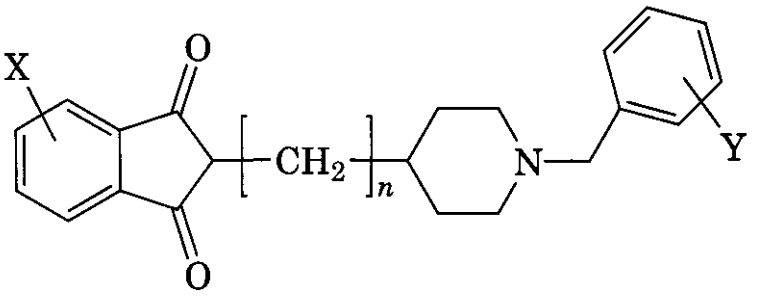
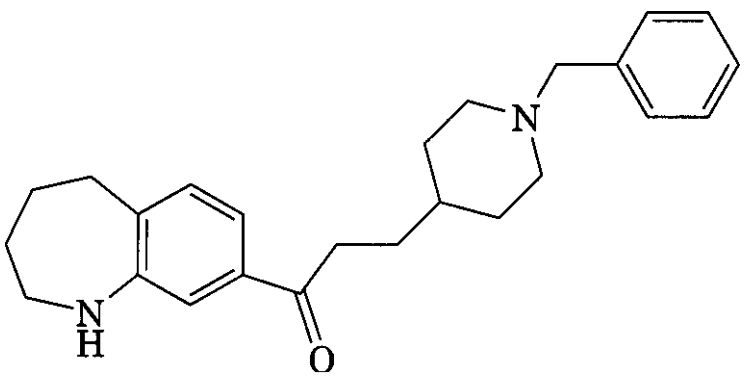
in peripheral tissues (140). This may be a consequence of the high serum levels required to get these highly cationic molecules to penetrate the blood–brain barrier.

In a discovery project that is reminiscent of the discovery of captopril, scientists at Takeda created a hypothetical structure for the active site of acetylcholinesterase, based on *SAR* from previous biochemical and medicinal chemical work (141). The model consisted of (in addition to the serine protease-like catalytic machinery) an anionic binding site separating two discrete hydrophobic binding sites. This model was then used to design inhibitors of the enzyme (reviewed in ref. 142). One set of analogs examined were based on the *N*-(ω-phthalimidylalkyl)-*N*-(ω-phenylalkyl)-amine (scaffold 66). An iterative process of testing,



(66)

analysis, design, and synthesis, by use of this and closely related scaffolds, resulted in the production of (67) (TAK-147), which is currently in clinical trials for treatment of the dementia resulting from Alzheimer's disease (142).



(67) TAK-147

The design of (66) was partially based on the structures of previously known inhibitors. The two aryl substituents were intended to bind to the hydrophobic binding sites, placing the central amine cation into the anionic binding site. The length of both alkyl linkers was varied, and the effect of adding a third alkyl substituent was examined. The phthalimide portion of the structure was chosen to improve the synthetic accessibility of the analogs needed for this exercise. The compounds were tested not only for inhibitory potency toward rat cerebral acetylcholinesterase, but also for peripheral response and toxicity in dosed intact rats. After the work was under way, Sussman and coworkers solved the atomic structure of acetylcholinesterase from the electric eel, including complexes with several inhibitors, by X-ray crystallography (143). The availability of this structure made it possible to retrospectively analyze the basis for the *SAR* in this series of compounds, by use of DOCK (144).

2.6.2 Neuraminidase. Influenza virus infections cause severe human suffering throughout the world and economic damage in the billions of dollars annually, although some years are worse than others. In 1918 a pandemic caused by this disease killed an estimated 40 million people (145). An important protein in the infectious process is the viral neuraminidase, an integral membrane protein whose catalytic domain is exposed on the viral surface. Neuraminidase catalyzes the hydrolytic cleavage of sialic acid (68, *N*-acetylneuraminic acid) from glycoproteins and extracellular mucin on the surface of the host cell. A different viral surface protein tightly binds to terminal sialic acid residues. which promotes the initial infection, but prevents release of viral progeny from the host cells, unless and until the terminal sialic acids are hydrolytically cleaved by viral neuraminidase. Thus, neuraminidase enables the infection to propagate.

The first X-ray structure of influenza neuraminidase was determined in the early 1980s (146). Ten years later, a landmark paper (147) described a highly efficient drug design project at Monash University in Australia. This project yielded antiviral compound (69)(zanamivir, Relenza, or Flunet), which was developed into one of the first drugs to be created through use of SBDD. Previous structural work had revealed that the active site of neuraminidase has several rigid pockets and nu-