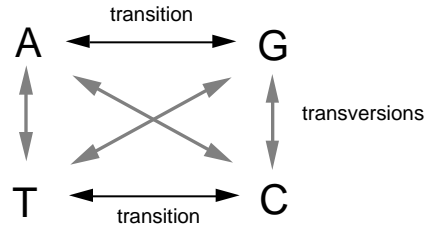


## Mutations and mutagens

## Transitions and transversions



## Causes of transitions

Agent (mutagen, etc.)	Example	Result
Nucleotide analogs	BrdUTP	transitions, e.g. AT to GC
Oxidizing agents	nitrous acid	transitions, e.g. CG to TA
Alkylating agents	nitrosoguanidine	transitions, e.g. GC to AT

## Causes of transversions

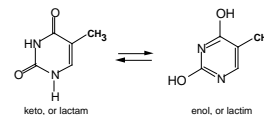
Agent	Example
Misincorporation: Altered DNA Pol III	<i>mutD=dnaQ</i> ; subunit of DNA PolIII
<b>Result</b>	transitions, transversions and frameshifts in mutant strains

## Errors in Replication

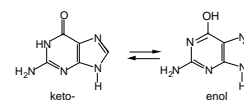
- **Origin:**
  - spontaneous (naturally occurring) or forced (mutagenesis)
- **Source:**
  - Incorporate the wrong base
    - base or nucleoside analogs
    - chemical modification of nucleosides
  - Slippage during replication
    - frameshift mutagens such as EtBr
  - Breaks in phosphodiester backbone
    - ionizing radiation
  - Blockage in replication
    - pyrimidine dimers induced by UV irradiation

## Keto and enol tautomers of bases

### Tautomers of thymine

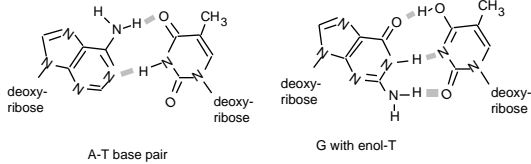


### Tautomers of guanine

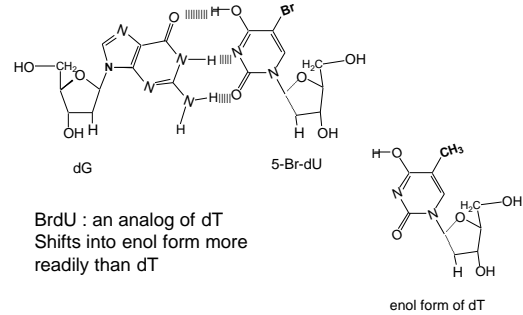


**Enol conformation : causes incorporation of the wrong base**

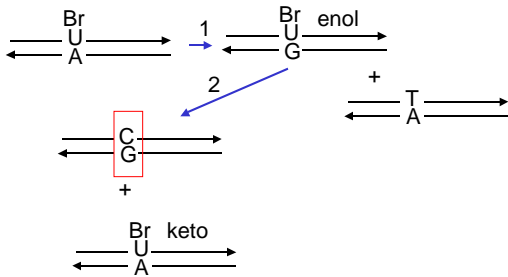
- Nucleotides in *enol* tautomer can pair with the "wrong" base



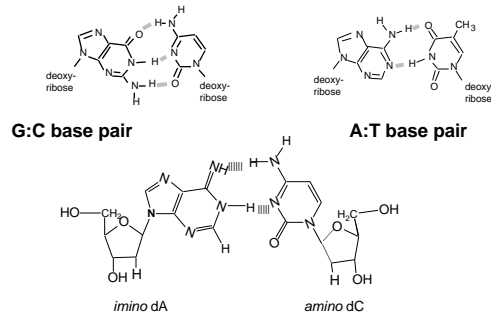
**Nucleoside analogs alter base pairing**



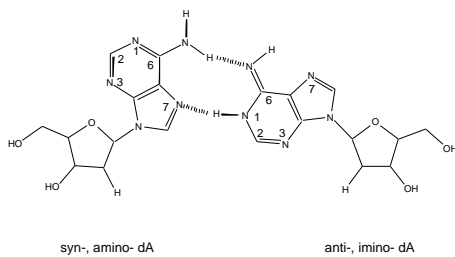
**Replication of a misincorporated nucleotide will leave a mutation**



**imino-dA paired with amino-dC**



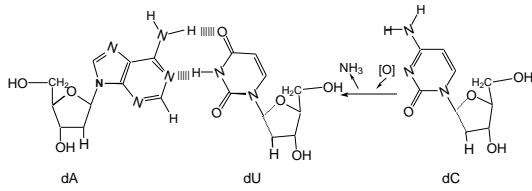
**syn-, amino-dA paired with anti-, imino-dA**



