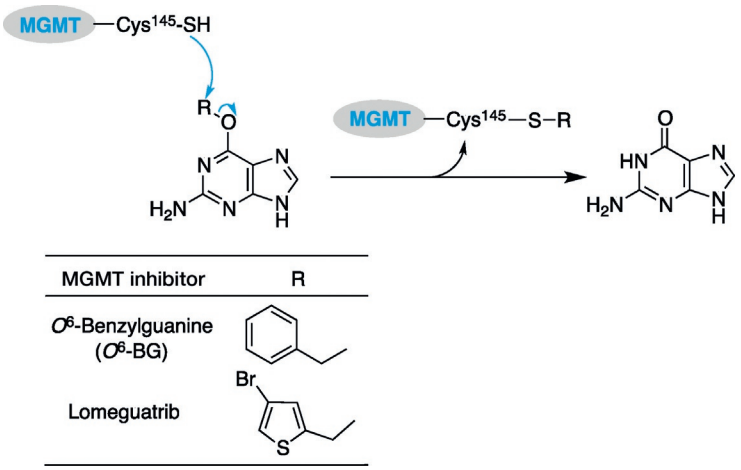

FIGURE 14.17

MGMT inactivation by O^6-benzylguanine and lomeguatrib.

group to its Cys-145 residue (Figure 14.17). Among these compounds, O^6-benzylguanine and lomeguatrib are being clinically evaluated in combination with temozolomide,[114,115] carmustine,[116] or BCNU. Triple combinations including a topoisomerase I inhibitor, such as irinotecan, are also under clinical evaluation.[117]

The acidic (pK_a 4.8) Cys-145 residue of MGMT is susceptible to nitrosylation. It has been proven that the potent nitrosylating agent nitroaspirin (NCX-4016), which may be useful to overcome tumor immunosuppression, is also a clinically relevant inhibitor of human MGMT that increases the efficacy of alkylating agents (Figure 14.18).[118]

Platinum anticancer drugs, which are not influenced by the MGMT proteins because their primary mode of action involves interaction with the guanine N-7 rather than with O-6, can reduce their

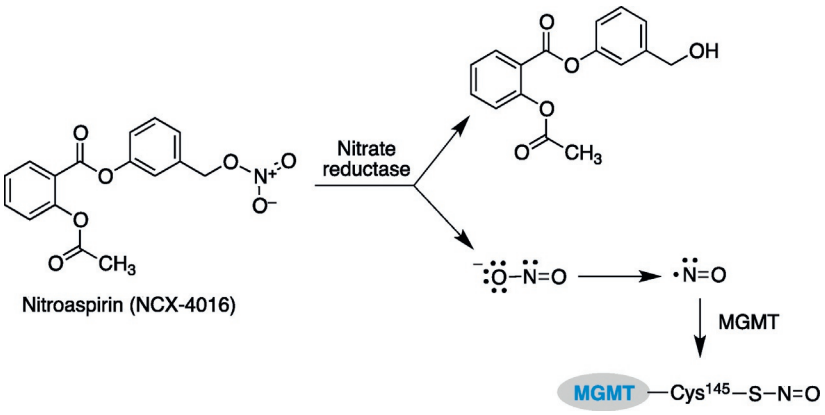

FIGURE 14.18

Nitrosylation of MGMT by nitroaspirin.