SECRETASE SUBSTRATES INHIBITORS BACHEM
PIONEERING PARTNER FOR PEPTIDES
SECRETASE SUBSTRATES AND INHIBITORS

The deposition of amyloid β-peptide (Aβ) in the brain represents a neuro-pathological feature of Alzheimer’s disease (AD). Aβ is generated from its precursor protein (APP) via cleavage by β- and γ-secretases. Reducing Aβ production by inhibiting β- and γ-secretases has been suggested as a specific therapeutic intervention in preventing the progression of the disease. The activation of α-secretase, which cleaves APP within the amyloid region and thereby increases the non-amyloidogenic processing of APP, has been considered as an additional approach.

Alzheimer’s disease (AD), first described by Alois Alzheimer in 1906, is the leading cause of dementia in elderly people. Throughout the world, approximately 10% of the people in their 70s and 30% in their 80s suffer from AD. Altogether more than 26 million individuals worldwide suffer from AD. Symptoms include forgetfulness, estrangement of the family members and friends, depression, and loss of homing instinct and sense of time. These changes are due to the progressive dysfunction and death of nerve cells that are responsible for the storage and processing of information. Death occurs on average 9 years after diagnosis.

In 1991, the search for genetic linkages yielded an important information: mutations in the amyloid β-precursor protein (APP) caused early-onset (familial) AD. These mutations occurred in and around the amyloid β-peptide region of the precursor protein. These findings, together with the observation that amyloid β-peptides (Aβ) readily form neurotoxic fibrils, confirmed the assumption that the accumulation and deposition of amyloid β-peptides in the brain over decades leads to neuronal dysfunction and eventually clinical manifestation of AD. Thus, the first step to slow amyloid β production is based on an understanding of the fundamental mechanisms of the proteolytic processing of APP by the α-, β-, and γ-secretases.

APP Processing
A key step in the pathogenesis of AD is the proteolysis of APP resulting in the formation of amyloid β-peptides, the principal components of the cerebral plaques found in the brains of patients with AD. These insoluble 40-/42-amino acid peptides are formed by the cleavage of APPs consisting of 695 to 770 amino acids. APPs are widely expressed in cells throughout
the body. They represent integral membrane proteins with a single membrane-spanning domain, a large extracellular glycosylated amino-terminus and a shorter cytoplasmic carboxy-terminus. The amyloid β-peptide is located at the cell surface, with part of the peptide embedded in the membrane. Proteolytic processing of APP can be considered as a two step process, which involves ectodomain shedding by either α-secretase (non-amyloidogenic pathway) or β-secretase (amyloidogenic pathway) and subsequent cleavage by γ-secretase. β-Secretase (BACE1) cleavage of APP results in the generation of a soluble 100 kD amino-terminal fragment (sAPPβ) and a 99-residue membrane-bound carboxy-terminal fragment (C99 or CTFβ, ~12 kD) (amyloidogenic pathway, Fig. 1a).

In contrast, α-secretase (TACE, TNF-converting enzyme) cleaves APP to produce secreted neurotrophic and neuroprotective APP (sAPPα) and an 83-residue carboxy-terminal fragment (C83, also known as CTFα) (non-amyloidogenic pathway, Fig. 1b). Production of sAPPα increases in response to electrical activity and activation of muscarinic acetylcholine receptors, suggesting that neuronal activity enhances α-secretase cleavage of APP. Both, CTFβ and CTFα can be further hydrolyzed by γ-secretase releasing amyloid β-peptides and P3 peptide, respectively. Recently, additional proteolytic sites between amino acid residues 49 and 50 (ε-cleavage site) and residues 46 and 47 (ζ-cleavage site) have been described. ε- and ζ-cleavage precedes the generation of Aβ40/42 by γ-secretase and results in the release of the APP intracellular domain (AICD).

Aβ40 is the major type of amyloid β-peptides secreted into normal human cerebrospinal fluid, whereas a small proportion represents a 42-residue carboxy-terminal variant (Aβ42). The longer and more hydrophobic Aβ42 is much more prone to fibril formation than Aβ40, and even though Aβ42 constitutes a minor component of all Aβ peptides, it is the major Aβ species found in cerebral plaques. AD-causing mutations in APP near the β- and γ-secretase cleavage sites promote the formation of Aβ42. The transformations near the β-secretase cleavage site augment β-site proteolysis, leading to the elevation of Aβ40 and Aβ42. Inhibiting β- and γ-secretases might reduce the burden of amyloid β-peptide in AD patients' brains, which might then slow the progression of the disease.

