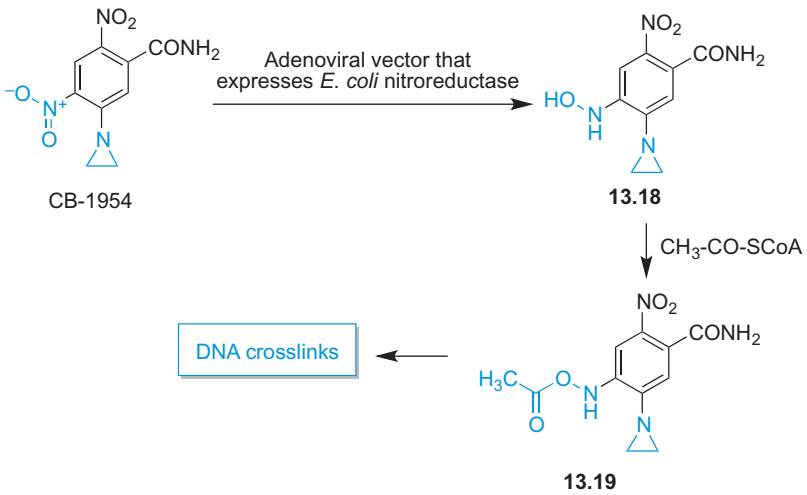

FIGURE 13.22

VDEPT-mediated bioactivation of the prodrug CB-1954.

A affords **13.19**, a potent DNA cross-linking agent (Figure 13.22).[25] Because the activated derivative of CB-1954 has a half-life of only a few seconds, very little of this toxic species is sufficiently stable to escape into the bloodstream and cause side effects. The clinical efficacy of this combination is limited by the low affinity and catalytic efficiency of the nitroreductase NfsB, despite several mutagenesis studies to improve the catalytic process.

It has been discovered that the activation of the prodrug CB-1954 by the enzyme quinone oxidoreductase 2 (NQO2) is dependent of the vitamin B-derived cofactor EP-0152R. This cofactor may travel through the blood, enter into cancer cells, and activate the enzyme NQO2 to efficiently reduce the prodrug CB-1954, allowing a greater than 10,000-fold increase in the prodrug cytotoxicity. This combination, considered as a possible treatment of hepatocellular cancer, has entered clinical trials.[26]

VDEPT approaches have also been used in the case of *N*-oxide bioreductive prodrugs by transfecting tumor cells with a mammalian expression vector, mainly adenovirus, containing the genes encoding for the enzymes necessary for their activation, namely CYP3A4 in the case of the previously discussed banoxantrone (AQ4N; Figure 13.23)[27] and cytochrome 450 reductase in the case of tirapazamine.[28]

VDEPT methodologies are not restricted to hypoxia-selective prodrug activation. For instance, *in situ* transduction by retroviral vectors of pancreatic tumor cells with the cytochrome P4502B1 (CYP2B1) suicide gene that encodes the enzyme responsible for activating cyclophosphamide increases the sensitivity of these cells to this drug. Redirecting adenoviruses to fibroblast growth factor receptors (FGFRs) localized to the plasma membrane of pancreatic tumor cells by using the FGF2-Ad-CYP2B/CPA system highly increases the potency of the CYP2B1/CPA suicide system.[29] In a related approach aimed at the treatment of gliomas, a mutant herpes simplex virus type 1 has been developed with insertion of two prodrug-activating genes—CYP2B1 and secreted human intestinal carboxylesterase. These enzymes can convert the inactive prodrugs cyclophosphamide and irinotecan (CPT-11) into their active metabolites.[30]