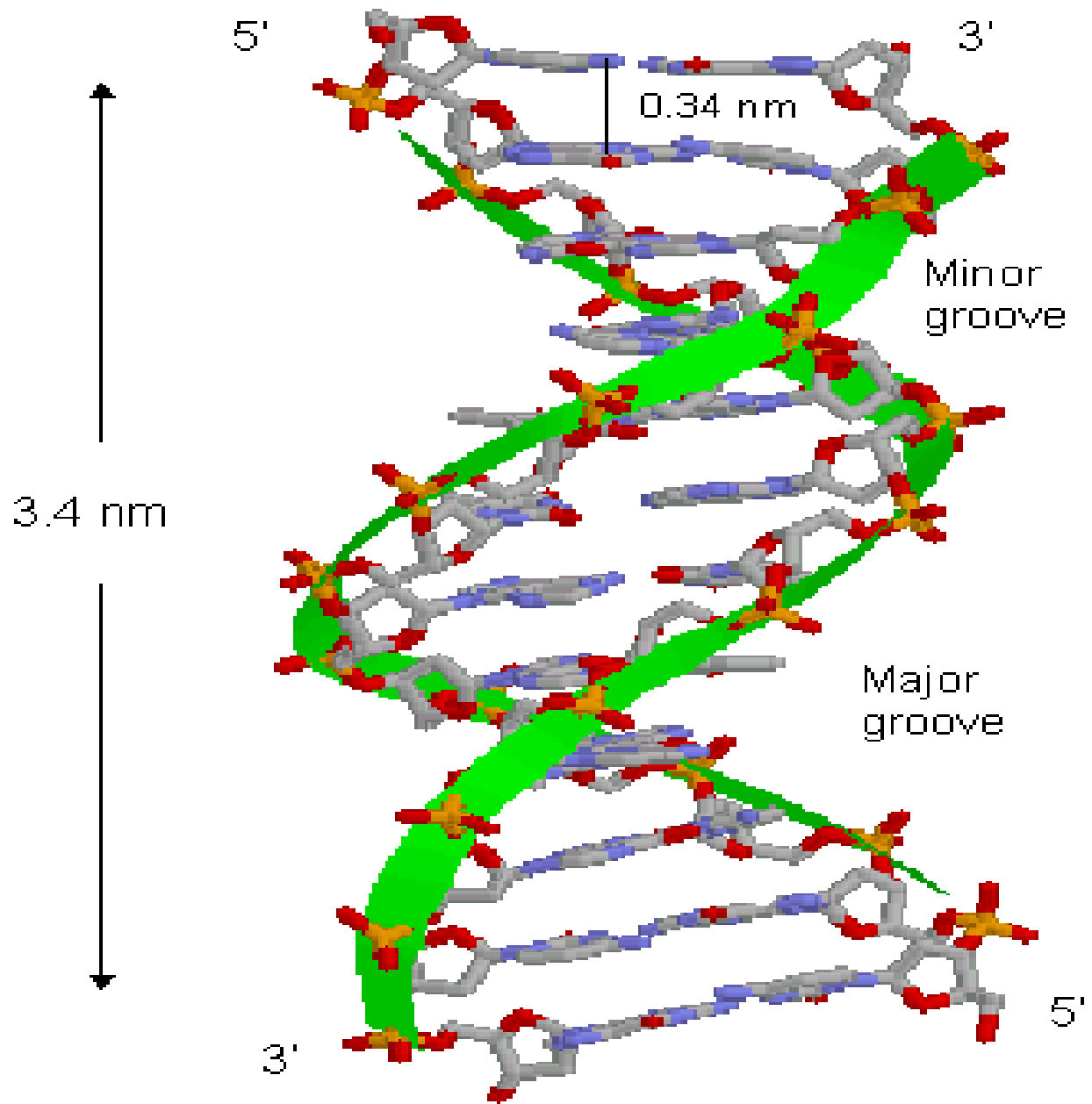
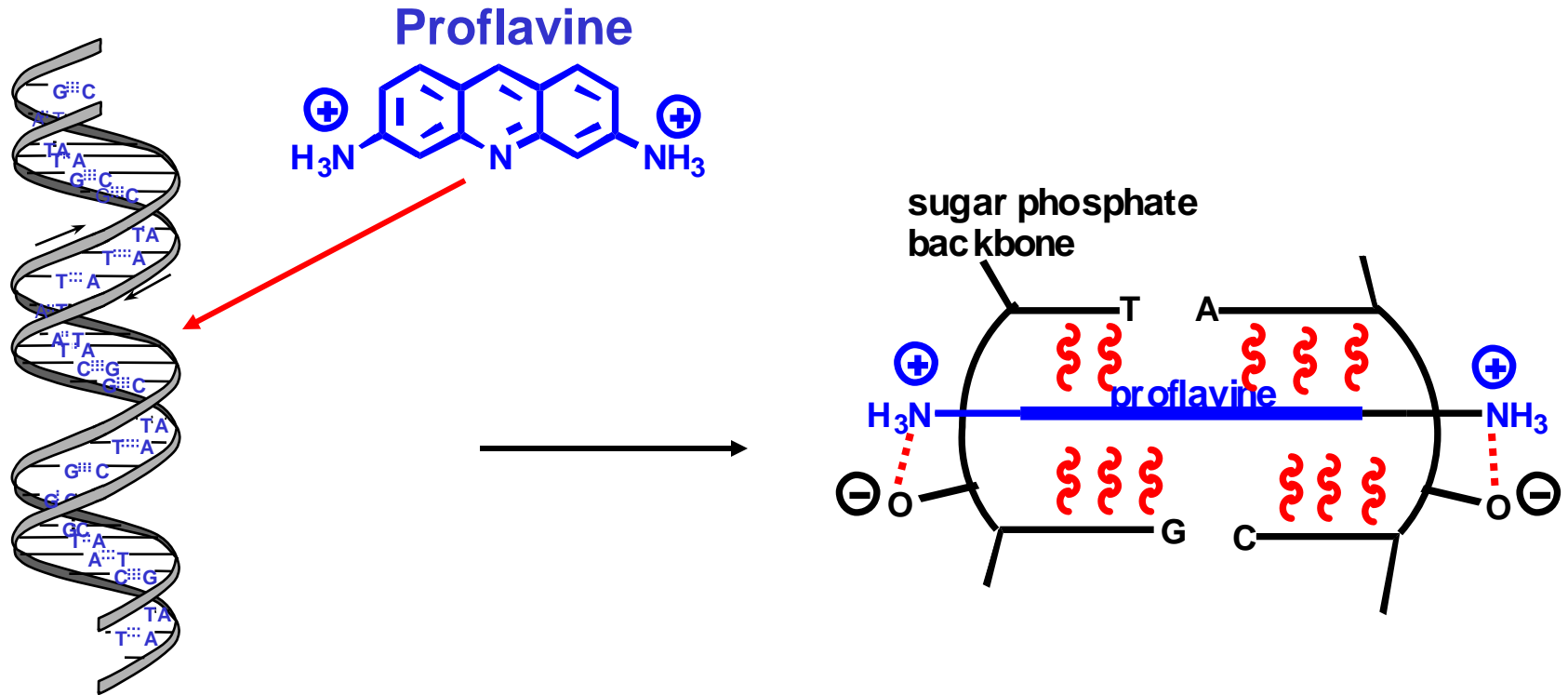


