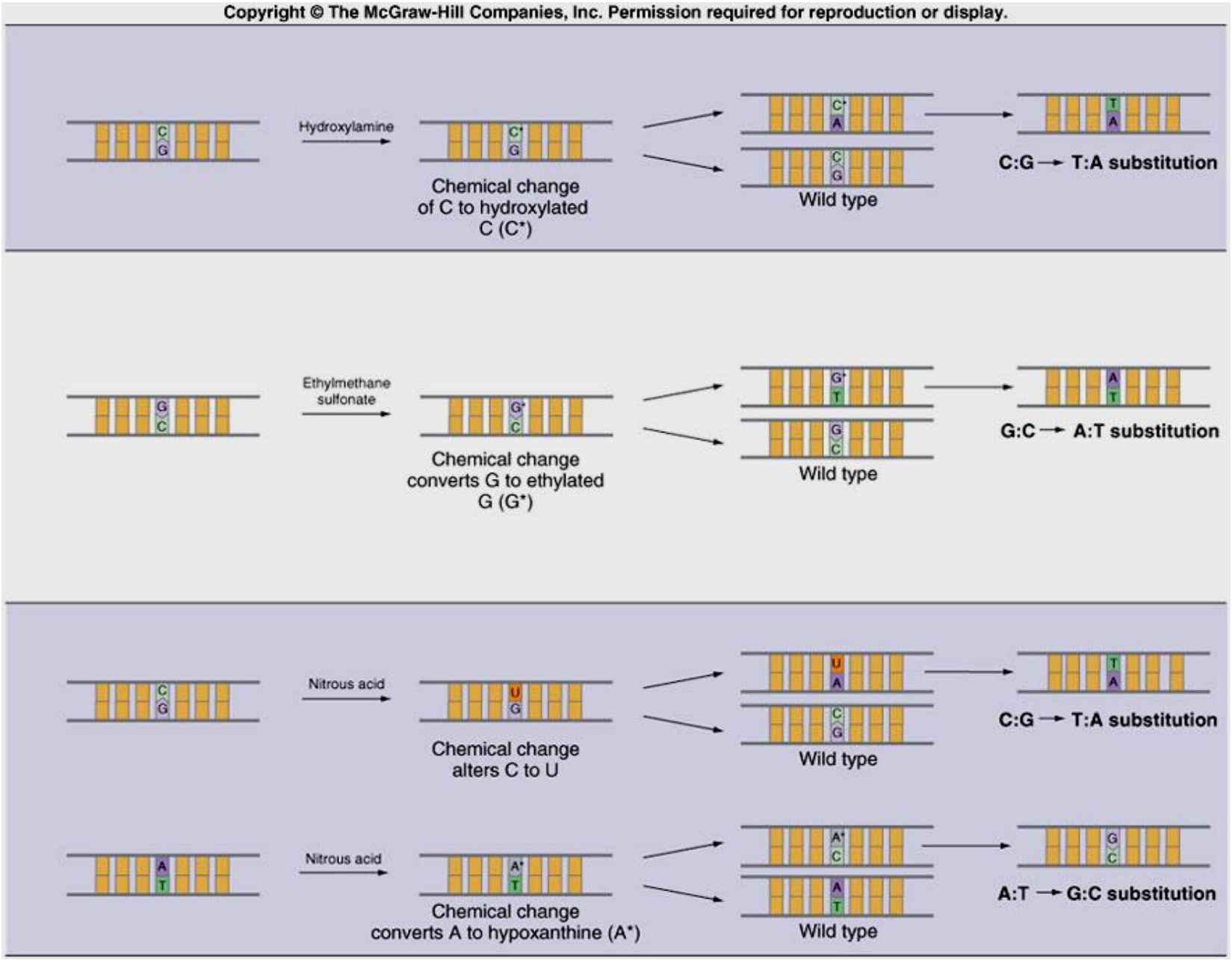
- It includes:
- hydroxylating agent (add OH-group to C)
- alkylating agent such as E!MS (ethylmethane sulfonate); chemical mutagens that react with bases and add methyl or ethyl groups
- deaminating agent such as nitrous acid; -formed by digestion of nitrites (preservatives) in foods. It causes C to U, C to T, and A to hypoxanthine deaminations. Deamination by nitrous acid, causes transitions.

