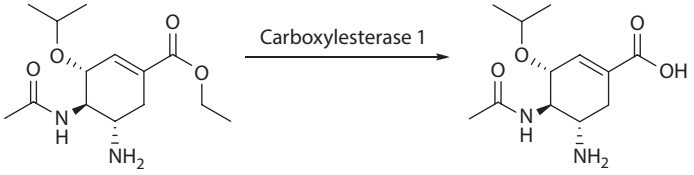
10.5.2 Improved Passive Permeability

During its absorption, the molecule has to pass through several cell membranes that represent an "impermeable" barrier which only relatively lipophilic uncharged molecules can cross by passive diffusion. However, the permeability across the biological membranes remains one of the major obstacles for polar and charged drugs. Their poor permeability tends to result in low and often variable oral absorption, low oral bioavailability, and low exposure for specific target organs. The improvement of passive drug permeation has been the most successful area of prodrug research so far, and most frequently the lipophilicity of the parent drug has been enhanced by masking its polar and ionized functionalities. Typically, short hydrocarbon moieties have been attached to the polar or ionized groups of the hydrophilic parent drug to increase its lipophilicity. Hydrophilic hydroxyl, carboxyl, phosphate, or amine groups have been converted to the more lipophilic alkyl or aryl esters, which are rapidly hydrolyzed back to their parent drugs in the body by the ubiquitous esterase activity. The majority of the lipophilic prodrugs have been developed for improved absorption from the gastrointestinal tract. Additionally, this prodrug strategy has been employed to improve topical administration of parent drugs through the skin or come in the eye.

Oseltamivir is a dosed active prodrug of oseltamivir carboxylate which is a selective inhibitor of neuraminidase enzyme of the influenza viruses A and B (Figure 10.8). As a more lipophilic ethyl ester, oseltamivir is rapidly and readily absorbed from the gastrointestinal track. In fact, almost 80% of an oral dose of oseltamivir reaches systemic circulation as oseltamivir carboxylate, whereas the oral bioavailability of hydrophilic oseltamivir carboxylate is only 5% in humans. Once absorbed, oseltamivir undergoes rapid bioconversion to its parent drug and ethanol by the catalytic action of human carboxylesterase 1, and the maximal plasma levels are reached within 3–4 hours after oral dose.

Sofosbuvir is a novel pyrimidine nucleotide analog that inhibits nonstructural protein 5B (NS5B) polymerase of hepatitis C virus and is used for the treatment of chronic hepatitis C infection in adults as a once-daily oral dose regimen. Initially, 2′-deoxy-2′-fluoro-2′-C-methyluridinemonophosphate was discovered as a precursor for the highly potent NS5B polymerase inhibitor 2′-deoxy-2′-fluoro-2′-C-methyluridinetriphosphate, but as a very hydrophilic compound it was unable to sufficiently cross biological membranes. Thus, a more lipophilic phosphoramidate prodrug of 2′-deoxy-2′-fluoro-2′-C-methyluridinemonophosphate, sofosbuvir which enable oral dosing, was developed. Sofosbuvir is metabolized at its desired site of action, in liver, to yield active tri-phosphorylated nucleotide. In fact, the release of an active triphosphate nucleotide is proposed to occur via four enzymatic steps and two spontaneous reaction (Figure 10.9). The key enzymes involved in the enzymatic steps include human catepsin A, carboxylesterase 1, and histidine triad nucleotide-binding protein 1.

Prostaglandin analogs latanoprost, bimatoprost, travoprost, and isopropyl unoprostone represent a class of lipophilic ocular prodrugs for the treatment of high intraocular pressure in glaucoma (Figure 10.10). Latanoprost, travoprost, and isopropyl unoprostone are isopropyl ester and bimatoprost is ethanolamine amide prodrugs, respectively, which are hydrolyzed in intraocular tissues to generate their biological active prostaglandins. Their active carboxylic acids are poorly permeable and cause eye irritation, whereas an improved ocular absorption and safety is achieved with their more lipophilic prodrugs.



Oseltamivir Oseltamivir carboxylate

FIGURE 10.8 Bioconversion of oseltamivir to more hydrophilic oseltamivir carboxylate.