**DRUG TARGETS:  
NUCLEIC ACIDS  
DNA & RNA**



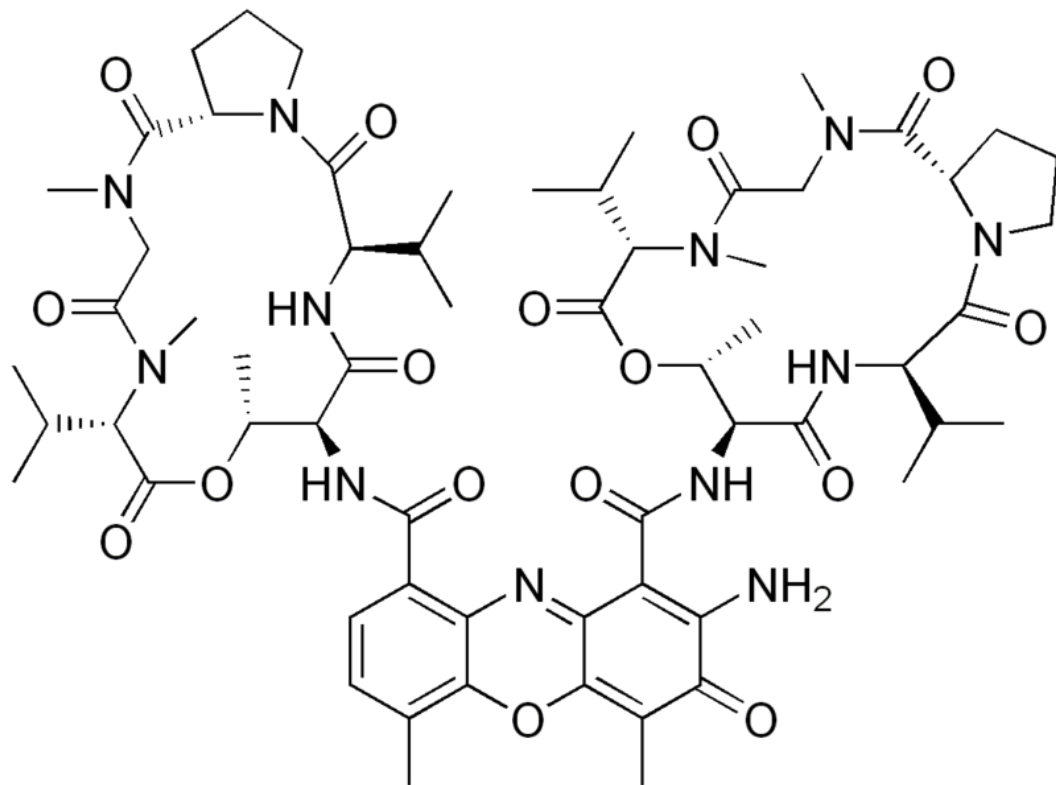
# Intercalating agents

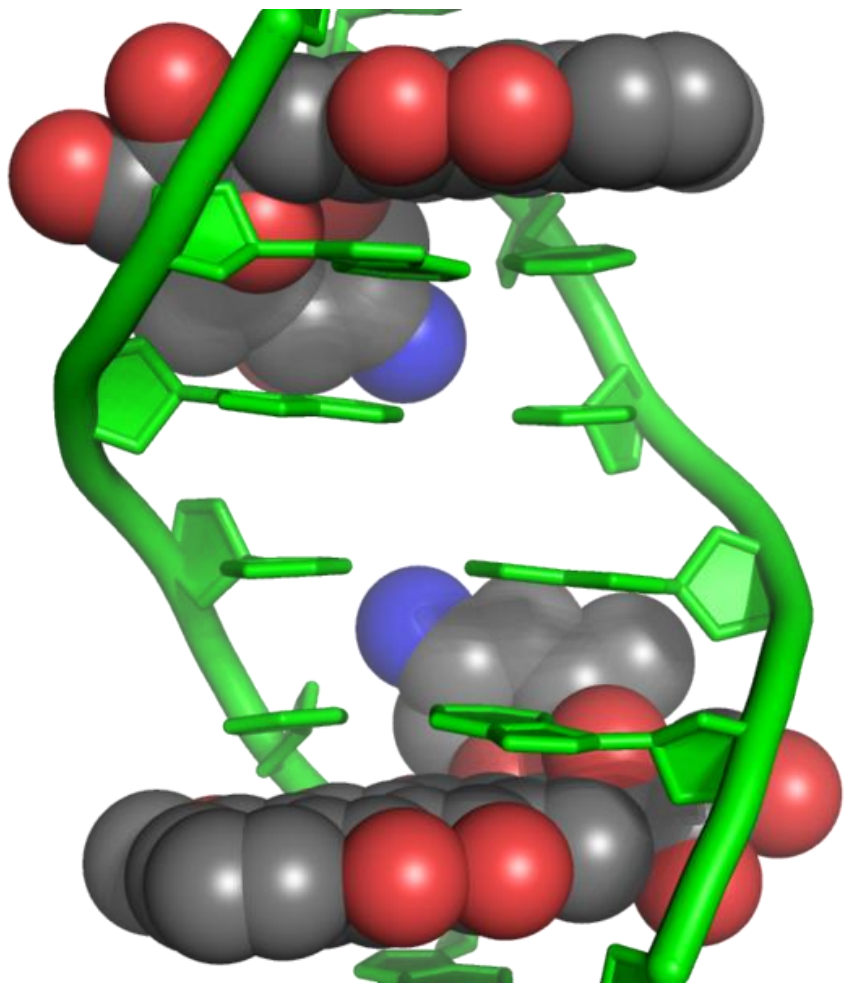
## Example – Proflavine (antibiotic)

