A combined approach to cancer: 4-thiothymidine analogues as UVA-assisted anti-cancer drugs

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Outline

- **Background**
  - **Cancer and Cancer therapies**
  - **DNA and DNA damage**
- **Research Results**
  - **Chemicals and Light**
  - **Thionucleosides as anticancer drugs**
  - **Mechanisms for photo-chemistry**

Background on Cancer

- **What ?**
- **Who (Where) and When ?**
- **Why and How ?**

What is Cancer ?

Cancer develops when cells in a part of the body begin to grow out of control.

Although there are many kinds of cancer, they all start because of out-of-control growth of abnormal cells.

(American Cancer Society, http://www.cancer.org/)

Who (Where) and When ?

Cancer is now the major killer particularly in developed countries. In Britain, the lifetime risk of developing cancer is more than one in three.

http://www.cancerresearchuk.org/aboutcancer

Why and How ?

- **All cancers are caused by damage to the genes**
- **Genes are a fragment of DNA**
- **The molecular trigger for cancer is**

DNA damage

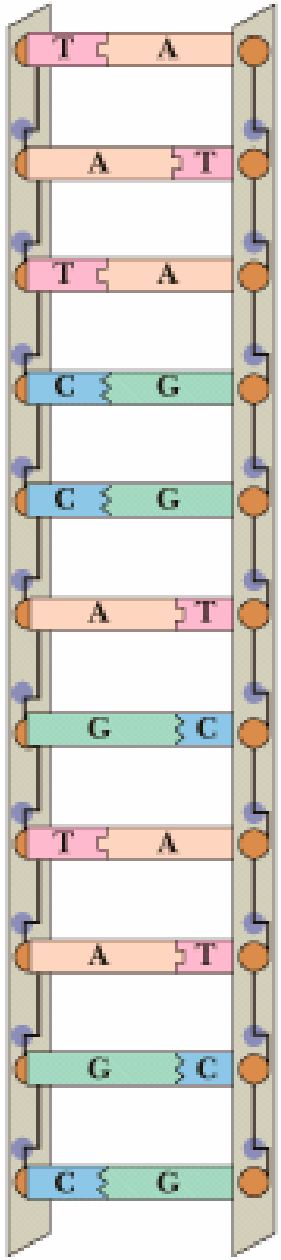
DNA ?

- **DNA Biological Functions**
  - **Produce DNA (replication)**
  - **Produce protein (translation)**
- **DNA Chemical Structures**
  - **Double stranded structure**
  - **Bases encoding genetic info**

(a) Ladder

Base-pair spacing

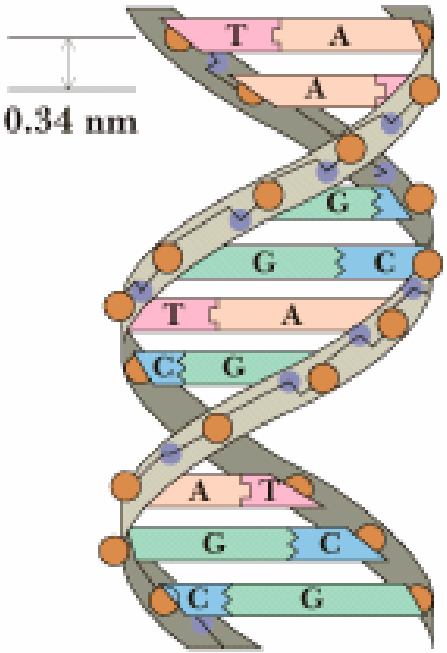
0.6 nm



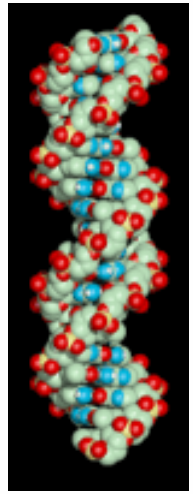
(b) Helix

Base-pair spacing

0.34 nm



Pitch length 3.4 nm



DNA structure: Double helix

The original model of DNA by Francis Crick and James Watson

We all know

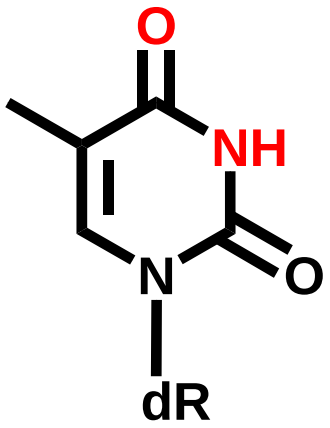
English is a **26**-letter language.

We now know

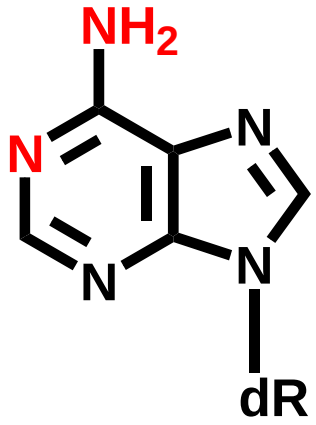
DNA is a **4**-letter language.

These 4 letters are A, G, C and T.