Type of mutagen	Chemical action of mutagen
(b) Alter base structure and properties: *Hydroxylating agents*: add a hydroxyl (–OH) group	 Hydroxylamine adds –OH to cytosine; with the –OH, hydroxylated C now pairs with A instead of G.
Alkylating agents: add ethyl ($-CH_2-CH_3$) or methyl ($-CH_3$) groups	 Ethylmethane sulfonate adds an ethyl group to guanine or thymine. Modified G pairs with T above, and modified T pairs with G (not shown).
Deaminating agents: remove amine ($-NH_2$) groups	 Nitrous acid modifies cytosine to uracil, which pairs with A instead of G; modifies adenine to hypoxanthine, a base that pairs with C instead of T.

Deamination of C and A

- C→U
  - 3 H-bonds w/G→2 H-bonds w/A
- A→Hypo-xanthine
  - 2 H-bonds w/G→3 H-bonds w/C





Chemical Mutagens

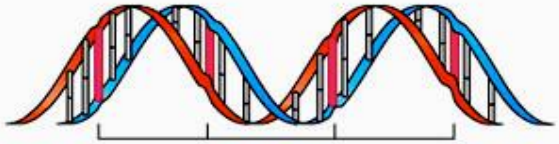
3.Intercalating agents

- acridine orange, proflavin, ethidium bromide
- All are flat, multiple ring molecules which interact with bases of DNA and insert between them.
- This insertion causes a "stretching" of the DNA duplex and the DNA polymerase is "fooled" into inserting an extra base opposite an intercalated molecule.
- The result is that intercalating agents cause frameshifts.

Chemical Mutagens

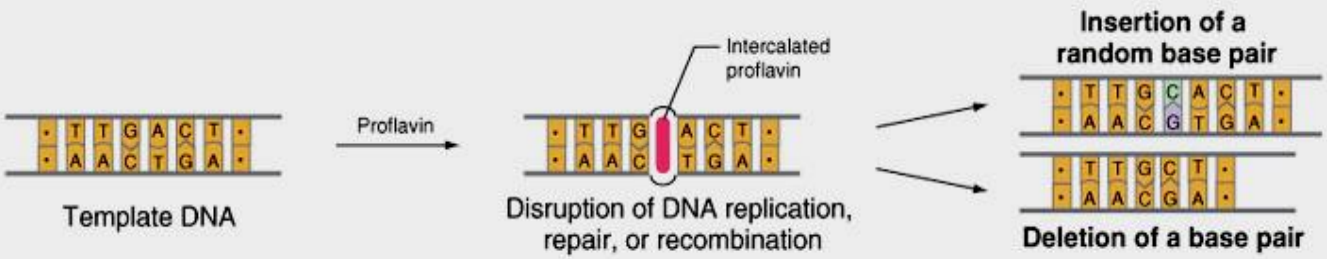
Type of mutagen	Chemical action of mutagen
(c) **Insert between bases:** Intercalating agents	

Proflavin



Intercalated proflavin molecules

Proflavin intercalates into the double helix. This disrupts DNA metabolism, eventually resulting in deletion or addition of a base pair.



