3.3 RADICAL SCAVENGERS

The best known inhibitor of ribonucleotide reductase is hydroxyurea (Hydrea®, Droxia®).[8] After oral administration, this compound is well absorbed and transported into cells, where it quenches the tyrosyl radical at the active site of ribonucleotide reductase, inactivating the enzyme (Figure 2.8).[9]

Nitric oxide, an important cell signaling molecule involved in many physiological processes, is one of the metabolic products of hydroxyurea, and its formation may contribute to the antitumor effect of the latter. In fact, nitric oxide is known to inhibit ribonucleotide reductase by itself, probably because it contains an unpaired electron and therefore it is able to quench the Tyr radical.[10] The mechanisms involved in the metabolic transformation of hydroxyurea into nitric oxide are multiple[11] and involve three-electron reduction processes. As an example, the mechanism of the peroxidase-mediated formation of nitric oxide from dismutation of the hydroxyurea radical to generate a nitroso derivative followed by hydrolysis of the latter is shown in Figure 2.9.

Hydroxyurea is primarily used in the management of myeloproliferative disorders, such as chronic granulocytic leukemia, polycythemia vera, and essential thrombocytosis, and is sometimes combined with other antitumor drugs such as the tyrosine kinase inhibitor imatinib.[12] Other applications of hydroxyurea include its use as a radiosensitizer and in AIDS therapy, in combination with didanosine. Hydroxyurea is also useful in the treatment of sickle cell anemia[13] because it eases the pain of the patients. This has been attributed to the previously mentioned generation of nitric oxide, a potent vasodilator.[14]

Thiosemicarbazones, represented by triapine, are another important class of inhibitors of ribonucleotide reductase. Triapine (3-aminopyridine-2-carboxaldehyde thiosemicarbazone, 3-AP) is a very strong iron chelator, and the iron chelate is probably the active species that quenches the active site

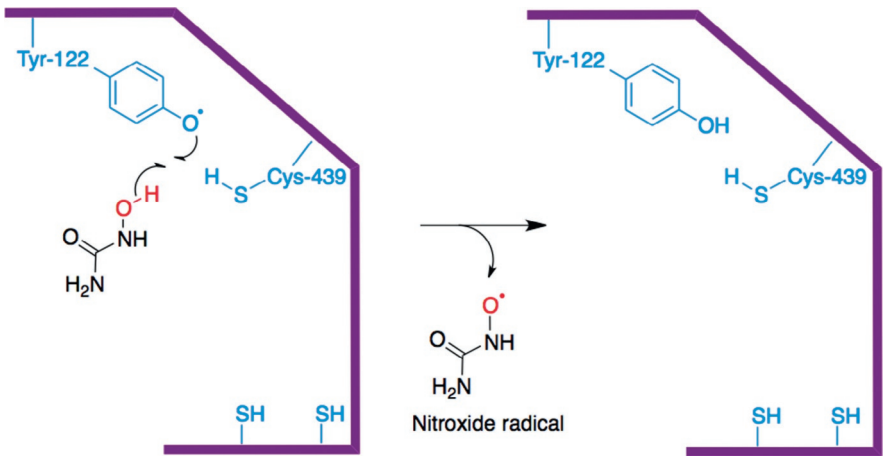

FIGURE 2.8

Mechanism of RNR inhibition by hydroxyurea.