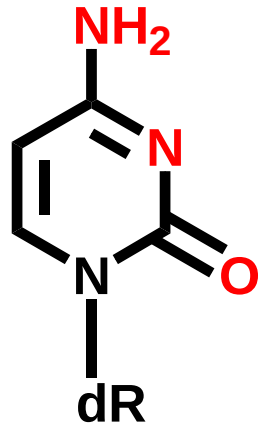
Structures of DNA Bases:



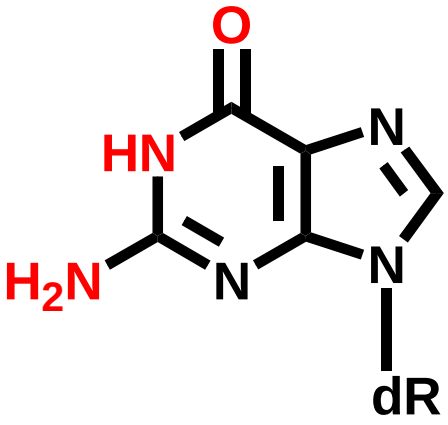
Thymine



Adenine



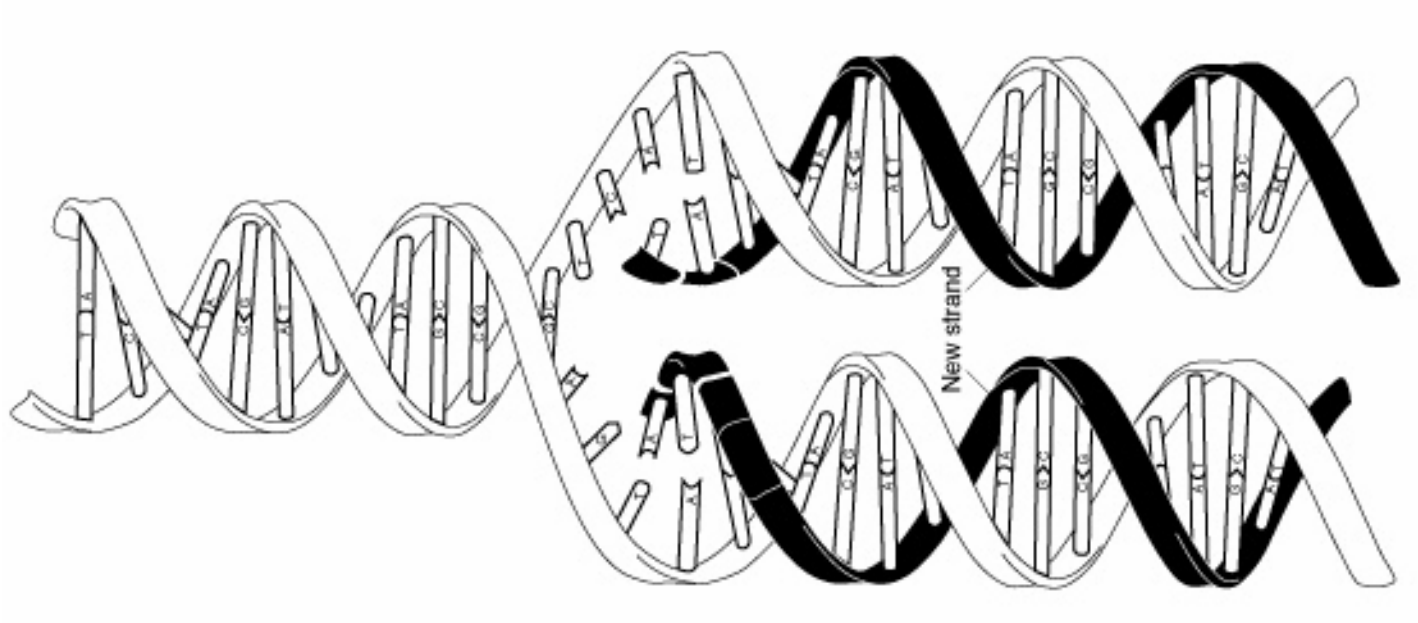
Cytosine



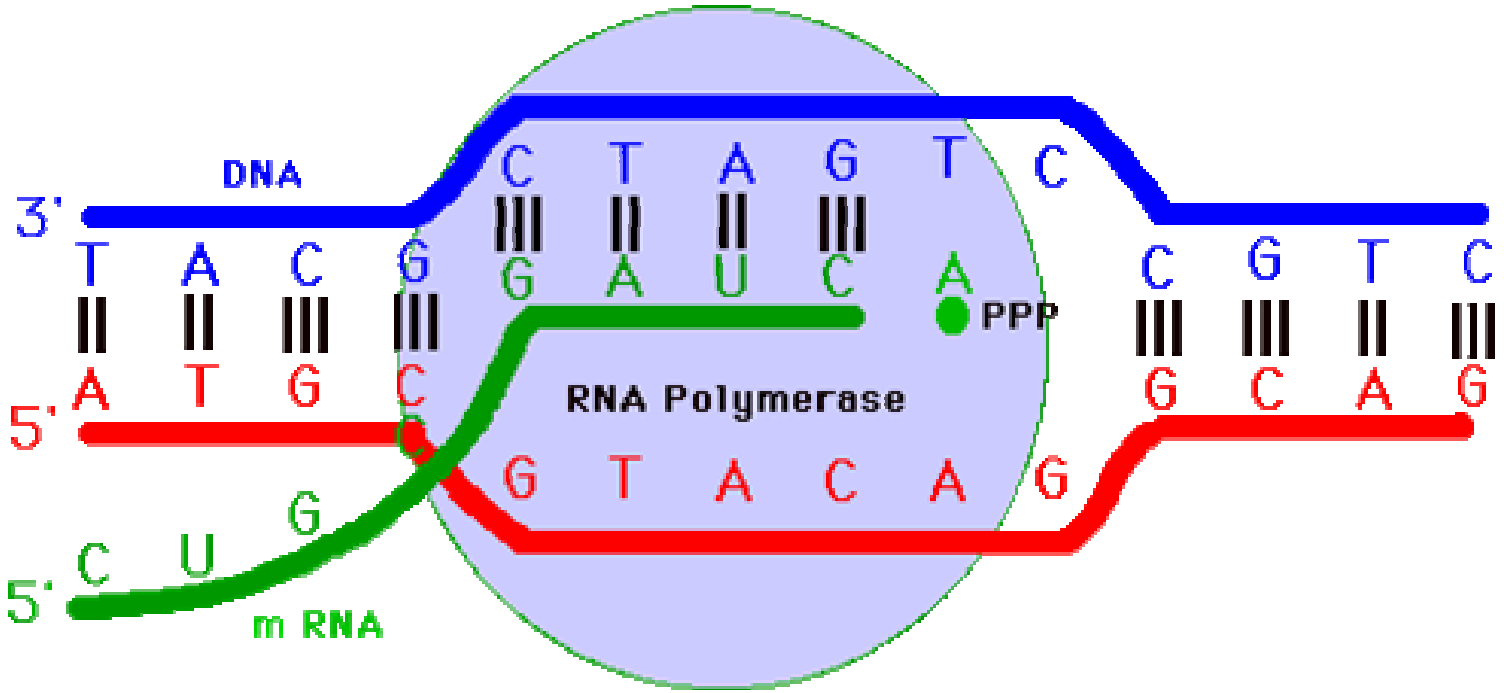
Guanine

"Watson" (Pyrimidine) Family	"Crick" (Purine) Family
Tina	**A**ndy
Clark	**G**eorgia

Biological Function (1)
DNA Replication



Function (2): Making Proteins
DNA to RNA to Protein



In this case, DNA = Gene

DNA Damages

- **Chemical damage**
  - **E.g. by small chemicals (drugs)**
- **Biochemical damages**
  - **E.g. DNA rearrangement (induced by proteins)**
- **Physical damages**
  - **E.g. X-ray, UV Radiation**

Cancer Therapies

