**Struggle Alert 5**

**Section 20.7.3.1** **Prodrugs of Transcriptase Inhibitors**

Adefovir dipivoxil and tenofovir disoproxil both contain a protected phosphonate group (Fig. 1).



**Figure 1** Structures of adefovir dipivoxil and tenofivur disoproxil.

A phosphonate group differs from a phosphate group in having a P-C bond in place of a P-O bond (Figure 2). In comparison with a P-O bond, the P-C bond is stable and is not susceptible to hydrolysis. Therefore, a phosphonate group can be used as a more stable bio-isostere for a phosphate group.



**Figure 2** Distinction between a phosphonate group and a phosphate group.

The phosphonate groups that are present in adefovir dipivoxil and tenofovir disoproxil are both protected by an 'extended' protected group - so called because the metabolic reaction that will result in deprotection occurs at a functional group which is separated from the phosphonate group itself (Fig. 3). In adefovir dipivoxil, the extended protecting groups are two esters, whereas in tenofovir disoproxil, the extended protecting groups are carbonates.



**Figure 3**  Metabolically labile functional groups in the extended protecting groups present in adefovir dipivoxil and tenofivur disoproxil.

Both of these functional groups are susceptible to hydrolysis by esterase enzymes in vivo once the prodrug has been administered. Esterase-catalysed hydrolysis of each ester group in adefovir dipivoxil results in the formation of a chemically unstable product which spontaneously decomposes with loss of formaldehyde to release the parent drug (Fig. 4). Once formed, the phosphonate undergoes enzyme-catalysed phosphorylation to produce the active form of the drug.



**Figure 4** Enzyme-catalysed hydrolysis and spontaneous decomposition of each protecting group in the prodrug adefovir dipivoxil to form the parent drug, followed by enzyme-catalysed phosphorylation to produce the active form of the drug. The protecting groups are coloured green.

The mechanism involved in the conversion of tenofovir disoproxil to the parent drug and its subsequent phosphorylation to the active form of the drug is very similar (Fig. 5).



**Figure 5** Enzyme-catalysed hydrolysis and spontaneous decomposition of each protecting group in the prodrug tenofovir disoproxil to form the parent drug, followed by enzyme-catalysed phosphorylation to produce the active form of the drug. The protecting groups are coloured green.