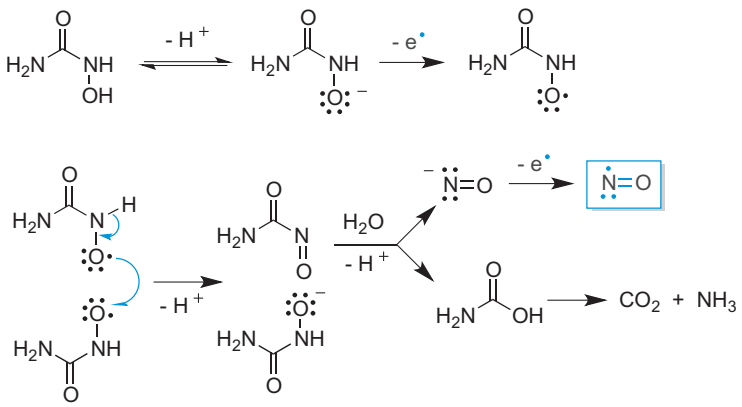
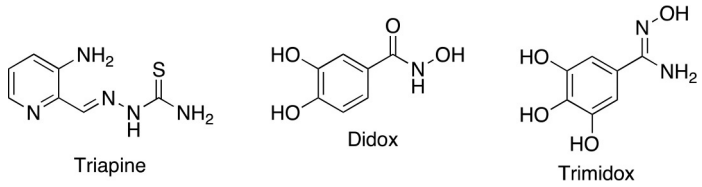


FIGURE 2.9

Mechanism of the peroxidase-mediated formation of nitric oxide from hydroxyurea.

tyrosyl radical of ribonucleotide reductase. 3-AP is a broad-spectrum anticancer agent[15] that has undergone phase I and II clinical studies for a variety of cancers, including solid tumors,[16] metastatic breast cancer,[17] and, in combination with cisplatin, locally advanced cervical cancer.[18]

Hydroxamic acid derivatives such as didox and trimidox are also RNR inhibitors. Didox, which is one of the most potent known inhibitors of the enzyme, has been recommended as a free radical scavenger to be used in combination with doxorubicin in order to lower its cardiotoxicity while enhancing its anticancer activity.[19] Trimidox was initially considered as an anticancer agent,[20] but it is employed mainly as an antibacterial agent for veterinary use.



Triapine Didox Trimidox

3.4 SUBSTRATE ANALOGS AS RIBONUCLEOTIDE REDUCTASE INHIBITORS

Ribonucleotide reductase substrate analogs are normally modified at C-2′, which is the position that undergoes reduction in the natural substrate. Many of these compounds bind covalently to the enzyme.

Tezacitabine (FmdC) is a nucleoside prodrug that shows a dual mechanism of action. Following intracellular phosphorylation, the tezacitabine diphosphate irreversibly inhibits ribonucleotide reductase, whereas the tezacitabine triphosphate can be incorporated into DNA during replication or repair, resulting in DNA chain termination.[21]