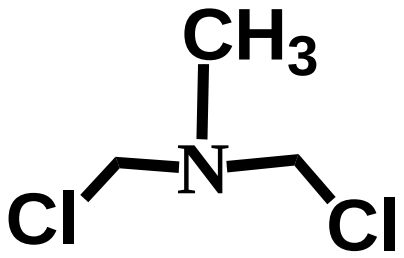
- **Ideal Therapy: by Repair Approach?**
  - **such as gene therapy (a future matter ?)**

- **Current Therapy: by Damage Approach**
  - **Surgery (therapy) (usually too late !!)**
  - **Chemotherapy**
  - **Radiotherapy**

Chemotherapy: high toxicity

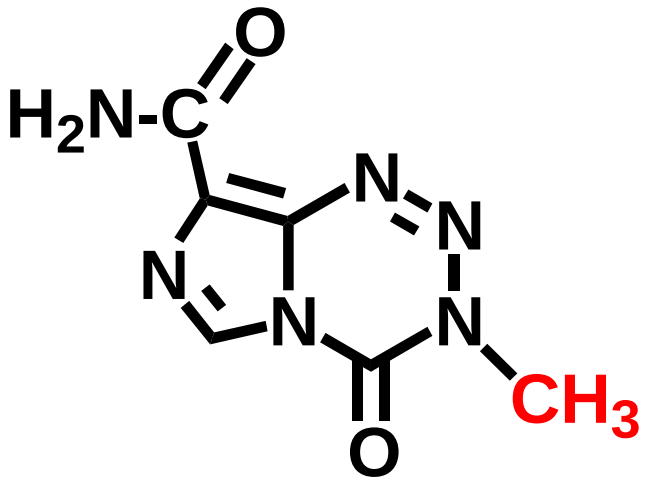
An old drug:

Nitrogen Mustard

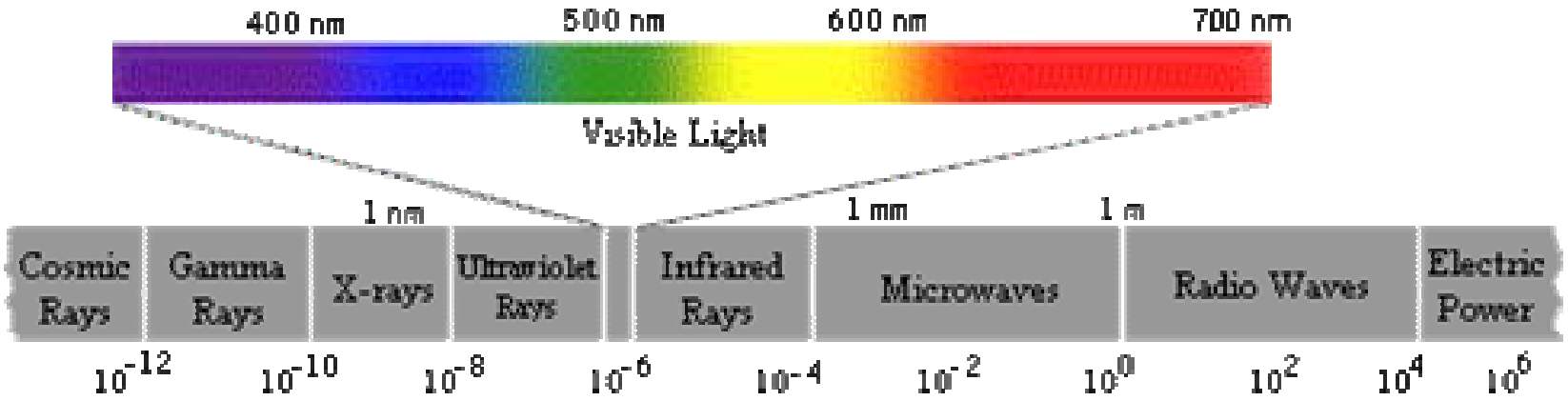


A newer drug:

Temozolomide



Radiotherapy : high energy



Energy and Wavelength

($E = h\upsilon = hc/\lambda$)

The Bad things with
Chemotherapy and Radiotherapy

These two therapies will kill both cancerous cells and normal cells indiscriminately and often have severe side effects.

