4.2.1 Inhibitors of DNA Glycosylases

DNA glycosylases monitor the presence of aberrant bases in order to remove them. They flip the damaged nucleotide out of the double helix and place it into their active site, where wrong bases are bound through π-stacking interactions. Glycosylases are grouped into four superfamilies, namely the UDG and AAG families, which are small, compact glycosylases, and the MutM/Fpg and HhH-GPD families, which comprise larger enzymes with multiple domains.

Monofunctional glycosylases, which normally are involved in the repair of deaminated or alkylated bases, hydrolyze the *N*-glycosidic bond that links these bases to the DNA backbone. The hydrolysis is carried out by a hydroxide anion generated by deprotonation of a molecule of water by an Asn or Asp enzyme residue (Figure 14.20).[122]

Bifunctional glycosylases normally remove bases that have sustained oxidative damage, and their catalytic cycle involves an initial S_N1-like attack at the C-1′ position by Lys or Pro residues that remove the aberrant base. In a second step, because of their purinic–apyrimidinic (AP) lyase activity, they catalyze a subsequent β-elimination reaction of the 3′-phosphodiester bond on the protonated Schiff base intermediate and subsequent hydrolysis, which results in strand scission (Figure 14.21).

Inhibition of the activity of DNA glycosylases can in principle be used to potentiate the activity of base-damaging anticancer drugs or radiation therapy, although the field is in its early stages of development and there are still no useful drugs based on this concept.[123] Some analogs of oligonucleotides, more chemically stable and obtained using solid phase DNA synthetic methodology,[124] are DNA glycosylase inhibitors because these enzymes are end product inhibited.[125,126] These compounds are reduced abasic site analogs (e.g., compound **14.1**), oligonucleotides containing pyrrolidine moieties that mimic the positive charge at the transition state (e.g., **14.2**), and nucleotides with stabilized glycosidic bonds that cannot be processed by DNA glycosylases (e.g., **14.3**).

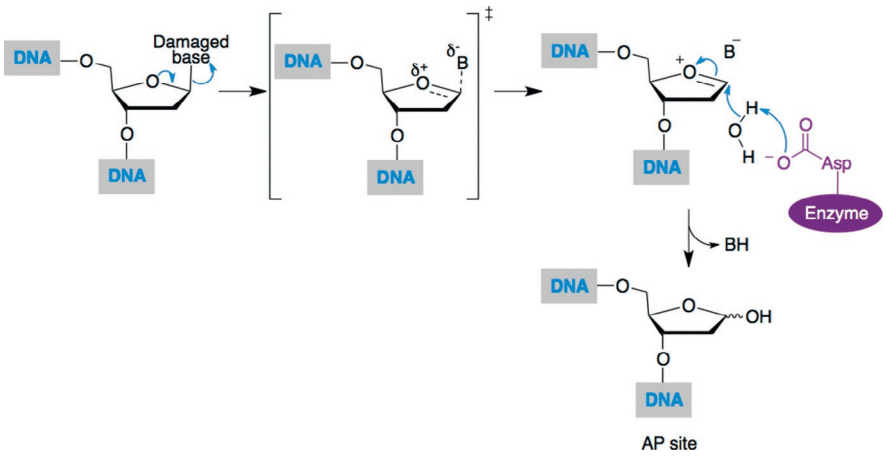

FIGURE 14.20

Mechanism of the reaction catalyzed by monofunctional DNA glycosylases.