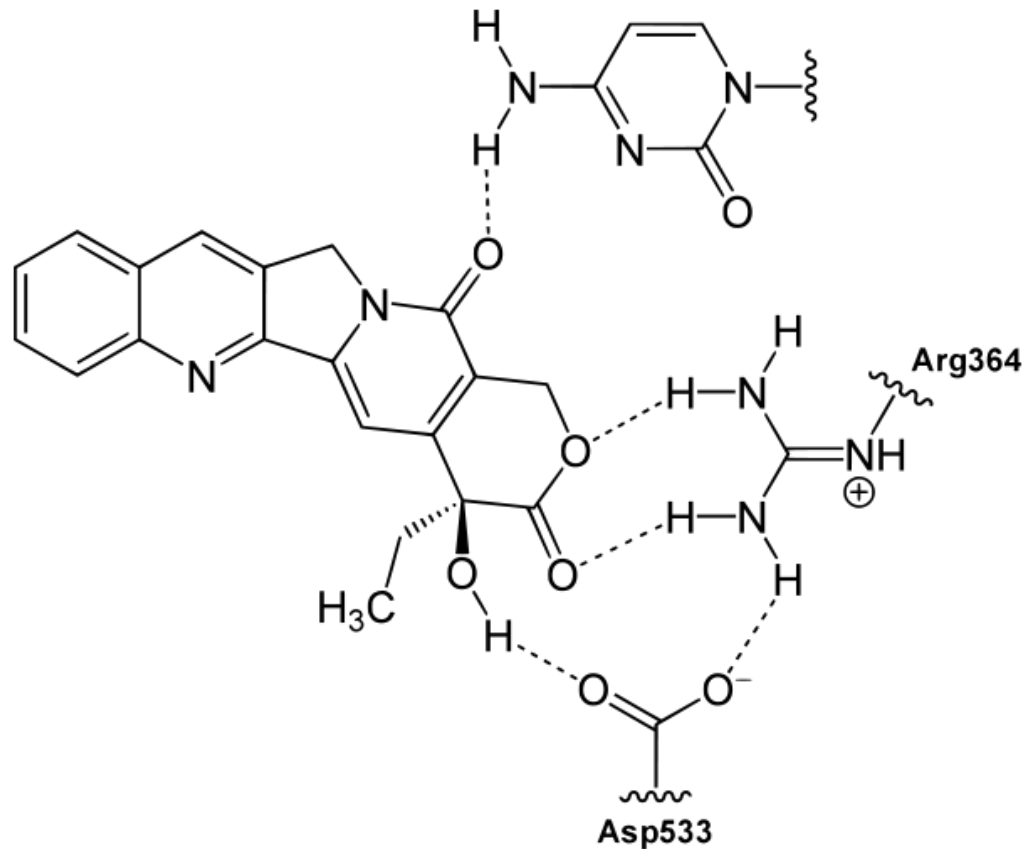


§ van der Waals interactions

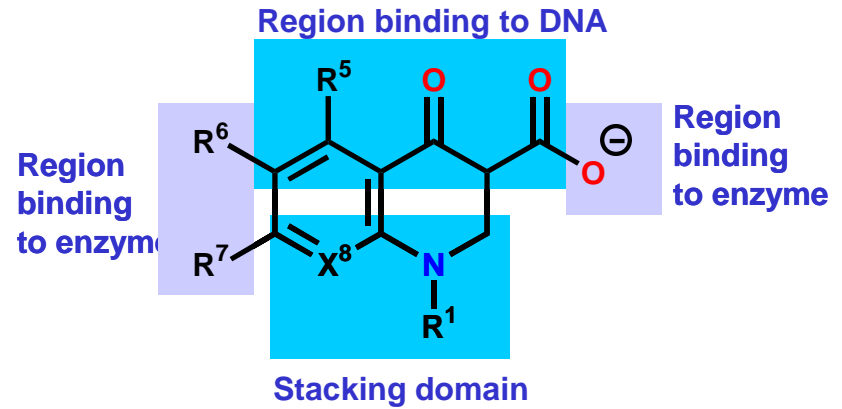
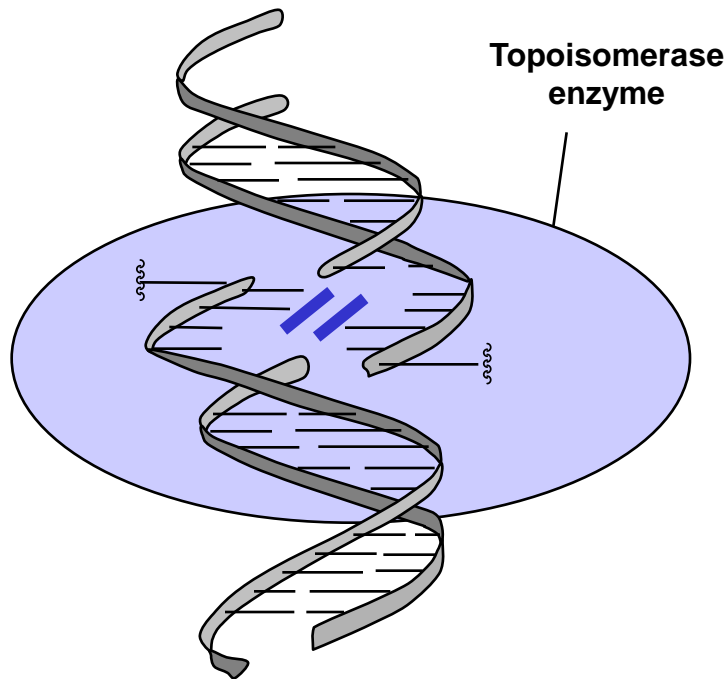
⋮ Ionic interactions







Proposed interaction of camptothecin with DNA and topo I, based on: (from wikipedia)  
Crystal Structures of Human Topoisomerase I in Covalent and Noncovalent Complexes with DNA  
Science 6 March 1998: Vol. 279. no. 5356, pp. 1504 – 1513. DOI: 10.1126/science.279.5356.1504  
Matthew R. Redinbo, \* Lance Stewart, \* Peter Kuhn, James J. Champoux, Wim G. J. Hol

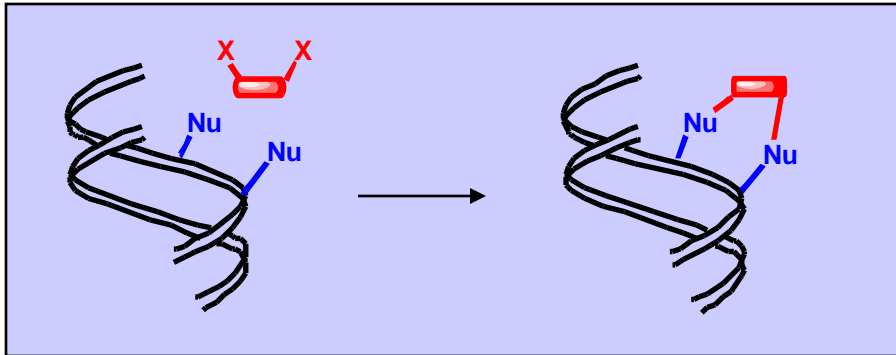


— Fluoroquinolones

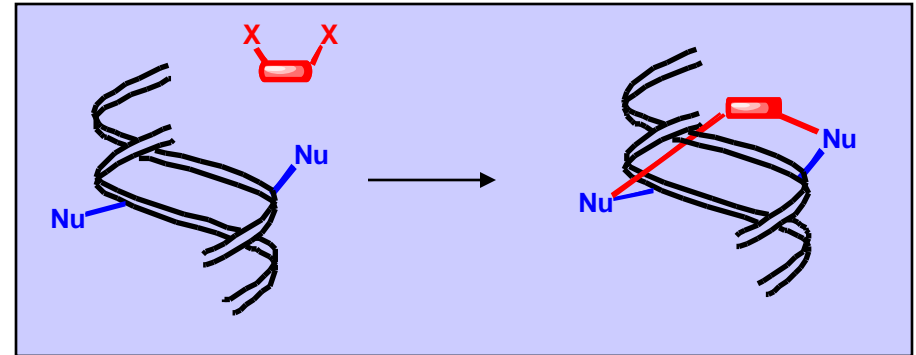
- Four drug molecules are stacked in the bound complex
- Bound to DNA and enzyme by hydrogen and ionic bonds