And Good things

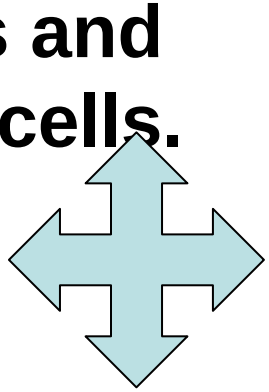
- **Chemotherapy**

  is a systemic treatment.

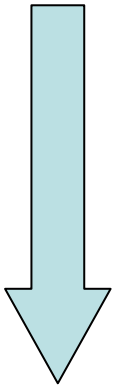
  Drugs can reach all effected areas and kill all cancer cells.

- **Radiotherapy**

  can focus on a small part of the effected area.



Complete + **Accurate**



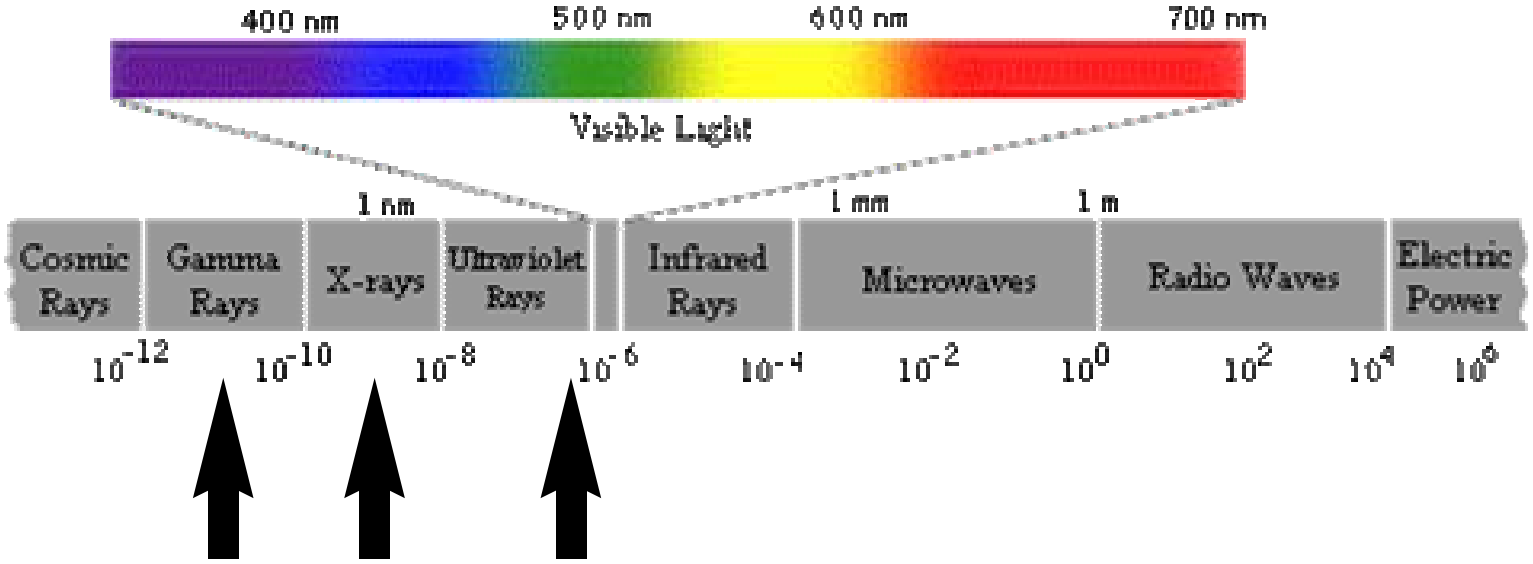
Our Combined Approach:

CHEMICAL + LIGHT

- **Less toxic or non-toxic chemicals**
  - **Thionucleosides**
- **Lower energy ray (light)**
  - **UVA light**

