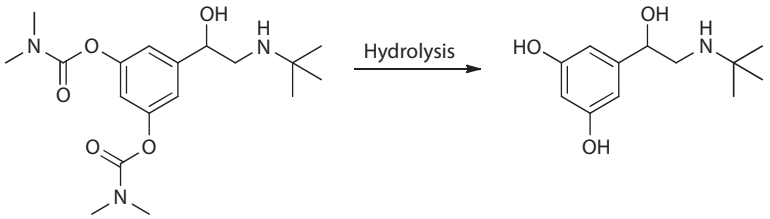

Bambuterol Terbutalin

FIGURE 10.17 Structure and butyrylcholinesterase catalyzed hydrolysis of bambuterol to active terbutaline.

of the sustained release, a once-daily bambuterol treatment provides the relief of asthma symptoms with a lower incidence of side effects than terbutaline taken three times a day.

10.5.6 Prolonged Duration of Drug Action

Prolonged duration of drug action, sustained plasma levels, and reduced dosing frequency are typically achieved by controlled-release formulations, such as suspensions, osmotic pumps, and polymeric matrixes. Using prodrug approaches, the controlled release of an active drug can be achieved by modifying its aqueous solubility, partition and dissolution properties in a way that affects the release rate of the active drug, the rate of absorption from injection site, or alter its tissue distribution. Prodrug approaches have been very successful in the development of several parenteral sustained release depot injections which maintain therapeutic plasma levels for weeks to months. In this approach, the free hydroxyl group of parent drug is esterified with a long-chain fatty acid to form respective ester prodrugs, such as decanoates, palmitates, cypionates, or valerates. These highly lipophilic prodrugs are formulated in a vegetable oil and slowly released in the systemic circulation from the site of subcutaneous or intramuscular injection resulting in sustained plasma levels of 2–8 weeks. This approach has resulted in many commercially available oily depot injection products from several drugs including estrogens (e.g., estradiol), neuroleptics (e.g., fluphenazine, flupentixol haloperidol, pipotiazine, and zuclopenthixol), contraceptive (e.g., hydroxyprogesterone and norethisterone), and steroids (e.g., nandrolone and testosterone).

Examples of other prodrugs with prolonged duration of action include lisdexamfetamine.

10.6 CHALLENGES AND CONSIDERATIONS IN PRODRUG DISCOVERY AND DEVELOPMENT

Prodrug strategies have been successful in a number of drug discovery cases based on clinically approved prodrugs and as illustrated earlier in the text. However, embarking on a prodrug strategy can bring some additional complications to the drug discovery and development processes. For example, synthesis difficulties, more complex analytical profiling, bioconversion, further metabolism and pharmacokinetic studies requiring the analysis of both the prodrug and parent drug as well as concerns about the toxicity of not only the prodrug and drug, but also the released promoieties or by-products bring an additional challenge to prodrug discovery and development strategy. In addition, navigating the regulatory environment with prodrugs is far from straightforward, particularly when prodrugs of already marketed drugs are developed.

10.6.1 Bioconversion of Prodrugs

Efficient and site-controlled conversion of a prodrug to the parent drug is critical for the prodrug approach to be successful. Typically, conversion involves metabolism by enzymes that are distributed throughout the body. The most common prodrug approaches rely on metabolic bioconversion to the