# Alkylating agents

## Cross linking



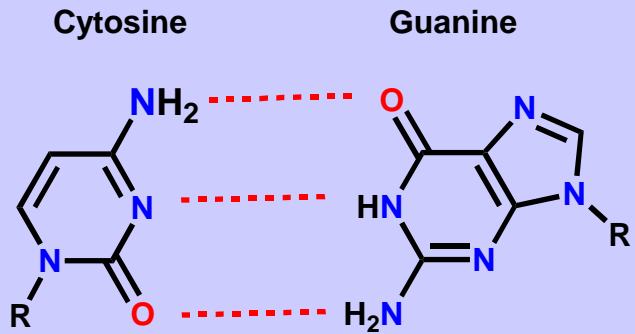
**Intrastrand cross linking**



**Interstrand cross linking**

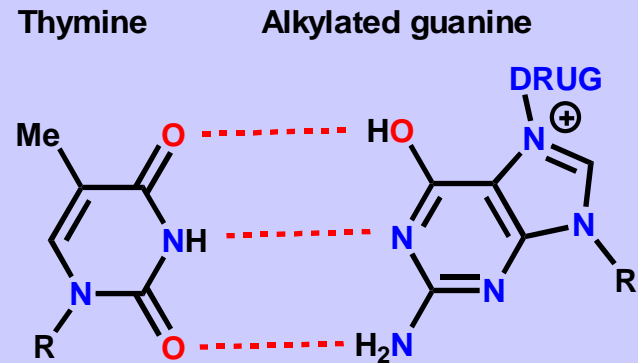
# Alkylating agents

## Normal base pairing

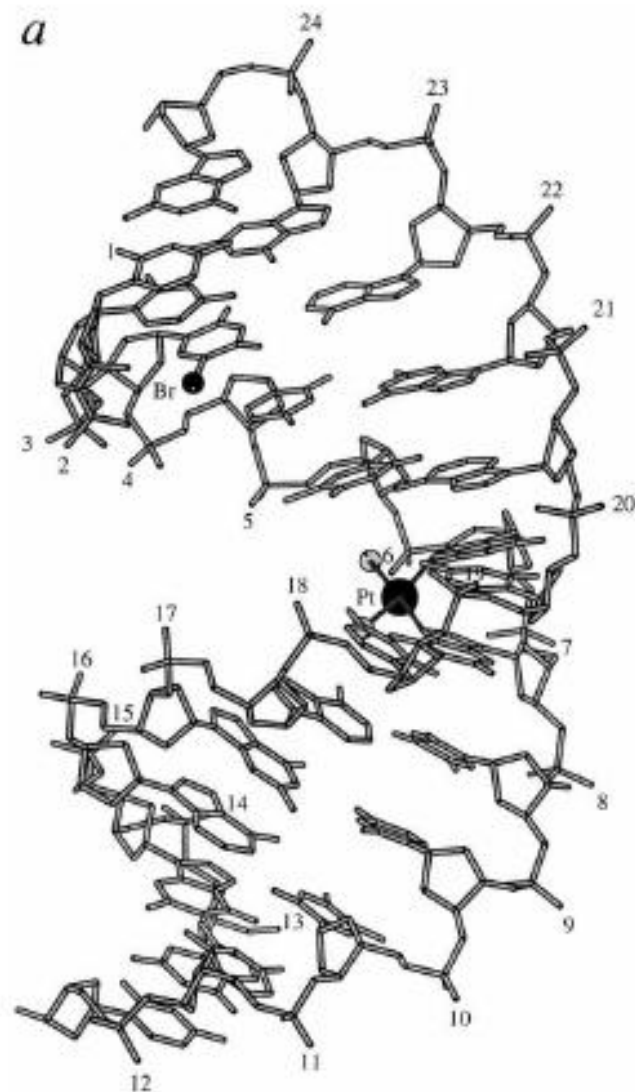


Guanine prefers  
keto tautomer

## Miscoding resulting from alkylated nucleic acid bases

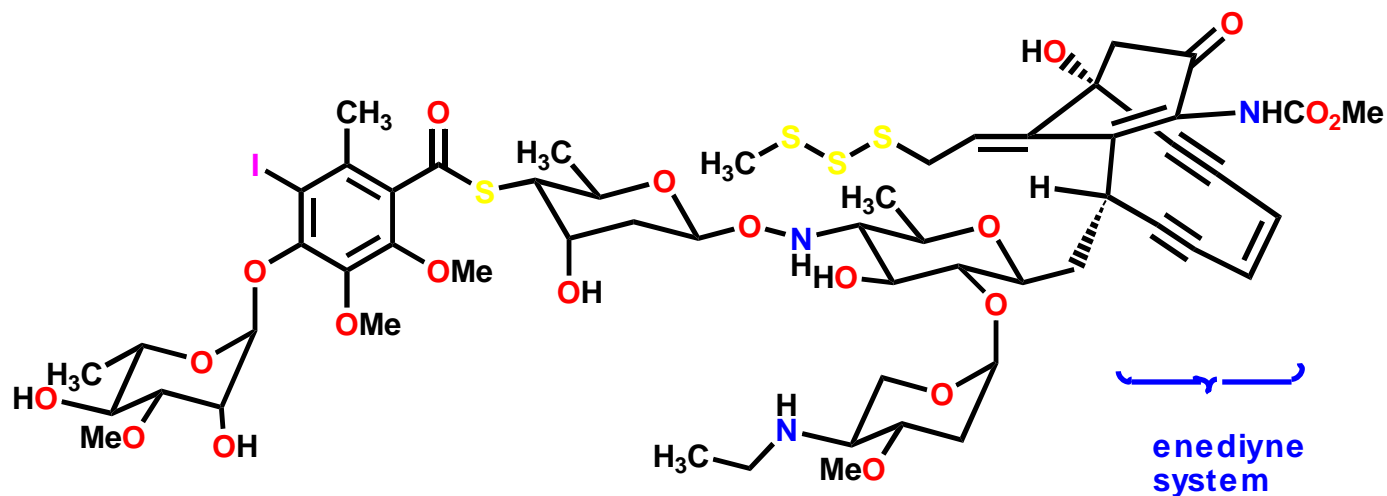


Abnormal base pairing.  
Alkylated guanine prefers  
enol tautomer



Crystal structure of double-stranded DNA containing the major adduct of the anticancer drug cisplatin, Patricia M. Takahara, Amy C. Rosenzweig, Christin A. Frederick, Stephen J. Lippard. *Nature*. **1995**. Vol. 377, Iss. 6550; p. 649.