- **High synergic effect (when combined)**

UVA Light is much weaker than x-ray and γ-ray

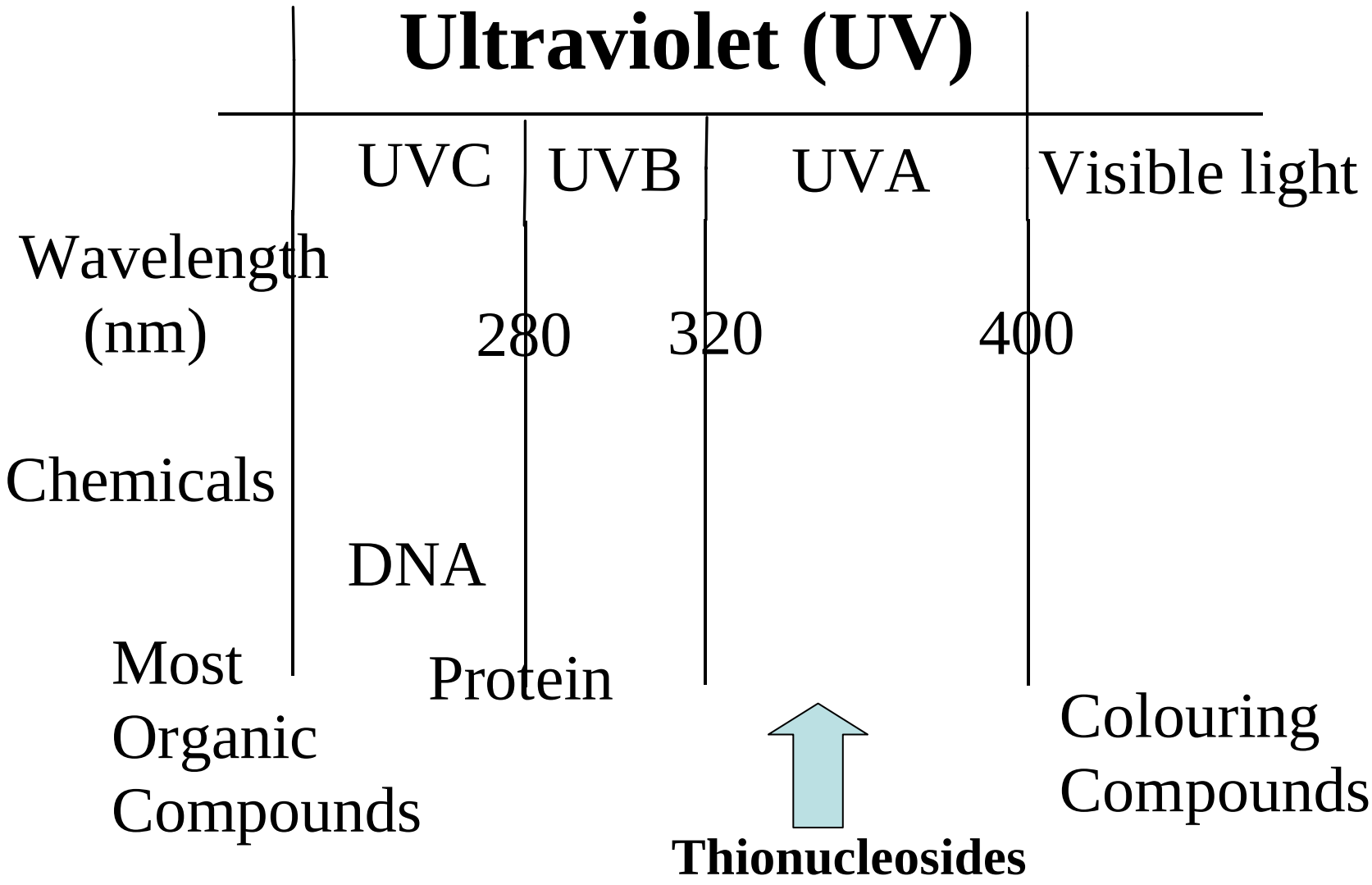


Energy **Wavelength**

($E = h\upsilon = hc/\lambda$)

