that a compound known to produce potential carcinogens, mutagens, and teratogens can remain on the market, especially in light of the strong focus on safety in the modern era of drug discovery?

The answer to this question is relieved by examining the pharmacokinetic properties of nitrofurantoin. When delivered orally, a 100 mg dose is rapidly removed after initial absorption. Approximately 75% of the dose is metabolized on first pass, while the remaining ~25% is excreted into the urinary tract as unchanged drug. As a result, the peak plasma concentration of a 100 mg dose of nitrofurantoin is less than 1 μg/mL and tissue penetration is negligible in all parts of the body except the urinary track. Drug concentration in the urinary tract, on the other hand, can exceed 200 μg/mL. This is in excess of the concentration required to kill invading bacteria.[27] Essentially, nitrofurantoin's pharmacokinetic properties prevent it from reaching other parts of the body, limiting its utility to urinary tract infections and preventing damage associated with its mechanism of action. Tissue distribution, metabolism, and excretion are key to the decades of success that this drug has seen. Interestingly, it is unlikely that this drug would have been developed in modern drug discovery programs. It would almost certainly been tossed aside based on possible risk associated with the aryl nitro group.

SELDANE® (TERFENADINE) VERSUS ALLEGRA® (FEXOFENADINE): METABOLISM MATTERS: SAFETY

The science of drug discovery and drug development is littered with examples of promising compounds and even marketed drugs that have encountered serious safety issues. In the case of marketed therapeutics, the sponsor companies often withdraw the drug from the market even if this is not required by regulators. The sudden and unexpected loss of revenue can radically change the fortunes of the sponsor company. At the same time, the removal from the market of a previously successful drug can provide an opportunity for the development of novel therapies, especially if a related compound with similar properties can be identified. Such is the case with the non-sedating antihistamine Allegra® (Fexofenadine, Figure 13.13(b)).

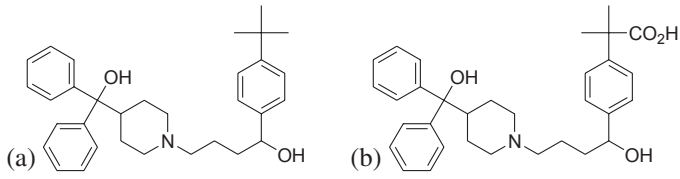

FIGURE 13.13 (a) Seldane® (terfenadine) and (b) Allegra® (Fexofenadine).