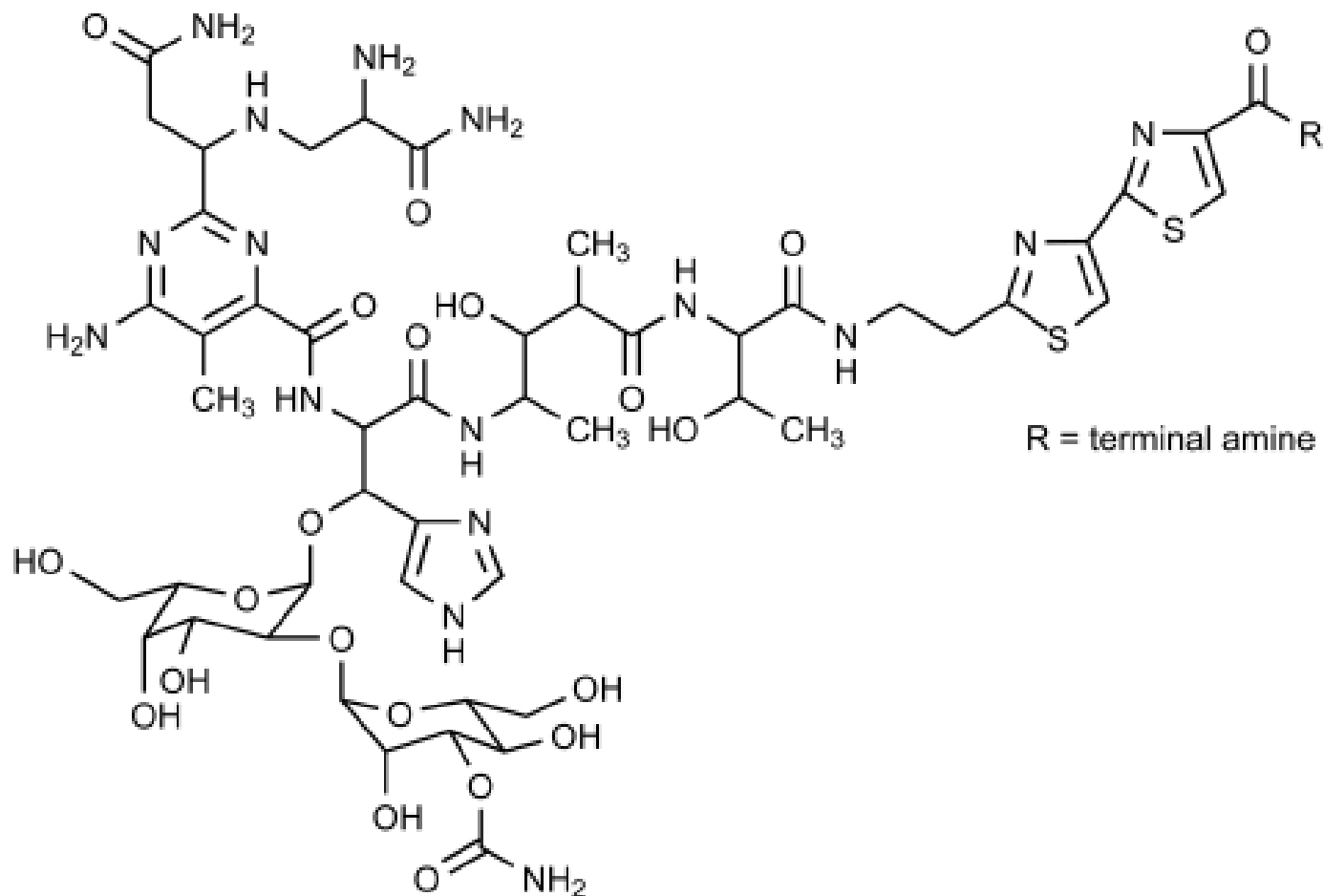
# Chain cutters



**Calicheamicin  $\gamma_1$**   
**Antitumour agent**

- **Generates DNA diradical**
- **DNA diradical reacts with oxygen**
- **Results in chain cutting**

# Chain cutters



R = terminal amine

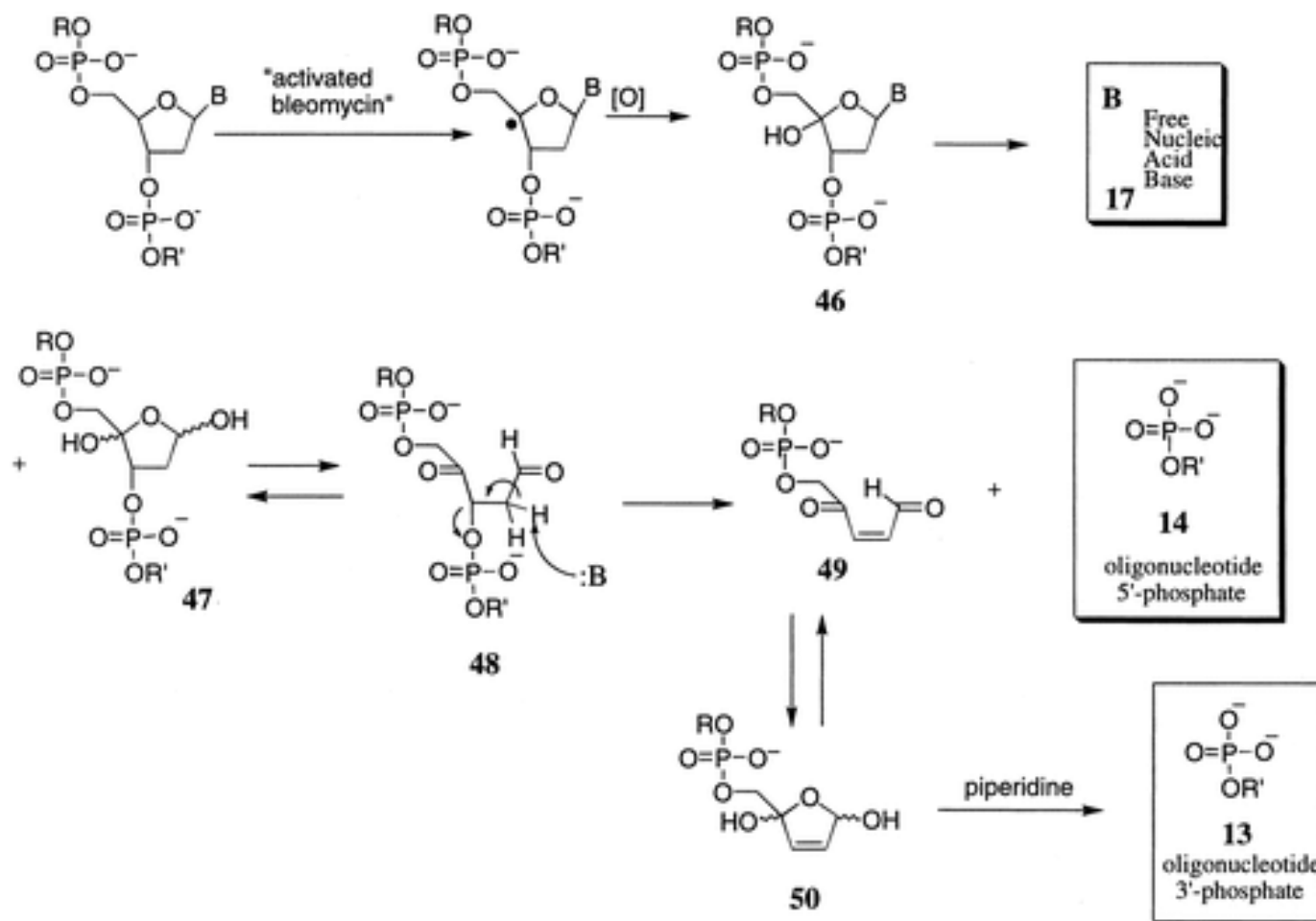
BLEOMYCIN A2

R = NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>SMe<sub>2</sub>

BLEOMYCIN B2

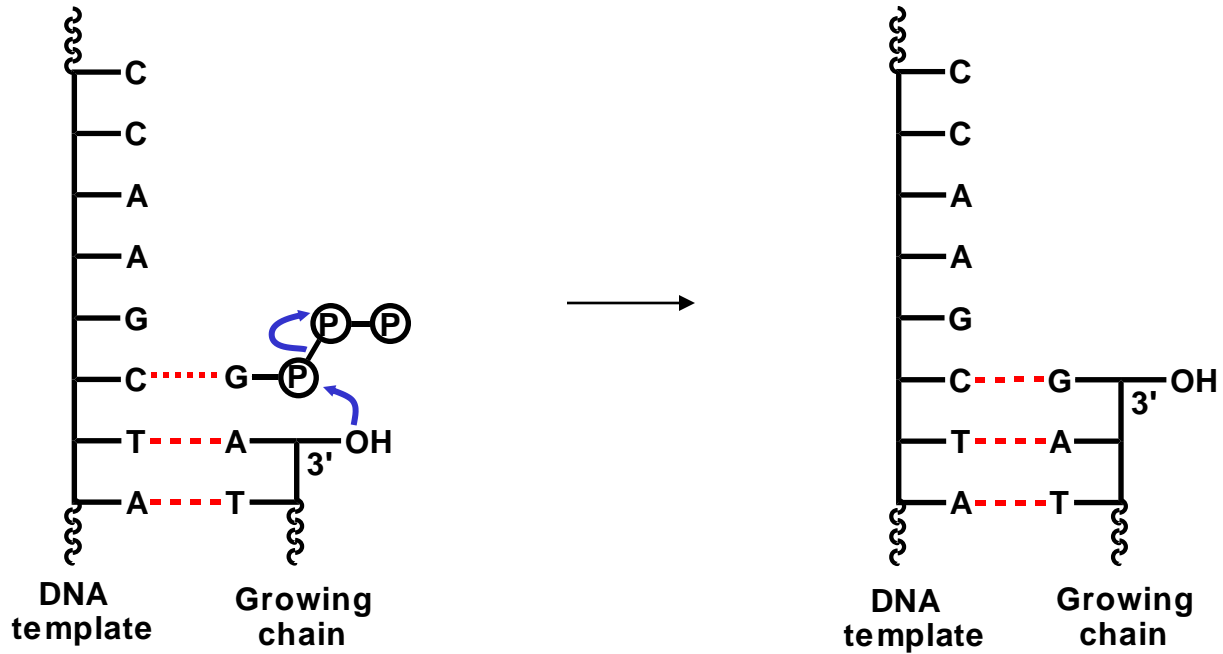
R = NHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>NHC(NH<sub>2</sub>)=NH