Chemical Mutagens

4.Agents altering DNA structure

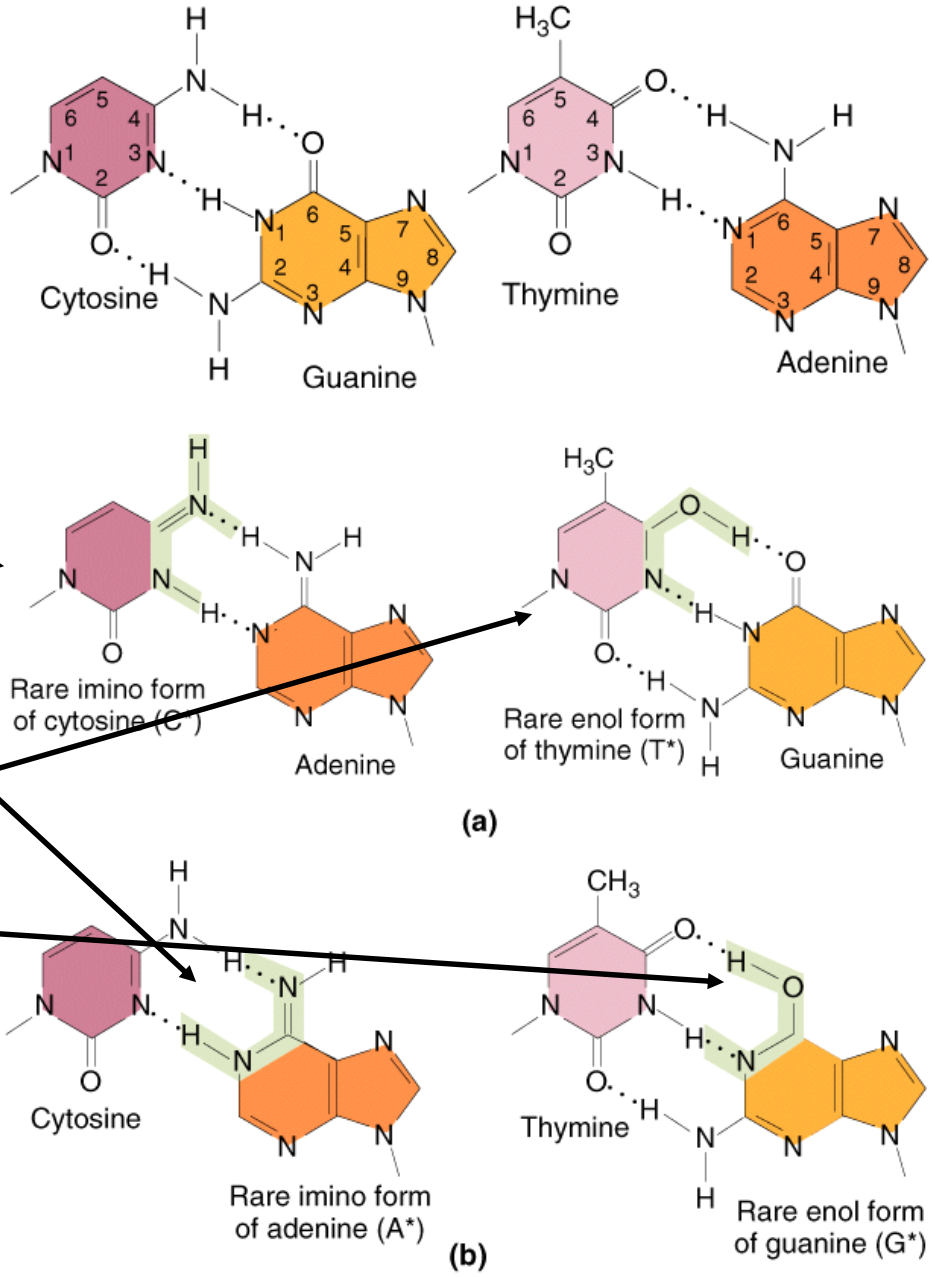
- This is a "catch-all" category which includes a variety of different kinds of agents. These may be:
- --large molecules which bind to bases in DNA and cause them to be noncoding--referred as "bulky" lesions.
- --agents causing intra- and inter-strand crosslinks (eg. **psoralens**--found in some vegetables and used in treatments of some skin conditions)
- --chemicals causing DNA strand breaks (eg. **peroxides**)

Tautomers and Mutation

Normal base pairing

Rare imino forms of adenine and cytosine

Rare enol forms of thymine and guanine



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