The assumption that amyloid β-peptides α-Secretase cleaves membrane-bound APP in the middle of the amyloid region, thereby preventing the formation of Aβ, whereas β-secretase is required for generating Aβ40 and homologs.

**Fig. 1a. Amyloidogenic Pathway.** Cleavage of APP by β-secretase (BACE1) and γ-secretase (a complex containing presenilin (PS) as the putative catalytic component) leads to the generation of Aβ.

**Fig. 1b. Non-amyloidogenic Pathway.** Processing of APP by α-secretase and γ-secretase yields P3.
play a crucial and early role in the pathogenesis of AD led to strategies for a pharmacotherapy aiming at the reduction of Aβ generation. The main targets so far have been β- and γ-secretases, the two proteases that cleave APP at the amino- and carboxy-terminus thereby enhancing Aβ generation. A different strategy, namely the activation of α-secretase, has also been investigated for its therapeutic potential. New results demonstrate that activation of α-secretase indeed reduces Aβ generation and the associated toxicity in vivo.

**α-Secretase**

α-Secretase cleaves membrane-bound APP in the middle of the amyloid region, thereby preventing the formation of Aβ. Classic inhibitory studies have shown that α-secretase represents a zinc-dependent metalloprotease belonging to the ADAM (a disintegrin and metalloprotease) family of proteases. These proteins rank among the membrane-anchored cell surface proteins. The ADAMs are involved in ectodomain shedding of membrane-anchored growth factors, cytokines and receptors. They have been shown to play a role in diverse biological processes such as fertilization, neurogenesis, and the activation of growth factors and immune regulators. Three candidates of this protease family have been reported to effectively process APP: ADAM9, ADAM10 and ADAM17 (also called TACE). These ADAM members contain an autoinhibitory domain that must be removed for activity, a proteolytic domain, a disintegrin domain, a cysteine-rich domain, and, most important for APP processing, a transmembrane domain. Several ADAMs have a consensus zinc-binding motif, HEXXH, in the catalytic domain. Therefore, ADAMs are thought to be potentially active metalloproteases. To investigate α-secretase activity, human ADAM9, ADAM10, and ADAM17 were cloned and expressed in COS-7 cells. All three ADAMs have been shown to exhibit α-secretase-like activity towards the endogenous APP in COS-7 cells. In addition, TACE cleaves pro-TNF-α, releasing the extracellular domain (TNF-α) in a manner similar to that of APP. It also processes a spectrum of type 1 membrane glycoproteins, including the p75 neurotrophin receptor, L-selectin adhesion molecule, TGF-α, and Notch receptor. ADAM10 in particular has also many properties of a physiologically relevant α-secretase: it is expressed in mouse and human brain, cleaves APP-derived peptides at the main α-secretase cleavage site between position 16 and 17 of the Aβ region, and has α-secretase activity in cultured cells. ADAM10-deficient mice have been generated, but their early lethality prevented a reliable analysis of ADAM10 function in vivo, especially in neuronal cells. Moreover, ADAM10 is involved in the cleavage of membrane proteins other than APP, such as Notch, EGF, TNF-α, and β-cellulin.

A study aiming at the tissue distribution of ADAM9, ADAM10, and ADAM17 showed that the mRNA of ADAM9 is ubiquitously expressed in human tissues, whereas ADAM10 mRNA is only observed in kidney, spleen, lymph node, thymus, liver, bone marrow, and brain. Strong expression of ADAM17 mRNA is found in macrophages. In human brain ADAM9 mRNA expression is higher than the expression of ADAM10 and ADAM17.

At present, it is still unclear whether only one of them or all three ADAMs together constitute the physiologically relevant α-secretase. Little is known about the underlying cellular pathways and mechanisms. Therefore, the identification of regulatory genes and chemical compounds, selectively affecting ADAM protease activity, may support research in this area to reveal new possibilities for pharmacological intervention in AD.

**β-Secretase**

In 1999, β-secretase was identified as a beta-site APP-cleaving enzyme (BACE1), a protease of the pepsin and renin family of aspartyl proteinases, which, together with its homolog BACE2, forms a new branch of the pepsin family. BACE1 is activated by a furin-like protease. This processing removes a propeptide domain to expose the active site. BACE is a type 1 transmembrane protease, containing a single transmembrane domain near the carboxy-terminus, a signal sequence including a propeptide region at the amino-terminus, and two aspartates in its ectodomain (Asp39 and Asp289). These
### α-Secretase Substrates

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<tr>
<th>α-Secretase</th>
<th>Substrates other than APP</th>
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<tr>
<td>ADAM9</td>
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Asp residues are essential for enzymatic activity. In addition to cleaving APP at the β-secretase site, BACE cuts APP further downstream within the amyloid region (between Tyr10 and Glu11 of Aβ), generating a truncated form of Aβ that is probably still amyloidogenic.