Proposed H-4'-Abstraction Pathway for DNA Strand Scission Mediated by Activated Bleomycin-Fe(II) under Anaerobic Conditions (adapted from Worth et al.<sup>39</sup> and Hecht<sup>90</sup>)

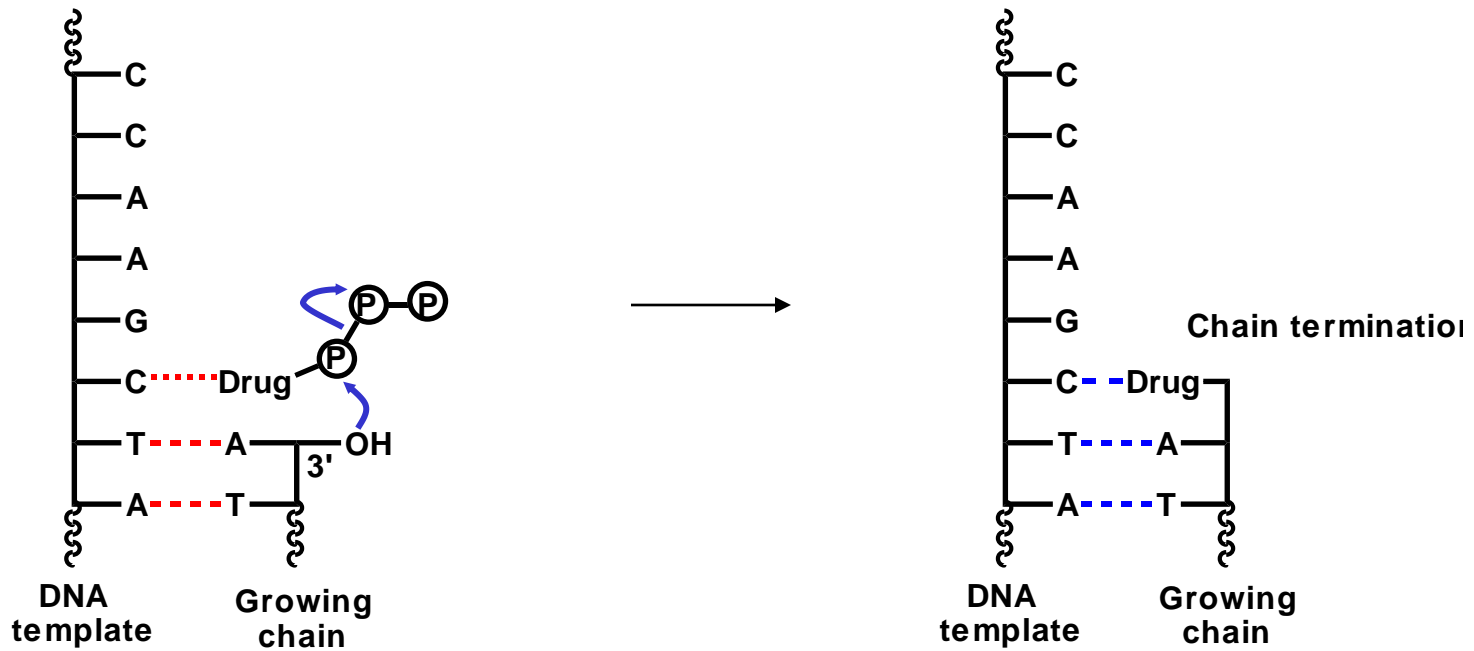


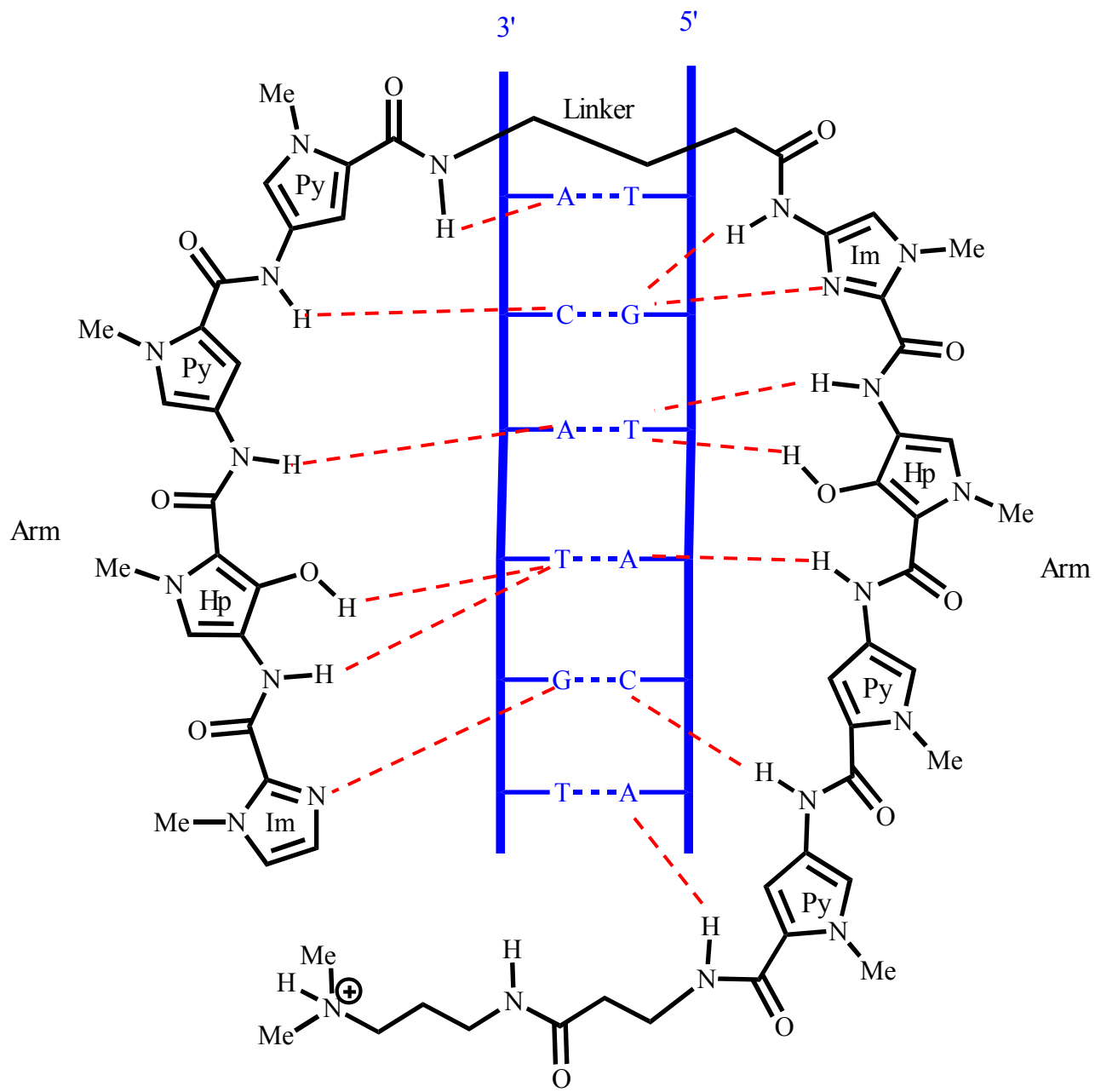
**Oxidative Strand Scission of Nucleic Acids: Routes Initiated by Hydrogen Abstraction from the Sugar Moiety**, *Chem. Rev.*, **1998**, 98 (3), pp 1089–1108, DOI: 10.1021/cr960437i Wendy Knapp Pogozelski<sup>‡</sup> and Thomas D. Tullius<sup>\*</sup>

