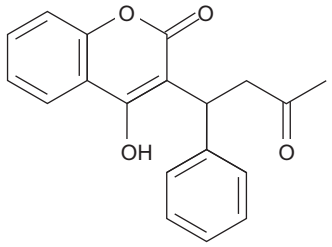
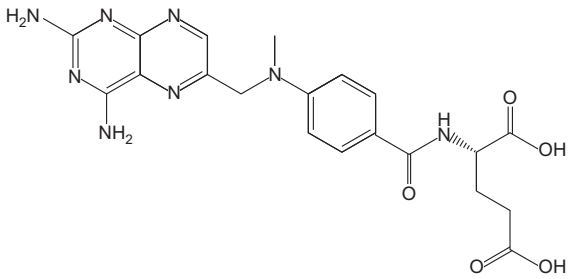
tested in rabbits. It was discovered that the best analog was warfarin (11). Warfarin is also the active ingredient in rodent poison.



Warfarin

b. Origins of Methotrexate and 5-Fluorouracil

The natural substrate of one particular enzyme, dihydrofolate reductase, inspired the design of methotrexate. This natural substrate is *dihydrofolic acid* (12). Dihydrofolic acid is the end-product of the biosynthetic pathway of folates (13). Anticancer drugs that inhibit dihydrofolate reductase were designed by synthesizing and screening chemicals that resembled dihydrofolate (14,15,16). Methotrexate, which is an analog of dihydrofolic acid, and also an analog of folic acid, inhibits dihydrofolic acid reductase. Another antifolate drug used in oncology is 5-fluorouracil. Fluorouracil was invented by Charles Heidelberger (17,18). The drug was developed on the basis of findings in the 1950s that cancer cells incorporated a larger amount of the uracil base into the DNA than normal cells. In testing a number of halogen-substituted uracil compounds, 5-fluorouracil appeared to be the most active and promising drug. Fluorouracil is a *suicide inhibitor* of thymidylate synthase. This means that the enzyme's own catalytic activity results in the activation of the drug, where this activation causes the drug to react covalently with the enzyme, thereby destroying the enzyme's catalytic activity.



Methotrexate

[11]Link KP. The discovery of dicumarol and its sequels. Circulation 1959;19:97–107.

[12]Folic acid is used as a vitamin supplement and for enzymatic studies of dihydrofolic acid reductase. But folic acid is not a naturally occurring chemical. Folic acid is formed during the breakdown of dihydrofolic acid, upon exposure to oxygen. Dihydrofolic acid is a natural product made by microorganisms and plants.

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