Besides APP and APP-like proteins (APLPs), a number of other BACE1 substrates has been identified. These include the sialyltransferase ST6Gal, the P-selectin glycoprotein ligand 1, neuregulin, the β-subunits of voltage-gated sodium channels, and the low density lipoprotein receptor-related protein (LRP).

The mRNA of β-secretase is overexpressed in neurons of the brain and is also found in a variety of human tissues. This is consistent with the finding that Aβ is normally produced by many cell types. The gene for β-secretase is located on chromosome 11, but no AD-causing mutation in this gene has been identified so far. However, the β-secretase homolog, BACE2, maps to chromosome 21, raising the possibility that this protease contributes to AD associated with Down syndrome. Down syndrome patients carry an extra copy of chromosome 21, secrete more Aβ from birth onwards and develop AD by age 50. Although BACE2 cleaves APP in a β-secretase-like manner, only low concentration of this protease is found in the normal brain (it is strongly expressed in heart, kidney, and placenta). This observation suggests that BACE2 plays a minor, if any, role in the formation of cerebral plaques seen in AD. Additional support comes from the finding that BACE1 deficiency results in an almost complete block of Aβ generation in neurons.

Comparison of BACE with other aspartic proteases such as cathepsin D and E, napsin A, pepsin, and renin revealed little similarity with respect to the substrate preference and inhibitor profile. The active site of β-secretase is more accessible than that of pepsin; the S2 and S4 subsites are relatively hydrophilic and open to solvent. These differences could be exploited for the design of selective inhibitors.

Several inhibitors of β-secretase activity have been designed from the β-site in APP and contain a moiety that mimics the transition state formed during aspartyl protease catalysis. These inhibitors are based on the amino acid sequence EVNLDAEF in APP which is cleaved by BACE between leucine (L) and aspartic acid (D). In addition, BACE1 has structural features that could be advantageous for the development of inhibitors with greater selectivity.

β-Secretase appears to represent an optimal therapeutic target for the prevention and treatment of AD, since BACE1-deficient mice show reduced Aβ production. The protein belongs to a well understood class of proteases for which therapeutically useful inhibitors have previously been developed (e.g., renin, HIV protease). The rational design of new inhibitors should be facilitated, as the X-ray crystal structure of BACE1 has been determined. Despite this optimism, the recent finding that BACE1 modulates myelination in the central and peripheral nervous system has raised some concerns about the usefulness of BACE1 inhibitors in the treatment of AD.

### γ-Secretase

γ-Secretase is a unique membrane-bound protease responsible for the intramembrane cleavage of a subset of type I membrane-spanning proteins including APP and Notch. γ-Secretase plays an important role in the pathogenesis of AD by generating the carboxy-terminus of Aβ, including the more amyloidogenic Aβ42.

γ-Secretase cleaves the hydrophobic integral membrane domain of its substrates, resulting in the release of protein fragments at the luminal (extracellular) and at the cytoplasmic side of the membrane. This cleavage represents an example of regulated intramembrane proteolysis (RIP). Recent work indicates that γ-secretase consists of a multiprotein complex of at least four proteins: presenilin, nicastrin, anterior pharynx (APH-1), and presenilin enhancer 2 (PEN-2) (Fig. 2). All four proteins are required for full proteolytic activity. The presenilins (−50 kD) constitute polytopic transmembrane proteins with nine putative transmembrane domains and appear to provide the active core of this protease. Two mammalian homologs, PS1 and PS2, exist. The presenilins undergo autocatalytic proteolysis to generate amino-terminal and carboxy-terminal fragments, which...
remain associated as functional heterodimer complexes. These contain nicastrin and other molecules that are important for γ-secretase activity.

Nicastrin represents a glycosylated ∼130 kD integral membrane protein that binds to both the amino-terminal and the carboxy-terminal fragments of presenilin. Nicastrin requires presenilin to leave the endoplasmic reticulum and to reach the cell surface. In presenilin deficient cells, the nicastrin receptor accumulates in the endoplasmic reticulum. Nicastrin is supposed to be one of the stabilizing factors of the presenilin fragments. But these two proteins are not sufficient to mediate γ-secretase activity. Therefore, further proteins facilitating the activation of γ-secretase have been investigated.