# Normal replication

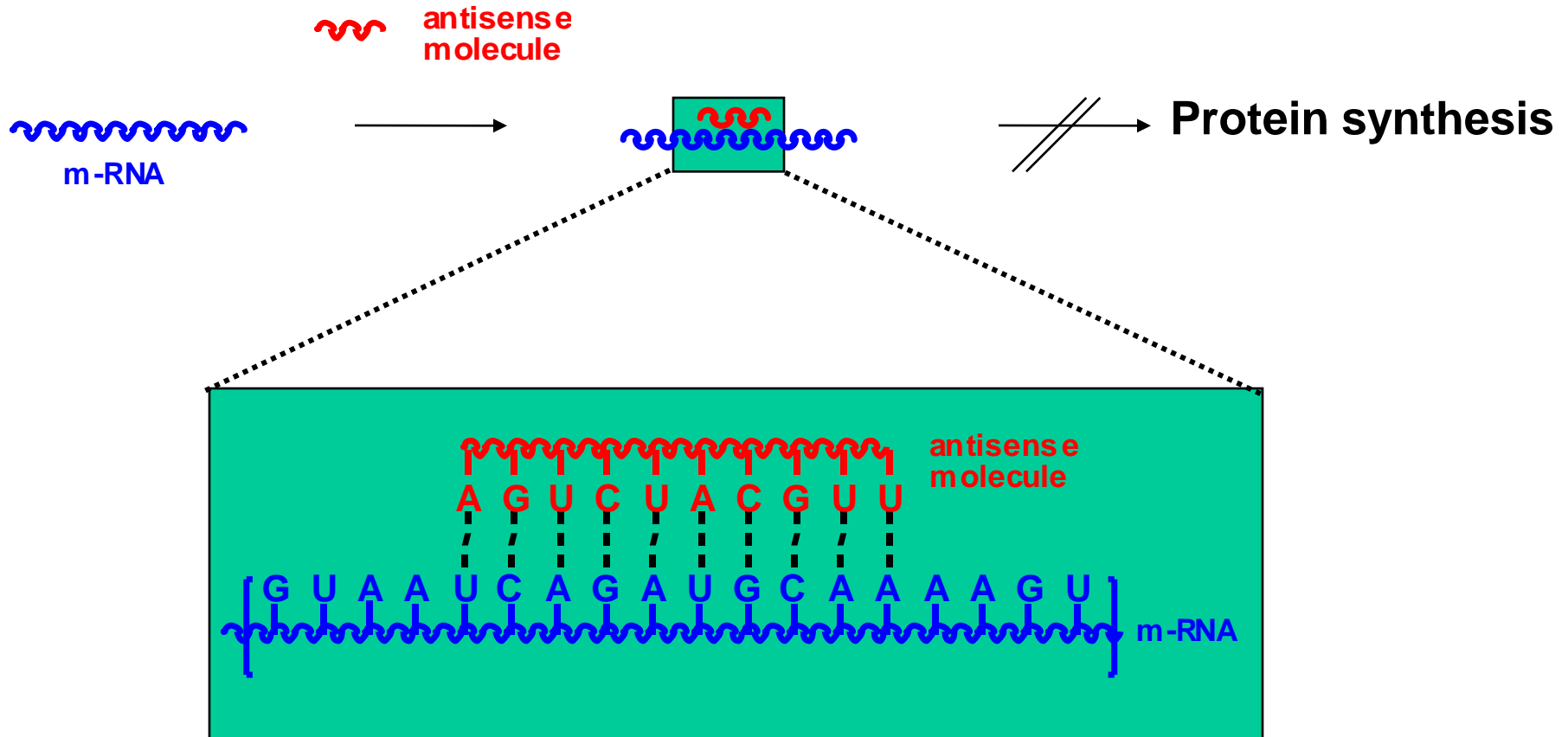


# Chain termination

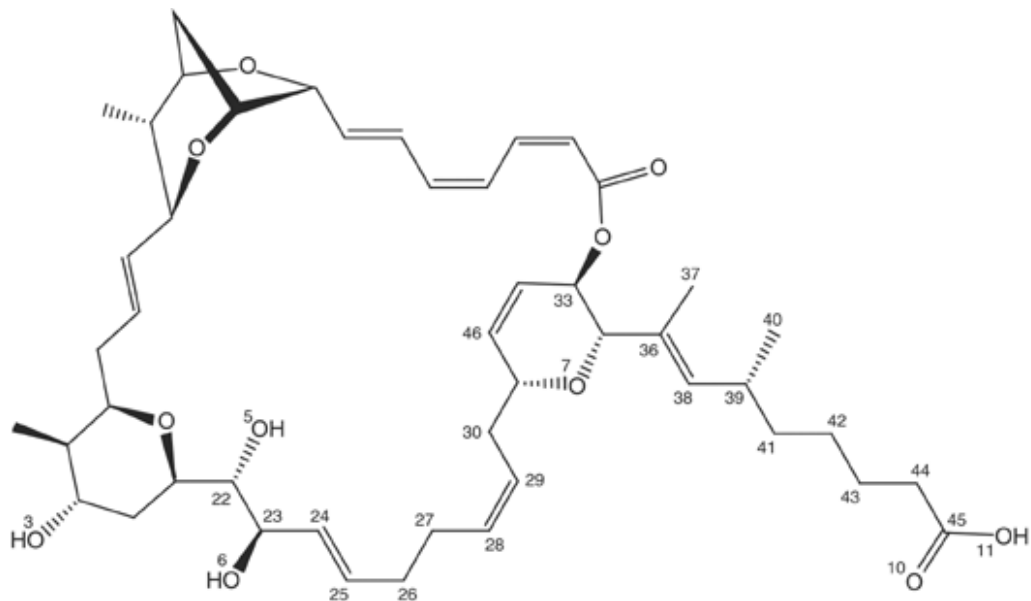




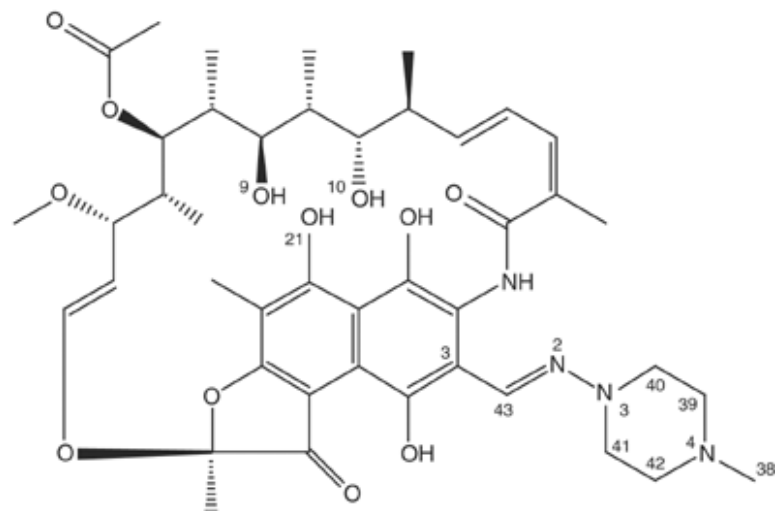
# Antisense Therapy



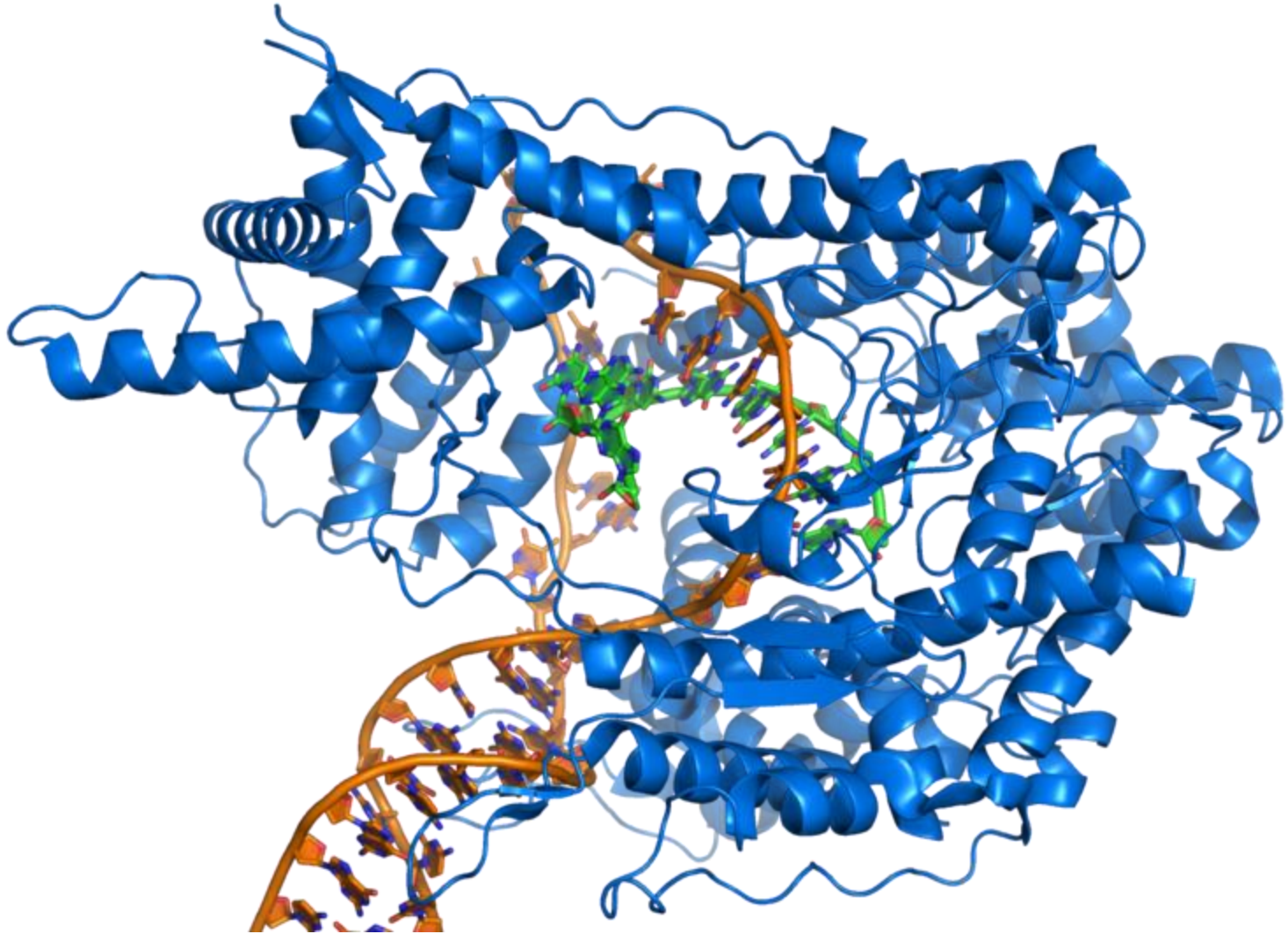
# Structural Comparison



**Sorangicin A**



**Rifampicin**

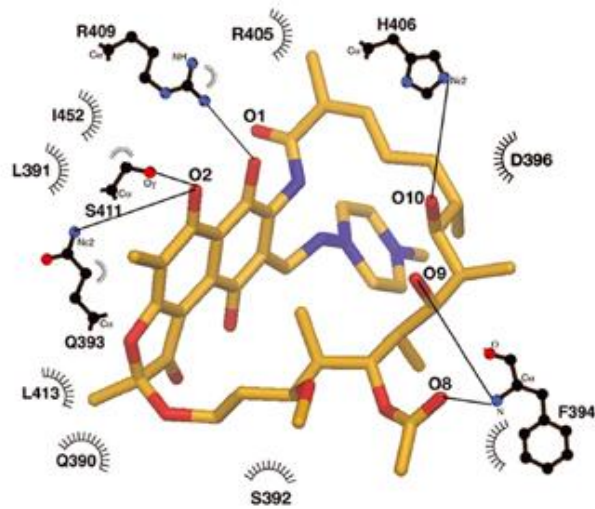