UV light is 300 to 10,000 weaker than X-ray
And 100,000 weak than Gamma ray

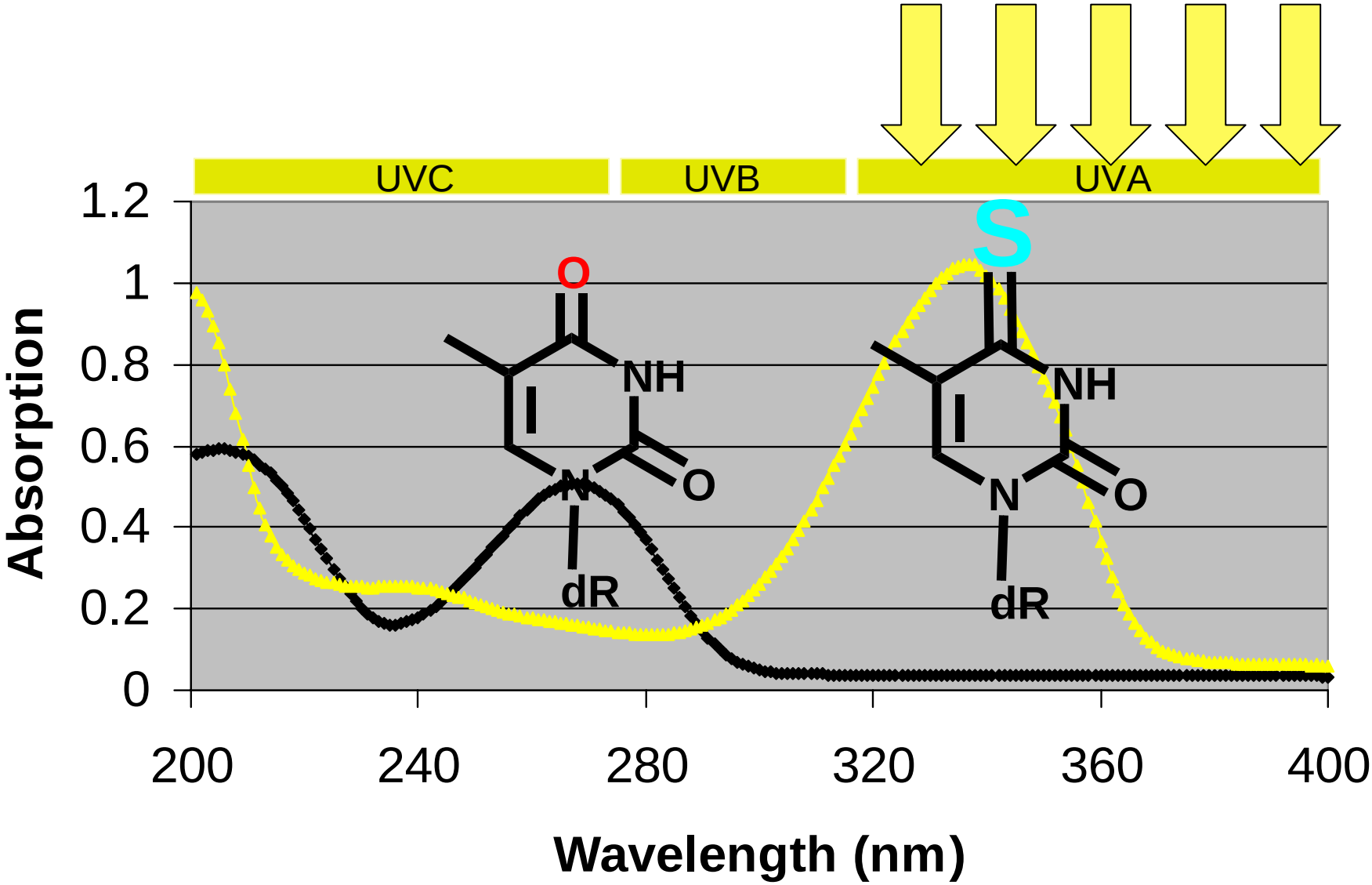
UV light and Chemicals



WHY Thionucleosides?

- Thionucleosides are the nucleosides in which an oxygen atom is replaced by a sulfur atom.
- They absorb UVA light.
- They can be incorporated into DNA and make DNA more sensitive to UVA damage.
- UVA light is not harmful to normal DNA.
- Thionucleosides plus UVA offers a possibility to selectively target cancer cells.

Thymidine and 4-thioThymidine

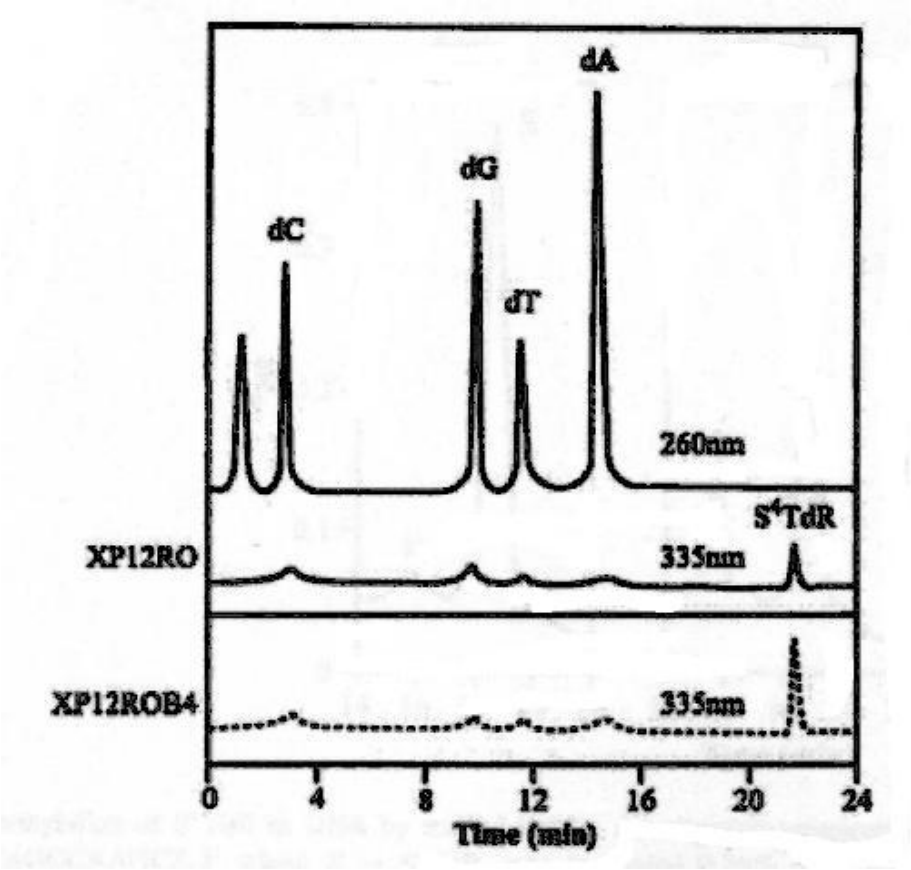


4-thioThymidine plus UVA light

- Neither 4-thioThymidine nor low dose UVA light alone is cytotoxic.
- Cells, treated with 4-thioThymidine, are extremely sensitive to a subsequent exposure to a low dose of UVA light.
- The synergism between 4-thioThymidine and UVA light depends on incorporation of 4-thioThymidine into DNA *via* thymidine kinase (TK).
- It is therefore highly selective for the cells that are replicating DNA as proliferating cells (such as cancer cells) have increased levels of TK enzymes.