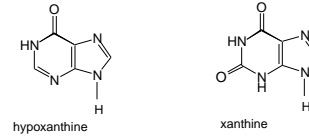
**Chemical modifications**

- Also alter base-pairing**
- Oxidative deamination**
  - Nitrous acid ( $\text{HNO}_2$ ) causes oxidation of C to U
  - C to U also occurs spontaneously:
    - 1 in 1000 C's would change to U during a human lifetime, if not repaired
- Alkylating agents**
  - transfer methyl group to guanine

### Oxidation of dC to dU allows pairing with dA

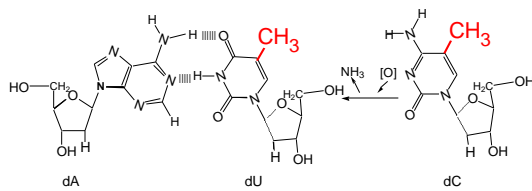


### Oxidation products of dA and dG



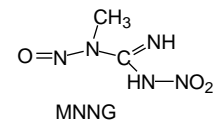
Either can pair with dC.

### 5-methyl-C is deaminated to dU --> T



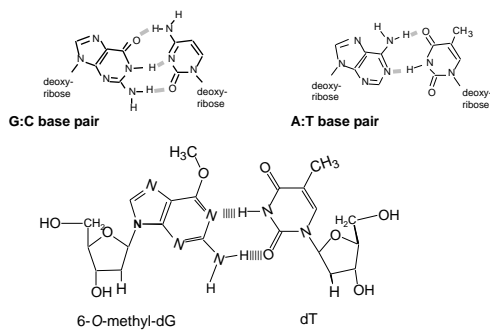
- C to T transitions at CpG are the most common mutations in humans.

### Alkylating agents

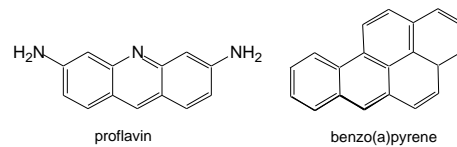


- Nitrosoguanidine derivatives, e.g. MNNG
- Cause methylation of G at O6 position and A at N3
- Addition of the bulky group distorts the helix and causes mispairing

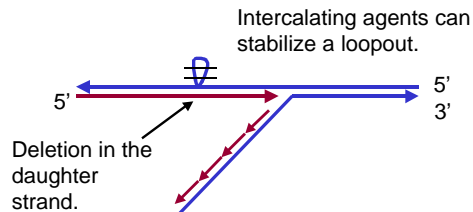
### 6-O-methyl G pairs with T



### Intercalating agents are planar aromatic rings



### Slippage during replication



### Ionizing radiation causes single-strand breaks

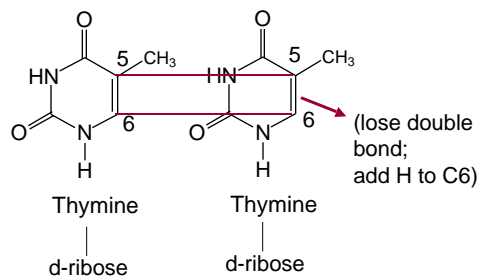
- X-rays,  $\gamma$ -rays, particles (electrons)
- cause single-strand breaks
- directly break phosphodiester backbone
- break imidazole ring of purines
  - subsequent removal by glycosylase generates an AP (apurinic or apyrimidinic) site

### UV radiation generates pyrimidine dimers

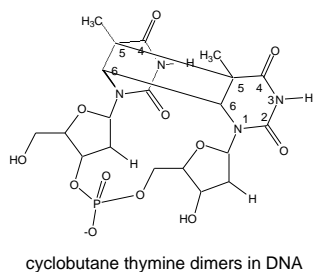
#### Ultraviolet radiation (260 nm)

- a) Causes pyrimidine dimers between adjacent pyrimidines. The dimers can be of two types :
- 1) The major product is a cyclobutane-containing thymine dimer (between C5 and C6 of adjacent T's)
  - 2) The "6-4" photoproduct is also formed, and this causes the major mutagenic effect
- b) The pyrimidine dimers cause a **distortion** in the DNA double helix
- c) The dimers **block** replication and transcription

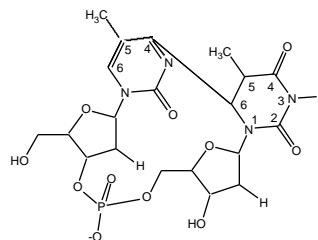
### Structure of pyrimidine dimers



### Another view of cyclobutane pyrimidine dimers in DNA



### 6-4 photoproducts of thymine dimers



## Causes of strand breaks

Agent	Example	Result
Frameshift mutagens	benzpyrene	deletions (short)
Ionizing radiation	X-rays, -rays	breaks and deletions (large)
UV	UV, 260 nm	Y-dimers block replication