**T7-RNA polymerase**

# Rifampin and Sorangicin bound to *Taq* RNA polymerase

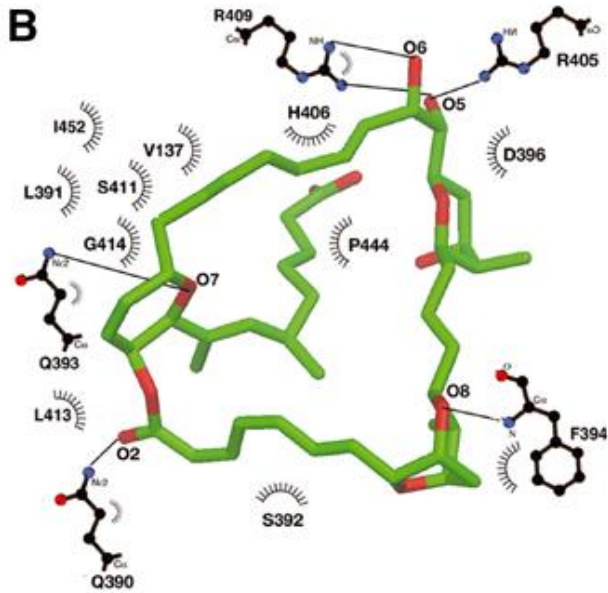
## Rifampin

A

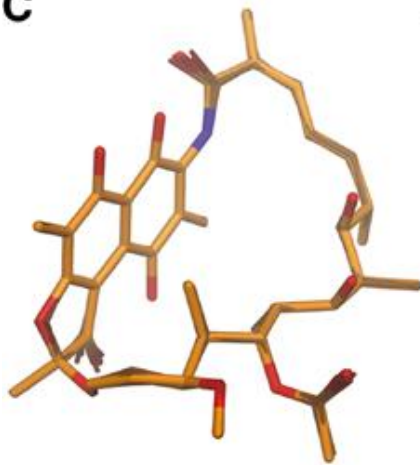


## Sorangicin

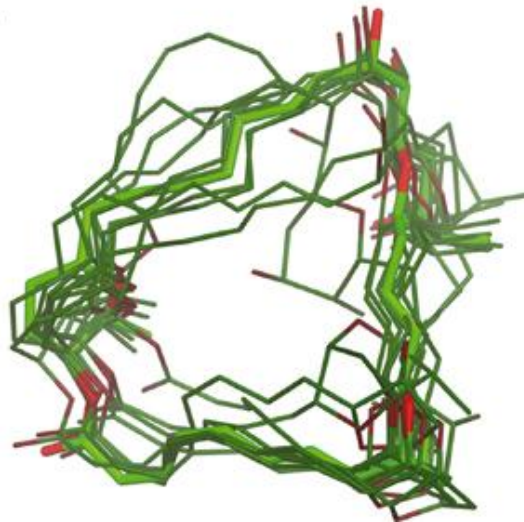
B



C



D



E

