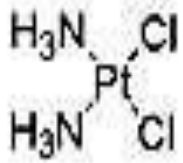
Organoplatinum compounds

- There are several organometallic compounds based on platinum that play a central role in many cancer treatment protocols. The first of these, cisplatin.

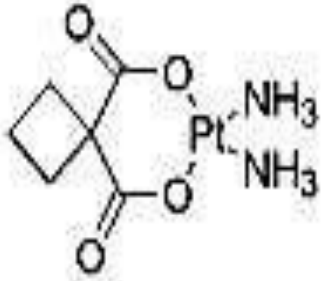
- Less reactive platinum compounds such as carboplatin and oxaliplatin in which the leaving group was incorporated into a chelate. satraplatin is currently in clinical trials. One advantage of these agents is the possibility of oral administration.

- Satraplatin has shown similar activity when given orally to that of cisplatin given by injection.

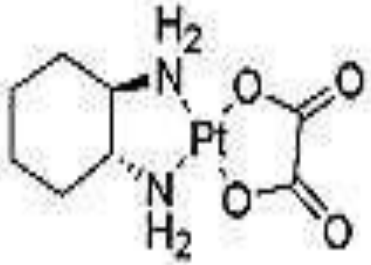
Platinum-containing anti neoplastics



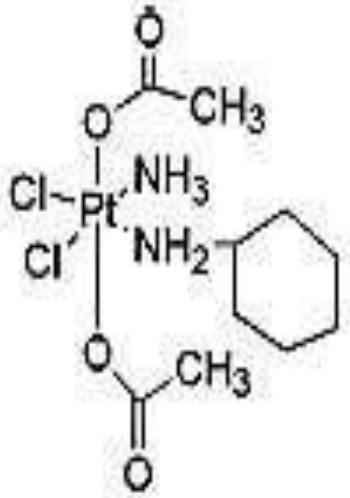
Cisplatin



Carboplatin

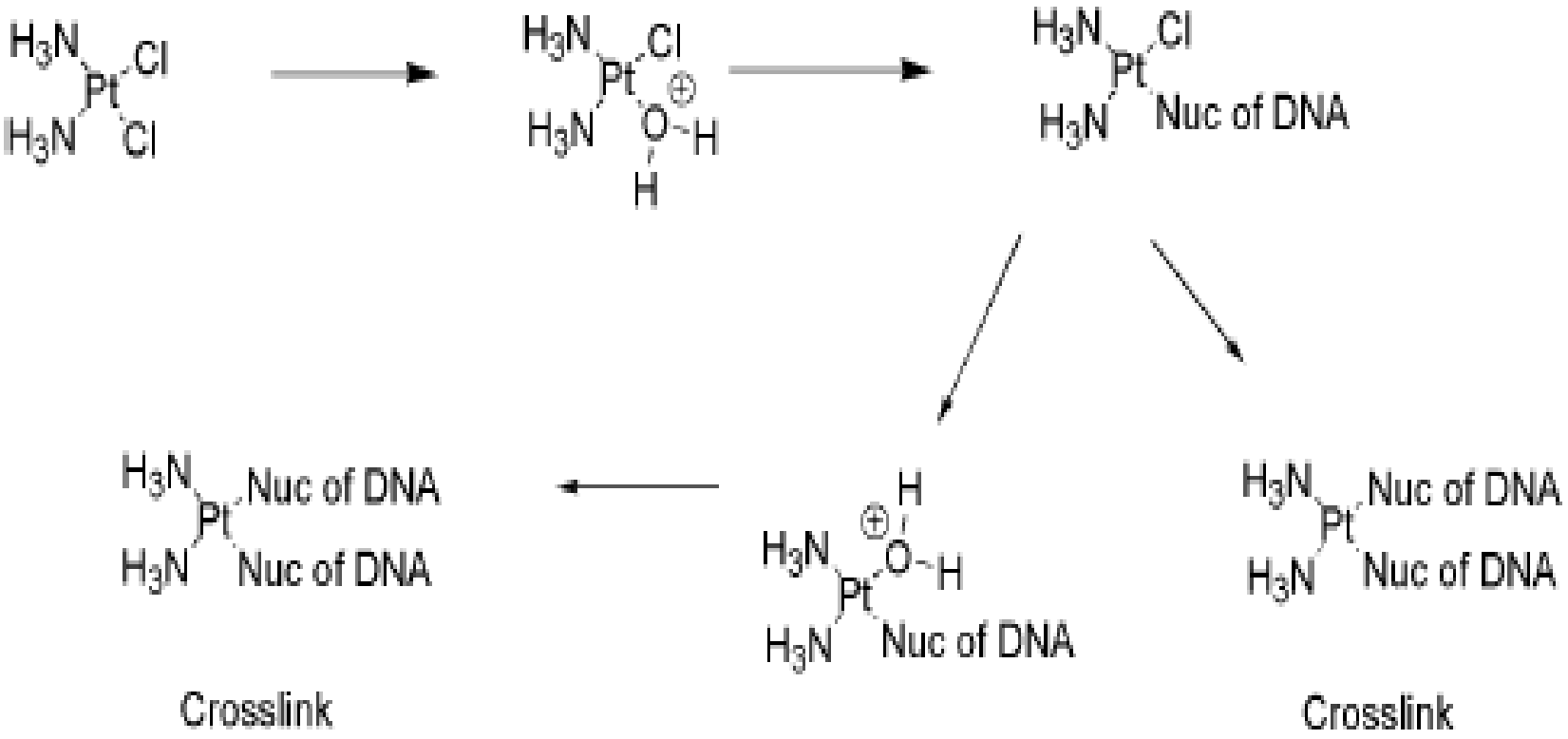


Oxaliplatin



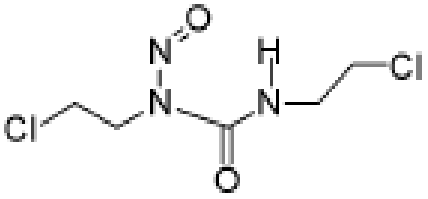
Satraplatin

Mechanism of cisplatin activation and formation of DNA adducts.

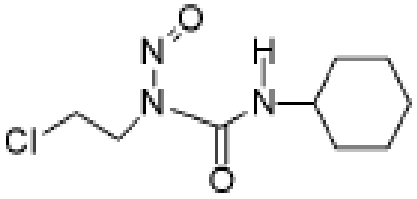


Nitrosoureas

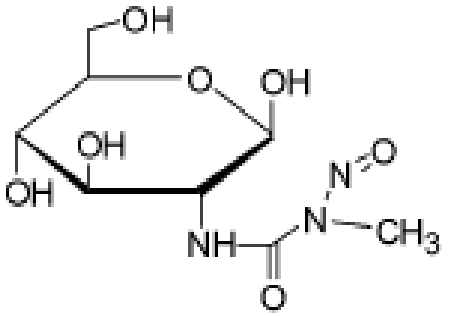
Compound was based on the idea that its chemical decomposition was leading to the formation of diazomethane (CH_2N_2) and subsequent alkylation of DNA, this led to the nitrosoureas, where it was found that activity could be enhanced by attachment of a 2-haloethyl substituent to both nitrogens



Carmustine (BCNU)



Lomustine (CCNU)



