functionality, it still exhibited poor oral bioavailability ($F = 4.3\%$). To improve the oral bioavailability, an ethyl ester prodrug of GS4071's carboxylic acid functionality was prepared.[17] This ester prodrug GS4104 (oseltamivir) (**9**, Figure 12.5) resulted in an oral bioavailability for the parent compound GS4071 of 30–35% in mice and rats, 73% in dog and 11% in ferrets.[17] Rats and mice were shown to convert GS4101 more rapidly to the parent GS4071 than dog and ferret, both of which showed significant circulating prodrug levels.[18] It was shown that this ester prodrug was readily hydrolyzed to the parent by esterases in the blood, but that the prodrug showed poor activity *in vitro* consistent with the need for esterase conversion. Oseltamivir was subsequently shown to be effective in the mouse and ferret models of influenza infection when given orally twice daily.[17,19] Human clinical PK studies showed that after a single dose (20, 50, 100, 200, 500, 1000 mg), oseltamivir levels were observed at ~1 h after administration and declined rapidly with concomitant emergence of the active parent GS4071.[20] Subsequent clinical studies revealed that oseltamivir is effective at inhibiting influenza virus infection in humans and it is now marketed as Tamiflu.

12.3 Prodrugs of Phosphates and Phosphonates

In order for a nucleoside analog to function as an inhibitor of a viral polymerase, it must be converted intracellularly to its 5′-triphosphate *via* the action of three separate kinases. Frequently, a nucleoside analog is a poor substrate for the first and most discriminating kinase in the phosphorylation cascade. In such cases, where the nucleoside triphosphate is a potent inhibitor of the target enzyme, it is desirable to deliver the nucleoside monophosphate (nucleotide) into the cell, thus bypassing the first non-productive phosphorylation step. In addition, methylene phosphonates have been used as stable surrogates for a phosphate moiety, especially in the case of acyclic nucleotide analogs. The presence of a charged phosphate or phosphonate moiety limits a nucleotide's ability to cross biological membranes and, in the case of a nucleotide containing a 5′-phosphate group, introduces a level of chemical and enzymatic instability resulting in poor pharmacokinetic and pharmaceutical properties. Consequently, phosphate and phosphonate prodrugs have been critical to enabling the development of nucleotide analogs to treat human diseases.

In the realm of antiviral therapy, nucleotide analogs have played a prominent role.[5–7,21] They have been shown to be potent inhibitors of viral polymerases in the treatment of viral diseases such as human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), herpes viruses (HSV-1, HSV-2), varicella zoster virus (VZV), Epstein–Barr virus (EBV) and cytomegalovirus (CMV). Many prodrug strategies have been developed for delivering nucleotide analogs (Figure 12.6), including the phosphoramidates, acyloxyalkyl esters, *S*-acylthioethyl esters (SATEs), aryl- and lipid phosphate esters and cyclic esters comprising HepDirect, cycloSal and 3′,5′-cyclic phosphates (Figure 12.6).[7,21,22] Each of these has proven effective at delivering