C. Goutte et al. identified two genes called aph-1 and aph-2. APH-2 represents the C. elegans homolog of the mammalian nicastrin, while APH-1 is a novel ∼30 kD multimembrane protein, which, similar to presenilin, is needed for the correct subcellular transport of nicastrin to the cell surface.

PEN-2 represents the fourth protein of the active γ-secretase. It is a small, hairpin-like membrane protein with a molecular weight of ∼12 kD. PEN-2 seems to be required for the cleavage of presenilin when it is incorporated in the complex with APH-1 and nicastrin. Apparently, all four proteins exert regulatory effects on each other. γ-Secretase requires the aspartyl protease activity of presenilin-1. Two aspartate residues (Asp257 and Asp385) located in the transmembrane domains 6 and 7 are essential for the catalytic activity of the protease. Therefore, γ-secretase may also be considered an aspartyl protease. However, the exact structure of the active site remains unknown. The molecular weight of this complex is still an issue of debate and estimates vary from 250 - 1000 kD.

Fig. 2. Activation Steps of the γ-Secretase Complex. Presenilin is rapidly degraded, while a fraction is stabilized to form a high-molecular weight complex by binding to APH-1 and nicastrin. PEN-2 facilitates endoproteolysis of presenilin and confers γ-secretase activity. Cylinders represent the putative transmembrane domains of each protein. The black stars within the 6th and 7th transmembrane domain of presenilin symbolize the inactive essential aspartate residues.
The identification of the γ-secretase components led to the rapid identification of several γ-secretase substrates other than APP, including Notch 1–4, the Notch ligands Delta and Jagged, and others. Notch is a cell surface receptor, which, when activated by ligands such as Jagged and Delta, is cleaved in the membrane resulting in the release of an intracellular domain of Notch. γ-Secretase-mediated Notch-signaling plays an essential role in the regulation of cell fate during the development of many organ systems including the brain as indicated by embryonic lethality and defective neurogenesis that is identical in Notch–1 and presenilin–1 deficient mice. Further studies are still needed to better understand the molecular function of the different subunits. In addition, the subcellular compartments in which the different subunits bind each other, remain to be determined. Aβ42 represents the main constituent of the amyloid plaques in the brain of AD patients. For this reason, the inhibition of γ-secretase may be therapeutically useful. A drawback for this approach, however, is given by the fact that Notch is the major physiological substrate. The design of γ-secretase inhibitors, which specifically block the proteolysis of APP without affecting the cleavage of Notch and other substrates, represents a strategy to circumvent this problem.

Certain non-steroidal anti-inflammatory drugs (NSAIDs) and other small organic molecules have been found to modulate γ-secretase and to selectively reduce Aβ42 levels without affecting Notch cleavage. Moreover, the recent finding that ATP binding to γ-secretase results in a selective activation of APP processing might lead to a novel therapeutic approach for reducing Aβ production in AD patients.

**Conclusion**

Treating Alzheimer’s disease represents one of the biggest medical needs in neurology. Current drugs, such as the acetylcholinesterase inhibitors tacrine, donezepil, galantamine, and rivastigmine as well as the NMDA receptor antagonist memantine only improve symptoms, and do not show profound disease-modifying effects. Inhibition of secretase activity, inhibition of amyloid-β aggregation, and immunotherapy are relevant therapeutic approaches, that might lead to successful drug development. Specific γ-secretase inhibitors have been produced, but their use in humans may be accompanied by side effects resulting from the inhibition of γ-secretase cleavage of Notch and other protein substrates. BACE1 inhibitors may prove beneficial in reducing Aβ production, since BACE1-deficient mice have shown reduced Aβ production. To date several drugs are in clinical trial.

In parallel to efficient disease-modifying therapy, effective ways of defining genetic predisposition and methods of early diagnosis, e.g. via biomarkers, are required.

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**Table 2. γ-Secretase Substrates**

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<thead>
<tr>
<th>γ-Secretase Substrates other than APP, APLP1 and APLP2</th>
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<tr>
<td>CD44</td>
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<td>Colony stimulating factor 1 (CSF1)</td>
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<td>E/N-cadherin</td>
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<tr>
<td>EphrinB1</td>
</tr>
<tr>
<td>EphrinB2</td>
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<tr>
<td>ErbB-4</td>
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<tr>
<td>Glutamate receptor subunit 3 (GluR3)</td>
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<tr>
<td>Growth hormone receptor</td>
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<td>HLA-A2</td>
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<tr>
<td>Low density lipoprotein receptor-related protein (LRP)</td>
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<tr>
<td>Syndecan 3</td>
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<td>Tyrosinase TYRP1 and TYRP2</td>
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<tr>
<td>Voltage-gated sodium channel B2 subunit (SCNB2)</td>
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</table>
Protein tangle in diseased brain cell.