Streptozocin

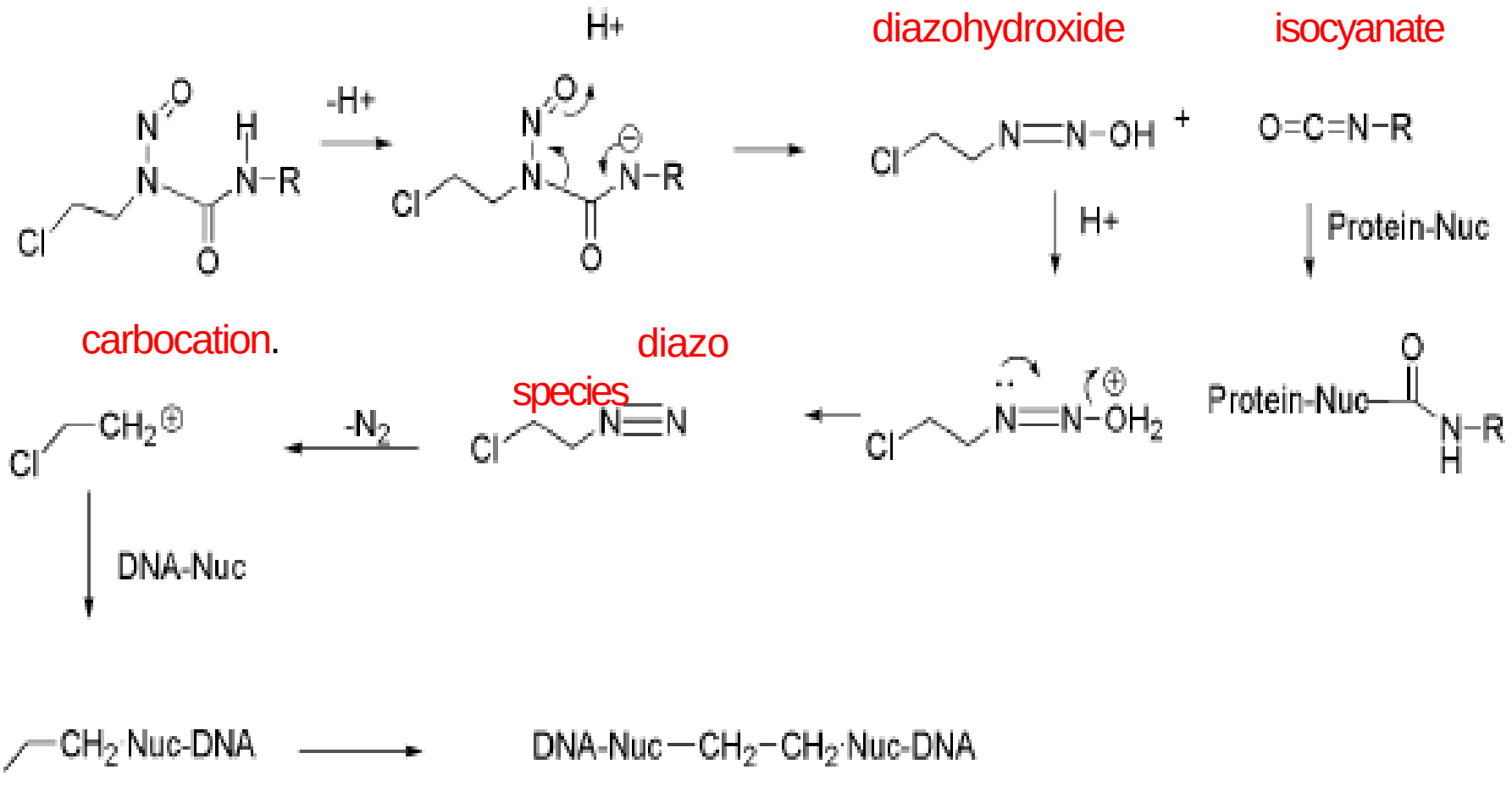
These compounds are reasonably stable at pH 4.5 but undergo both acid and base catalyzed decomposition at lower and higher pH, respectively.

There are several pathways of decomposition that are possible for these compounds, but the one that appears to be most important for alkylation of DNA involves:

Abstraction of the NH proton, which is relatively acidic (pKa 8–9). Rearrangement to give an isocyanate and a diazohydroxide. The diazohydroxide, upon protonation followed by loss of water, yields a diazo species that decomposes to a reactive carbocation.

The isocyanate functions to carbamylate proteins and RNA, whereas the carbocation is believed to be the agent responsible for DNA alkylation.