Get into cells

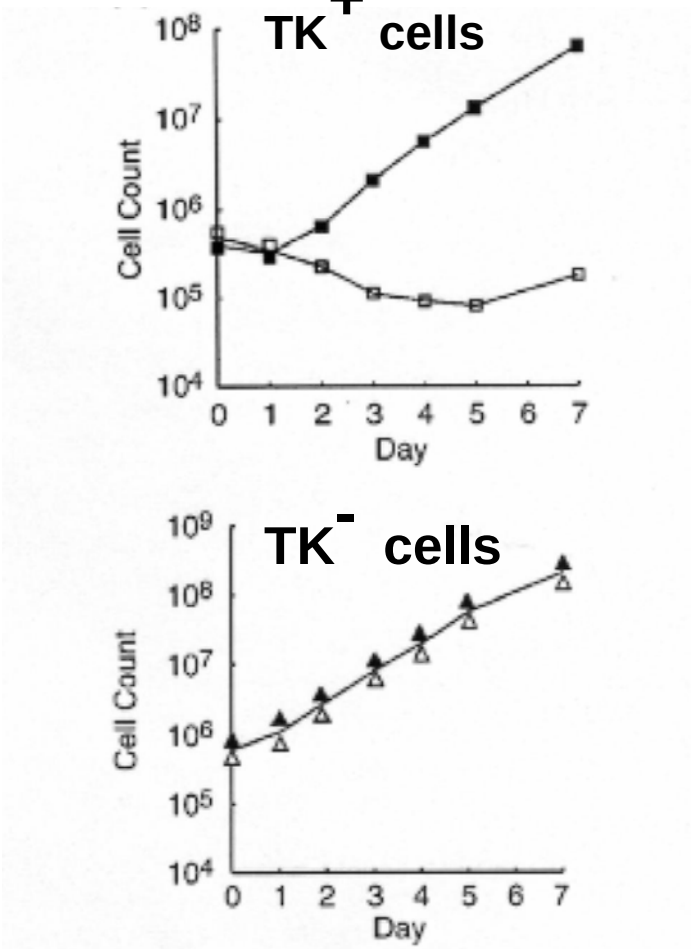
- Feed cells with thioThymidine
- Isolate DNA from the cells
- Digest DNA to its nucleosides
- HPLC analysis of nucleosides



Massey, Xu, Karran, DNA Repair (2002) 275-286

Prefer dividing cells (cancer)

- **Incorporation of thio-Thymidine requires TK enzymes.**
- **TK is active in dividing tissues (e.g. cancer cells), but low in-non-growing tissues (normal cells).**



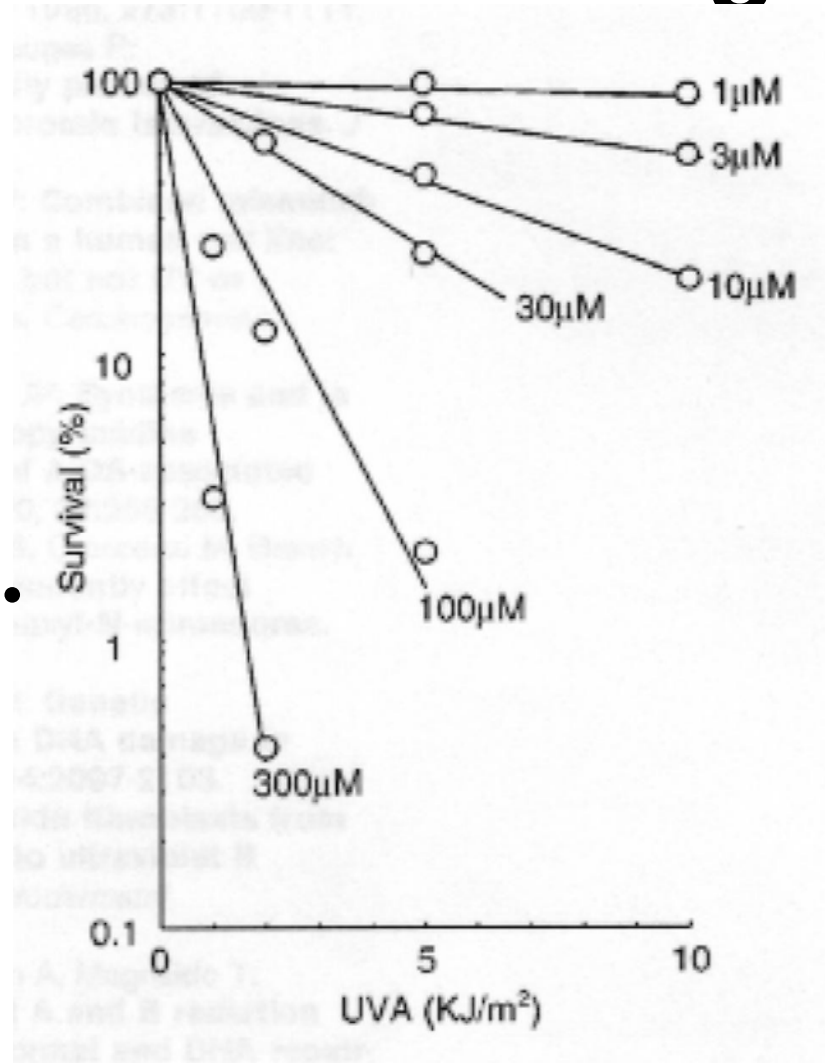
Massey, Xu, Karran, Current Biology (2001) 11 1142-46

Sensitises cells to UVA light

Cells are cultured in thioT media

UVA light is then applied to the cells.

Survival rate are measured.



