Chapter XXV
Development of Specific Gamma Secretase Inhibitors

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ABSTRACT

Secretases are aspartic proteases, which specifically trim important, medically relevant targets such as the amyloid-precursor protein (APP) or the Notch-receptor. Therefore, changes in their activity can lead to dramatic diseases like M. Alzheimer caused by aggregation of peptidic fragments. On the other hand, the secretases are interesting targets for molecular therapy of the multiple myeloma, because the over-expressed Notch-receptor does not emerge into the native conformation until the cleavage by the presenilin, the active and catalytic subunit of the gamma secretase, occurs. Here, we focus on a novel methodology of structure-based drug development, feasible without prior knowledge of the target structure—analogy modeling. This combination of similarity screening, fold recognition, ligand-supported modeling, and docking is exemplarily illustrated for the structure of presenilin and specific inhibitors thereof.

INTRODUCTION

Aspartic proteases have received considerable attention as potential targets for pharmaceutical intervention since many play important roles in physiological and pathological processes. Despite numerous efforts, the only inhibitors for aspartic proteases currently on the market are directed against the HIV protease, an aspartic protease of viral origin (Eder et al. 2007). All other known aspartic protease inhibitors including those targeting renin, BACE1 and gamma secretase (Tsai et al. 2002) did not yet overcome the clinical or preclinical development due to problems regarding their specificity.

Alzheimer disease (AD) is the most frequent cause of dementia. About five million patients in the seven largest Western economies suffer from that disease. The common form affects humans over 60 years of age and its incidence increases as age advances. AD is characterized by a progressive loss of short-term memory and impaired cognitive function. In later stages additional symptoms aggravate the

Figure 1. Processing scheme for the ß-amyloid precursor protein. APP (Amyloid Precursor Protein) is processed in two steps. First, beta secretase generates two fragments, the beta-amyloid precursor peptide and the C-terminal fragment (CTF-ß) C99 fragment. In a second step, the gamma secretase cleaves the C99 fragment into an Aß fragment and AICD (APP Intracellular Domain). Sometimes the gamma secretase generates an Aß fragment with 42 amino acids instead of 40. The 42 peptide aggregates rapidly to amyloid plaques with the fatal consequence that the nerve cell degrades (Figure adopted from Wrede, 2005).