Alzheimer's disease brain cell. Coloured transmission electron micrograph (TEM) of a neurofibrillary tangle in a nerve cell from the brain of a patient with Alzheimer's disease. The tangle (red) lies in the cytoplasm (yellow) of the cell body, adjacent to the nucleus (green). It consists of abnormal aggregates of the protein tau, which in the healthy cell stabilises microtubules in the cytoplasm. It is not known precisely how the tangles are formed, nor their impact on the neuron's function, but they are seen in a range of neural disorders including Alzheimer's disease, Creutzfeldt-Jakob disease (CJD), some forms of Parkinson's disease, and supranuclear palsy.

KEYSTONE/SCIENCE PHOTO LIBRARY/ THOMAS DEERINCK, NCMIR
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Substrates and inhibitors for β- and γ-secretase and related products can be found on shop.bachem.com
**β-SECRETASE SUBSTRATES**

DABCYL-(Asn⁶⁷⁰,Leu⁶⁷¹)-Amyloid β/A4 Protein Precursor₇₇₀ (661-675)-EDANS

M-2445
DABCYL-IKTEIESEVNLDAEF-EDANS

H-Lys-Thr-Glu-Glu-Ile-Ser-Glu-Val-Lys-Met-pNA
(APP₇₇₀ (662-671)-pNA)
L-1905
IKTEIESEVNLDAEF-pNA

Mca-(Asn⁶⁷⁰,Leu⁶⁷¹)-Amyloid β/A4 Protein Precursor₇₇₀ (667-674)-Dap(Dnp)

M-2425
Mca-SEVNLDAEF-Dpa

(Asn⁶⁷⁰,Leu⁶⁷¹)-Amyloid β/A4 Protein Precursor₇₇₀ (667-675)

H-4836
SEVNLDAEF

DABCYL-(Asn⁶⁷⁰,Leu⁶⁷¹)-Amyloid β/A4 Protein Precursor₇₇₀ (667-675)-EDANS

M-2435
DABCYL-SEVNLDAEF-EDANS

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M-2485
Mca-SEVNLDAEFK(Dnp)-NH₂

Amyloid β/A4 Protein Precursor₇₇₀ (667-676)

H-4842
SEVKMDAEFR

(Asn⁶⁷⁰,Leu⁶⁷¹)-Amyloid β/A4 Protein Precursor₇₇₀ (667-676)

H-4834
SEVNLDAEFR

(Swedish Double Mutation K670N / M671L)

(Val⁶⁷⁷)-Amyloid β/A4 Protein Precursor₇₇₀ (667-676)

H-4838
SEVKVDAEFR

Lys(Dabsyl)-(Asn⁶⁷⁰,Leu⁶⁷¹)-Amyloid β/A4 Protein Precursor₇₇₀ (667-676)-Gln-Lucifer Yellow

M-2570
K(Dabsyl)SEVNLDAEFRQ-Lucifer Yellow

Mca-Amyloid β/A4 Protein Precursor₇₇₀ (667-676)-Lys(Dnp)-Arg-Arg amide

M-2460
Mca-SEVKMDAEFRK(Dnp)RR-NH₂

Mca-(Asn⁶⁷⁰,Leu⁶⁷¹)-Amyloid β/A4 Protein Precursor₇₇₀ (667-676)-Lys(Dnp)-Arg-Arg amide

M-2465
Mca-SEVNLDAEFRK(Dnp)RR-NH₂

MeOSuc-Glu-Val-Lys-Met-pNA
(MeOSuc-APP₇₇₀ (668-671)-pNA)
L-1740
MeOSuc-EVKM-pNA

Arg-Glu(EDANS)-(Asn⁶⁷⁰,Leu⁶⁷¹)-Amyloid β/A4 Protein Precursor₇₇₀ (668-675)-Lys(DABCYL)-Arg