Nitrosoureas: Pathways of decomposition and DNA alkylation

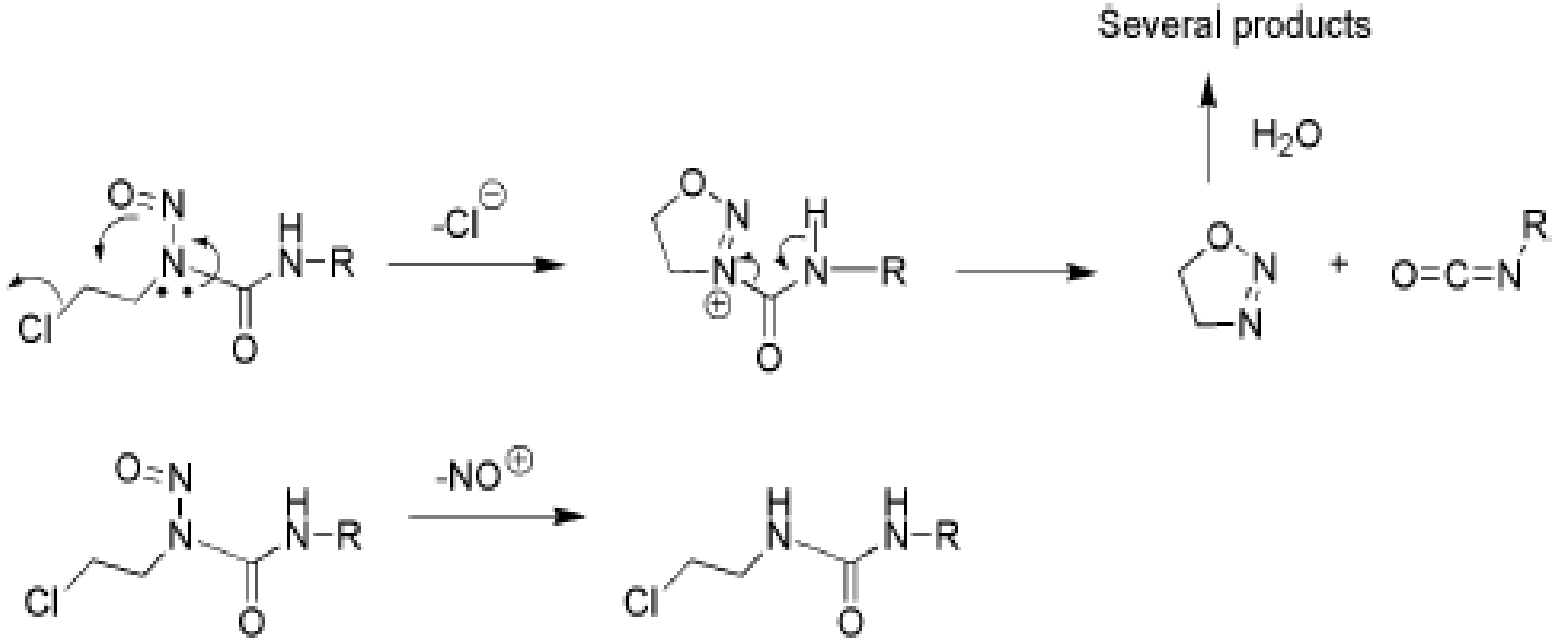


Detoxification pathways of the nitrosoureas

Detoxification pathways of the nitrosoureas are also possible and can play a role in resistance to this group of agents.

The first of these involves dechlorination, which is facilitated by CYP participation.

The second route involves denitrosation



2.Antimetabolites

Most antimetabolites are effective cancer chemotherapeutic agents via interaction with the biosynthesis of nucleic acids.

Therefore, several of the useful drugs used in antimetabolite therapy are purines, pyrimidines, folates, and related compounds.

The antimetabolite drugs may exert their effects by several individual mechanisms involving enzyme inhibition at active, allosteric, or related sites. The purine and pyrimidine antimetabolites are often compounds incorporated into nucleic acids and the nucleic acid polymers (DNA, RNA, etc.).

The antifolates are compounds designed to interact at cofactor sites for enzymes involved in the biosynthesis of nucleic acid bases.

A. Pyrimidine Drugs (uracil derivatives)

The pyrimidine derivative 5-fluorouracil (5-FU) was designed to block the conversion of uridine to thymidine.

The normal biosynthesis of thymidine involves methylation of the 5-position of the pyrimidine ring of uridine.

The replacement of the hydrogen at the 5-position of uracil with a fluorine results in an antimetabolite drug, leading to the formation of a stable covalent ternary complex composed of 5-FU, thymidylate synthase (TS), and cofactor (a tetrahydrofolate species).