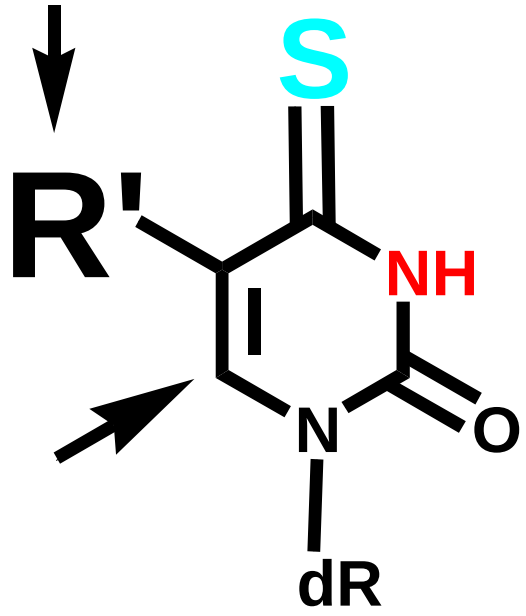
Massey, Xu, Karran, Current Biology (2001) 11 1142-46

Work in progress

- **Mechanism elucidation**
- **New drug development**

New drug ?

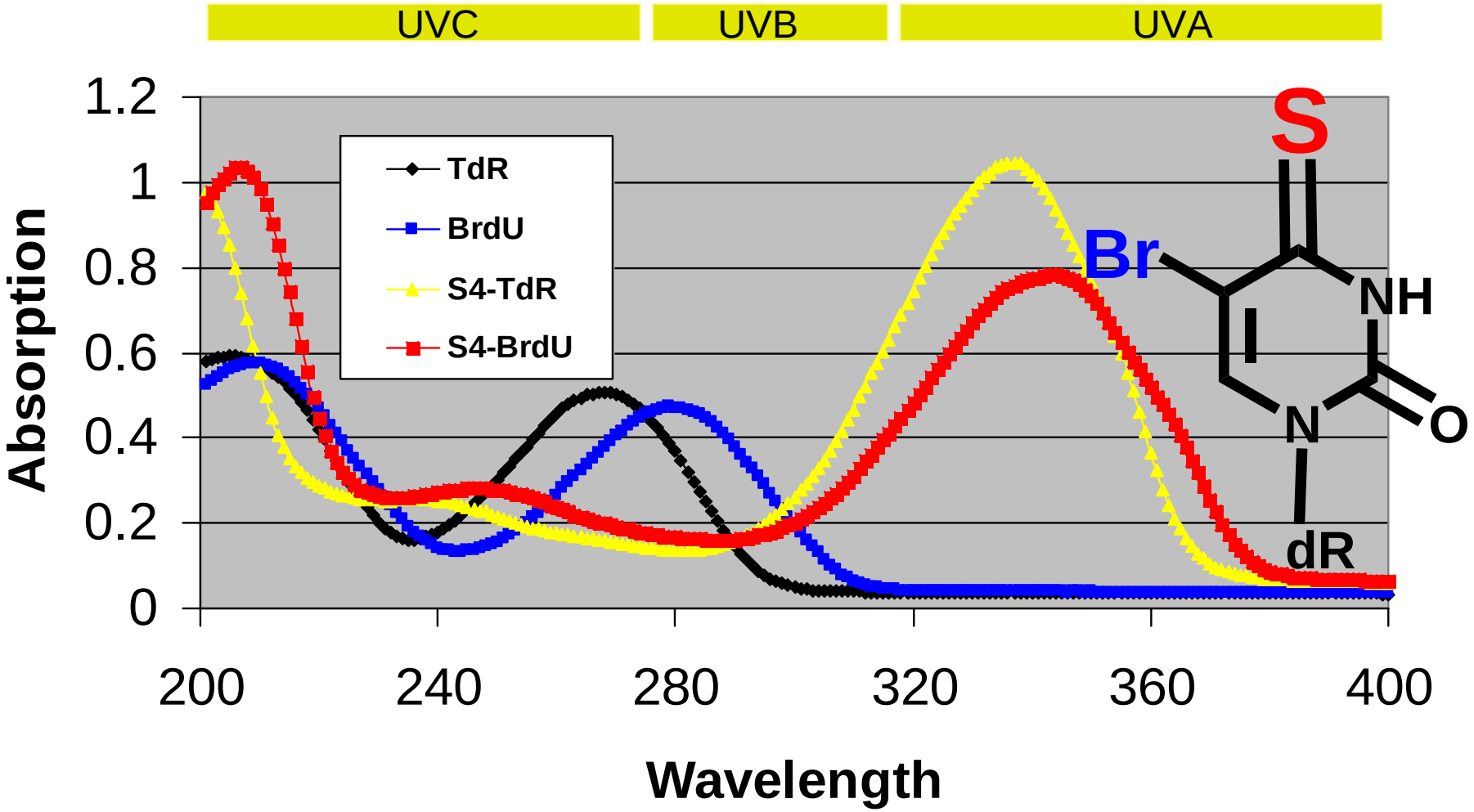
- **Modification at 5 or 6-position**
- **Br- has a similar size to CH_3-.**
- **Br is more sensitive to radical reaction induced by UVA**



R' : Br & others

Xu, et al Bioorganic and Medicinal Chemical Letters (2004) 14 995-997

UV of Thymidine and Analogues



Summary

- **DNA damage is the cause of cancer**
- **Damaging DNA is used for cancer therapy.**
- **Our Novel cancer therapy**
  - **Using thionucleosides plus UVA light**
- **Chemistry and photochemistry of the drugs are still being exploited.**

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