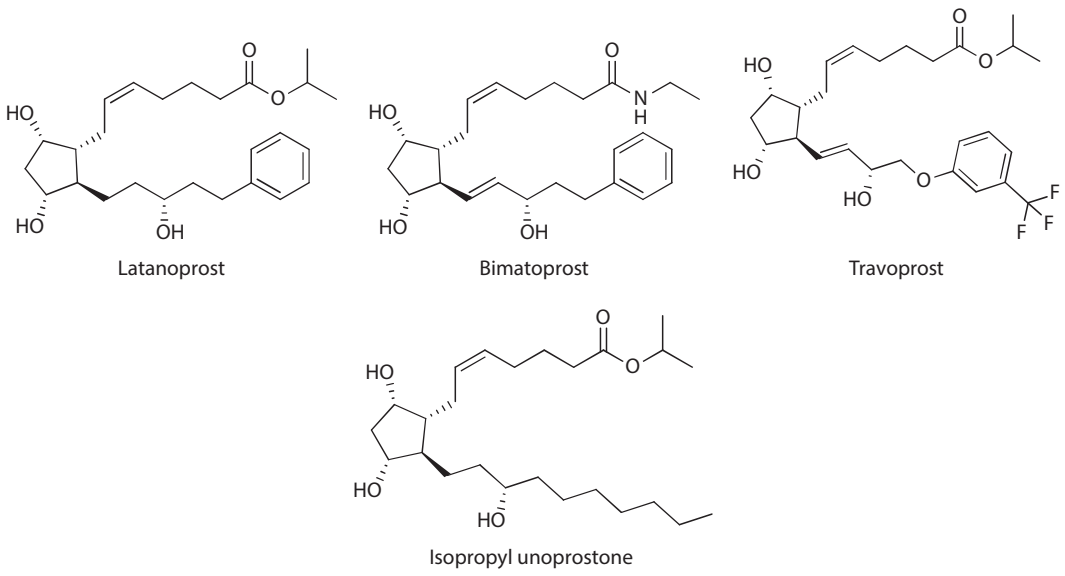

FIGURE 10.10 Chemical structures of latanoprost, bimatoprost, travoprost, and isopropyl unoprostone.

Other examples of prodrugs with improved lipophilicity or permeability include enalapril, pivampicillin, fenofibrate, olmesartan medoxomil, adefovir dipivoxil, tenofovir disoproxil, tenofovir alafenamide, famciclovir, dabigatran, and tazarotene.

10.5.3 Improved Transporter-Mediated Permeability

Transporters are membrane proteins that act as gatekeepers for cells, controlling the intake and efflux of crucial polar endogenous compounds. The specificity of these transporters is, however, not limited to their endogenous substrates, and other molecules that bear a close structural resemblance can be transported across cell membranes by these transporters as well. Transporter-mediated permeability is particularly important for polar and charged drugs which have negligible passive absorption. While surprisingly many drugs already exploit the transporters of gastrointestinal tract during their absorption, a number of prodrugs have designed as substrates of these transporters. Successful design of transporter-targeted prodrugs requires good knowledge about the structure–activity features of the transporter in question.

Valacyclovir and valganciclovir, the L-valine amino acid esters of acyclovir and ganciclovir, respectively, are probably the first examples of commercially available prodrugs that utilize intestinal peptide transporter 1 (PepT1) to overcome the limited and variable oral bioavailability of their highly polar parent drugs (Figure 10.11). PepT1 is an active influx mechanism for dietary di- and tripeptides located in the small intestine, and its utilization by L-valyl prodrug strategy increased the intestinal permeation of acyclovir and valganciclovir by 3–10-fold. After their absorption, both prodrugs are rapidly converted to their parent drugs by intracellular hydrolytic enzymes. Actually, both valacyclovir and valganciclovir act as double prodrugs, since like other nucleosides, they require triphosphorylation prior to formation of the active antiviral agents.

Gabapentin enacarbil is an acyloxyalkylcarbamate prodrug of analgesic and anticonvulsant drug gabapentin which has problematic pharmacokinetic properties, including short half-life, saturable absorption, high inter-patient variability, and lack of linear dose–response relationship. Gabapentin enacarbil was designed to be absorbed throughout the entire length of the gastrointestinal tract, and its absorption is mediated by high-capacity nutrient transporters,