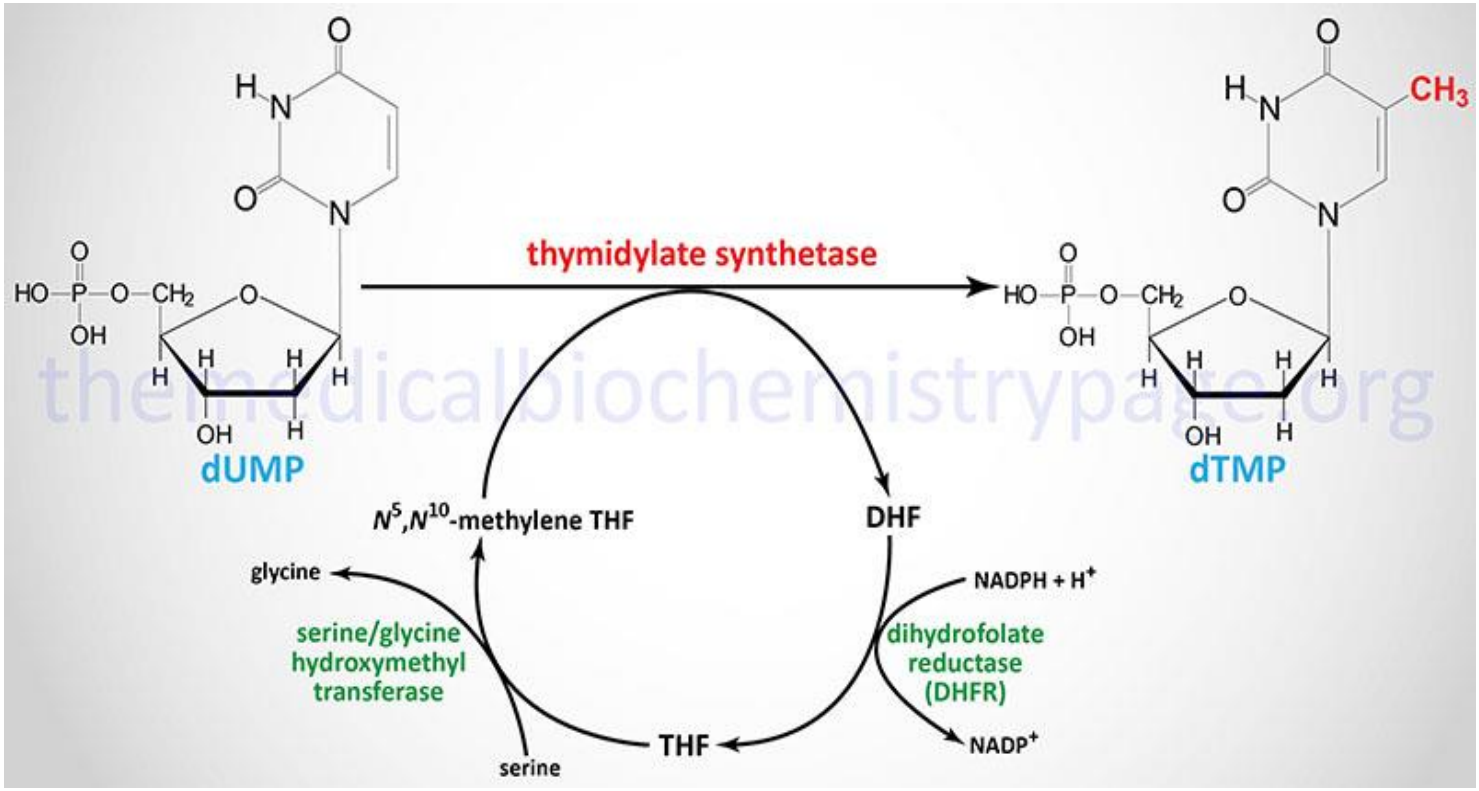
The metabolic activation (anabolism) of 5-FU required to produce the anticancer effects accounts for no more than 20% of the administered amount of drug in most patients.

- Catabolic inactivation via the normal pathways for uracil consumes the remaining approximate 80% of the dose. The major enzyme of pyrimidine catabolism is dihydropyrimidine dehydrogenase (DPD), and 5-FU is a substrate for this enzyme.
- Uracil is a substrate for this enzyme system also and has been dosed with 5-FU and 5-FU prodrugs in an attempt to saturate DPD and conserve active drug species.
- Variability in the levels of DPD activity among the patient population is a major factor in the bioavailability of 5-FU.

- low bioavailability of 5-FU as a result of the catabolic efficiency of DPD and other enzymes has lead to the development of unique dosing routes and schedules as well as the development of prodrug forms of 5-FU.
- TS is responsible for the reductive methylation of deoxyuridine monophosphate (dUMP) by 5,10-methylenetetrahydrofolate to yield dTMP and dihydrofolate.
- Because thymine is unique to DNA, the TS enzyme system plays an important role in replication and cell division.
- The tetrahydrofolate cofactor species serves as both the one-carbon donor and the hydride source in this system.