M-2470
RE(EDANS)VNLDAEFK(DABCYL)R

Z-Val-Lys-Met-AMC
(Z-APP₇₇₀ (669-671)-AMC)
I-1625
Z-VKM-AMC

Abz-Amyloid β/A4 Protein Precursor₇₇₀ (669-674)-EDDnp

M-2560
Abz-VKMDAE-EDDnp

Abz-(Asn⁶⁷⁰,Leu⁶⁷¹)-Amyloid β/A4 Protein Precursor₇₇₀ (669-674)-EDDnp

M-2565
Abz-VNLDAE-EDDnp

DABCYL-(Asn⁶⁷⁰,Leu⁶⁷¹)-Amyloid β/A4 Protein Precursor₇₇₀ (669-674)-EDANS

M-2430
DABCYL-VNLDAE-EDANS

Mca-(Asn⁶⁷⁰,Leu⁶⁷¹)-Amyloid β/A4 Protein Precursor₇₇₀ (669-674)-Lys(Dnp)

M-2440
Mca-VNLDAEK(Dnp)
**β-SECRETASE INHIBITORS**

- Ac-Val-Met-[(2S,4S,5S)-5-amino-4-hydroxy-2-isopropyl-7-methyl-octanoyl]-Ala-Glu-Phe-OH  
  N-1815  
  Ac-VML-psi[CHOHCH$_2$]VAEF

- (Asn$_{670}$,Sta$_{671}$,Val$_{672}$)-Amyloid β/A4 Protein Precursor$_{770}$ (662-675)  
  H-4848  
  KTEEISEVN-Sta-VAEF

- H-Glu-Leu-Asp-[(2R,4S,5S)-5-amino-4-hydroxy-2,7-dimethyl-octanoyl]-Ala-Glu-Phe-OH  
  N-1825  
  ELDL-psi[CHOHCH$_2$]AAEF

  (OM00-3)$_r_9$  
  N-1920  
  ELDL-psi[CHOHCH$_2$]AVEFGrrrrrrrrr

- OM99-2  
  H-5108  
  EVNL-psi[CHOHCH$_2$]AAEF

- Z-Leu-Leu-4,5-dehydro-Leu-aldehyde  
  N-1590  
  Z-LLαL-CHO

**γ-SECRETASE SUBSTRATES**

- Abz-Amyloid β/A4 Protein Precursor$_{770}$ (708-715)-Lys(Dnp)-D-Arg-D-Arg-D-Arg amide  
  M-2540  
  Abz-GGVVIATVK(Dnp)rrr-NH$_2$

- N-Me-Abz-Amyloid β/A4 Protein Precursor$_{770}$ (708-715)-Lys(Dnp)-D-Arg-D-Arg-D-Arg amide  
  M-2555  
  N-Me-Abz-GGVVIATVK(Dnp)rrr-NH$_2$

**γ-SECRETASE INHIBITORS**

- L-685,458  
  H-5106  
  Boc-F-psi[CHOHCH$_2$]FLF-NH$_2$

- 3,5-Difluorophenylacetyl-Ala-Phg-OMe  
  N-1890

- Z-Ile-Leu-aldehyde  
  N-1895  
  Z-IL-CHO

- Z-Leu-Leu-Nle-aldehyde  
  N-1695  
  Z-LL-Nle-CHO
### ADAM-17 (TACE) SUBSTRATES

- **Abz-Lys-Pro-Leu-Gly-Leu-Dap(Dnp)-Ala-Arg-NH$_2$**
  - H-2638
- **Abz-KPLGL-Dpa-AR-NH$_2$**
- **DABCYL-TNF-α-EDANS (-4 to +6) (human)**
  - M-2155
  - DABCYL-LAQAVRSSSR-EDANS
- **Mca-(endo-1a-Dap(Dnp))-TNF-α (-5 to +6) amide (human)**
  - M-2255
  - Mca-PLAQAV-Dpa-RSSSR-NH$_2$
- **Dnp-Pro-TNF-α (71-82) amide (human)**
  - M-2290
  - Dnp-SPLAQAVRSSSR-NH$_2$

### RELATED PRODUCTS

- **Presenilin-1 (331–349)-Cys (human, mouse)**
  - H-3988
  - NDDGGFSEEEWEAQRDSDLGC
- **PACAP-27 (human, mouse, ovine, porcine, rat)**
  - H-1172
  - HSDGIFTDSYRKYRQMAVKKYLAVAL- NH$_2$
- **PACAP-38 (human, mouse, ovine, porcine, rat)**
  - H-8430
  - HSDGIFTDSYRKYRQMAVKKYLAVALG-KRYQVRKKK-NH$_2$