Biosynthesis of Thymidine

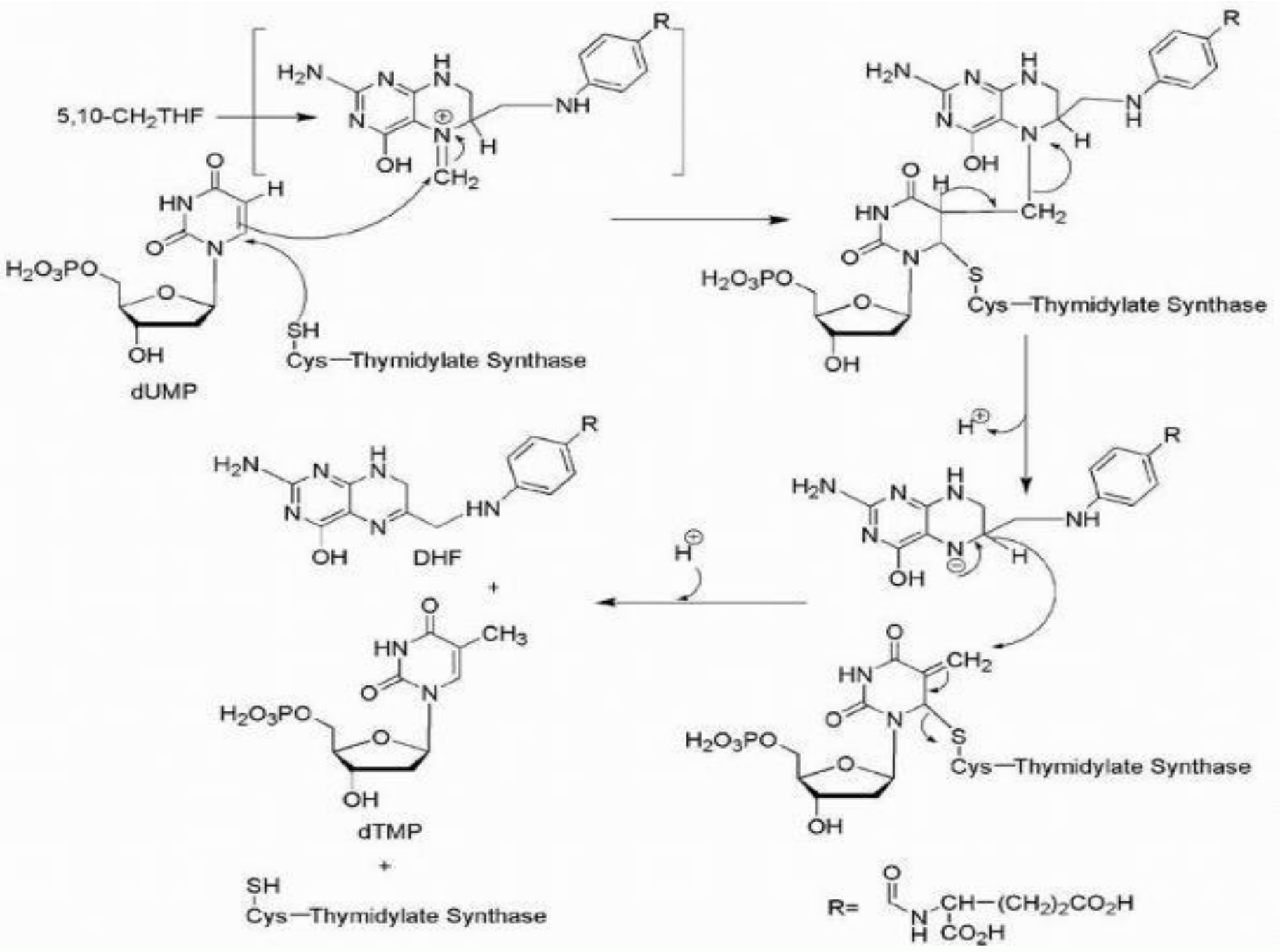
The normal biosynthesis of thymidine involves methylation of the 5-position of the pyrimidine ring of uridine.



- The initial step of the process involves the nucleophilic attack by sulfhydryl group of a cystine residue at the 6-position of dUMP.
- The resulting enolate adds to the methylene of 5,10- CH2-THF perhaps activated via the very reactive N-5- iminium ion .
- The iminium ion likely forms at N-5 and only after 5,10-CH2-THF binds to TS.

The iminium ion is likely formed at N-5 because it is the more basic of the two nitrogens, whereas N-10 is the better leaving group.

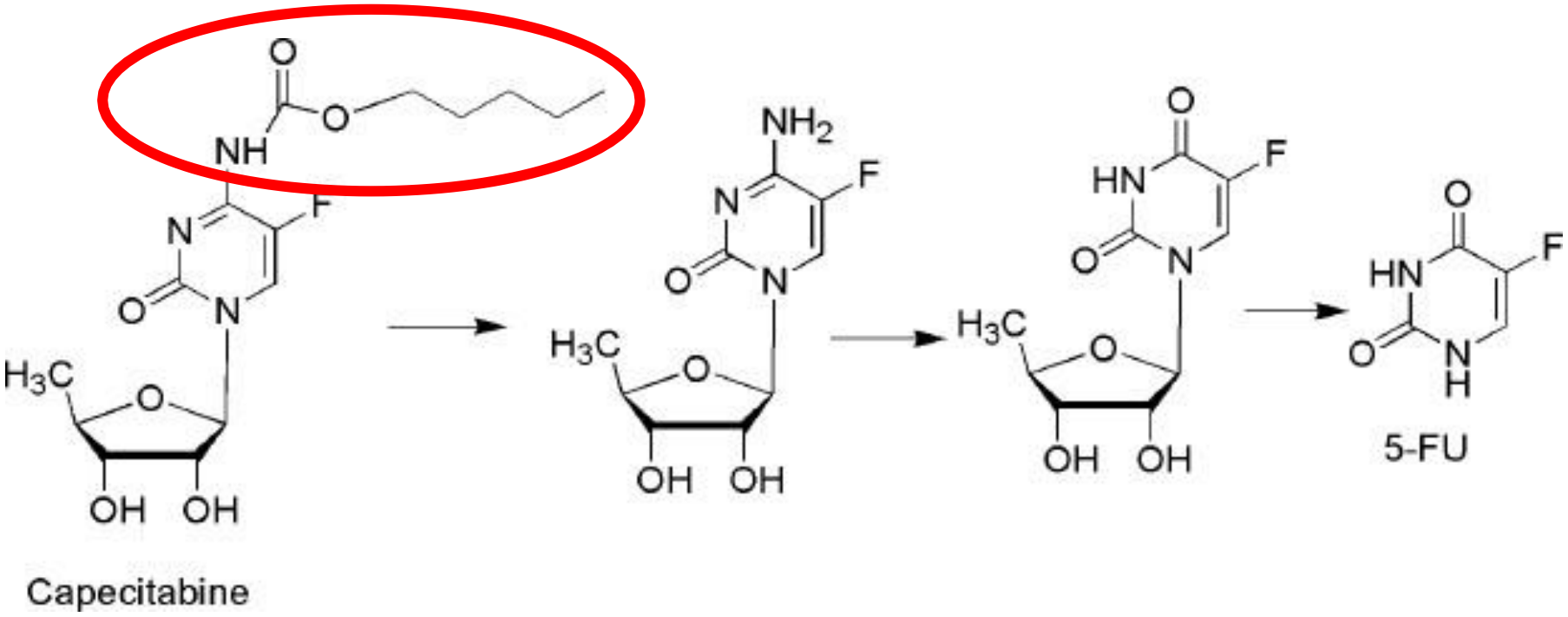
- The loss of the proton at the 5-position of dUMP and elimination of folate yields the exocyclic methylene uracil species.
- The final step involves hydride transfer from THF and elimination to yield the enzyme, DHF, and dTMP.


5,10-CH2THF
dUMP
SH
Cys—Thymidylate Synthase
Cys—Thymidylate Synthase
H+
DHF
+
dTMP
+
SH
Cys—Thymidylate Synthase
Cys—Thymidylate Synthase
R=

- Attempts at chemical modification of 5-FU to protect from catabolic events have produced several prodrug forms, which are converted via in vivo metabolic and/or chemical transformation to the parent drug 5-FU.
- The carbamate derivative of 5-deoxy-5-fluorocytidine is known as capecitabine, and it is converted to 5-FU through a series of activation steps.
- The tetrahydrofuran derivative tegafur is slowly converted to 5-FU but requires quite high doses to reach therapeutic plasma concentrations.
- Esters of the N-hydroxymethyl derivative of tegafur show greater anticancer activity than tegafur.

Metabolic activation of capecitabine to 5-FU

1. Carbamate hydrolysis (decarbamylation).
2. Deamination.
3. Hydrolysis of the sugar moiety to yield 5-FU.



Capecitabine