The \(\gamma\)-secretases are intramembrane cleaving protein complexes responsible for the generation of amyloid \(\beta\) (A\(\beta\)) from the amyloid precursor protein (APP). Apart from presenilins (PSEN), a mature and active \(\gamma\)-secretase complex consists of three additional subunits: Nicastrin (Nct), PSEN enhancer 2 (Pen-2), and either anterior pharynx 1 (APH-1) A or B. The \(\gamma\)-secretase complexes proteolyse type 1 transmembrane proteins, among them the APP, the Notch receptors and ligands, the Erb4 receptor and N-Cadherin.

Inhibition of \(\gamma\)-secretase with DAPT significantly reduced the production of extracellular A\(\beta\)38, A\(\beta\)40, and A\(\beta\)42 in neurons of all genotypes.

Compounds that inhibit or modulate \(\gamma\)-secretase can be considered as a potential therapeutics for AD because their use appears to be a rational strategy to prevent senile plaque (SP) formations.
### γ-secretase Inhibitors & Modulators

**Avagacestat**  
(BMS-708163)  
Cat. No.: HY-50845

Avagacestat (BMS-708163) is a potent inhibitor of γ-secretase, with $IC_{50}$ of 0.27 nM and 0.30 nM for Aβ42 and Aβ40 inhibition; Avagacestat (BMS-708163) also inhibits NICD (Notch IntraCellular Domain) with $IC_{50}$ of 0.84 nM and shows weak inhibition of CYP2C19, with $IC_{50}$ of...

Purity: 99.93%  
Clinical Data: Phase 2  
Size: 10 mM × 1 mL, 5 mg, 10 mg, 50 mg

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**Aβ42-IN-1**  
Cat. No.: HY-130609

Aβ42-IN-1, compound 1v, is a novel, potent and orally active γ-secretase modulator (GSM). Aβ42-IN-1 potently reduced Aβ levels with an $IC_{50}$ value of 0.091 µM without CYP3A4 inhibition. Aβ42-IN-1 shows a sustained pharmacokinetic profile.

Purity: >98%  
Clinical Data: No Development Reported  
Size: 1 mg, 5 mg

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**Begacestat**  
(GSI-953)  
Cat. No.: HY-14175

Begacestat (GSI-953) is a selective thiophene sulfonamide inhibitor of amyloid precursor protein (IC$_{50}$ Aβ = 15 nM) for the treatment of Alzheimer’s disease.

Purity: >99.0%  
Clinical Data: No Development Reported  
Size: 10 mM × 1 mL, 1 mg

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**BI-1408**  
Cat. No.: HY-112282

BI-1408 is a potent γ-secretase modulator with an $IC_{50}$ of 0.04 µM for Aβ$_{42}$.

Purity: >98%  
Clinical Data: No Development Reported  
Size: 1 mg, 5 mg

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**BMS 906024**  
Cat. No.: HY-15670

BMS 906024 is an oral and selective γ-secretase inhibitor with an $IC_{50}$ of 7 nM for Aβ production inhibition in HEK293 cells stably overexpressing amyloid precursor protein (APP).

Purity: >98%  
Clinical Data: Phase 1  
Size: 1 mg, 5 mg

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**BPN-15606**  
Cat. No.: HY-117482

BPN-15606 is a highly potent, orally active γ-secretase modulator (GSM), attenuates the production of Aβ42 and Aβ40 by SHSY5Y neuroblastoma cells with $IC_{50}$ values of 7 nM and 17 nM, respectively.

Purity: 99.24%  
Clinical Data: No Development Reported  
Size: 10 mM × 1 mL, 5 mg, 10 mg, 50 mg, 100 mg

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**BPN-15606 besylate**  
Cat. No.: HY-117482A

BPN-15606 besylate is a highly potent, orally active γ-secretase modulator (GSM), attenuates the production of Aβ42 and Aβ40 by SHSY5Y neuroblastoma cells with $IC_{50}$ values of 7 nM and 17 nM, respectively.

Purity: >98%  
Clinical Data: No Development Reported  
Size: 1 mg, 5 mg
<table>
<thead>
<tr>
<th>Compound</th>
<th>Cat. No.</th>
<th>Purity</th>
<th>Clinical Data</th>
<th>Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound E</td>
<td>HY-14176</td>
<td>99.87%</td>
<td>No Development Reported</td>
<td>10 mM × 1 mL, 1 mg, 5 mg, 10 mg, 25 mg</td>
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<tr>
<td>Crenigacestat</td>
<td>HY-12449</td>
<td>98.62%</td>
<td>No Development Reported</td>
<td>10 mM × 1 mL, 2 mg, 5 mg, 10 mg, 25 mg, 50 mg, 100 mg</td>
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<tr>
<td>DAPT (GSI-IX)</td>
<td>HY-13027</td>
<td>99.97%</td>
<td>No Development Reported</td>
<td>10 mM × 1 mL, 5 mg, 10 mg, 50 mg</td>
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<tr>
<td>E 2012</td>
<td>HY-10016</td>
<td>96.91%</td>
<td>No Development Reported</td>
<td>10 mM × 1 mL, 5 mg, 10 mg, 50 mg</td>
</tr>
<tr>
<td>ELN318463</td>
<td>HY-50882</td>
<td>&gt;98%</td>
<td>No Development Reported</td>
<td>5 mg, 10 mg, 50 mg, 100 mg</td>
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<tr>
<td>ELN318463 racemate</td>
<td>HY-50882A</td>
<td>&gt;98%</td>
<td>No Development Reported</td>
<td>1 mg, 5 mg</td>
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<tr>
<td>gamma-secretase modulator 1</td>
<td>HY-10043</td>
<td>&gt;98.0%</td>
<td>No Development Reported</td>
<td>5 mg, 10 mg, 25 mg, 50 mg, 100 mg</td>
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<tr>
<td>gamma-secretase modulator 1 hydrochloride</td>
<td>HY-10043A</td>
<td>98.59%</td>
<td>No Development Reported</td>
<td>10 mM × 1 mL, 5 mg, 10 mg, 25 mg, 50 mg, 100 mg</td>
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<tr>
<td>gamma-secretase modulator 2</td>
<td>HY-50754</td>
<td>98.59%</td>
<td>No Development Reported</td>
<td>10 mM × 1 mL, 10 mg, 50 mg</td>
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<tr>
<td>gamma-secretase modulator 3</td>
<td>HY-50889</td>
<td>99.35%</td>
<td>No Development Reported</td>
<td>10 mg, 100 mg</td>
</tr>
<tr>
<td>Name</td>
<td>Cat. No.</td>
<td>Description</td>
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<td>------------------------------------------------------------------------------</td>
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<tr>
<td>Itanapraded (CHF5074; CSP-1103)</td>
<td>HY-14399</td>
<td>Itanapraded (CHF5074) is a novel γ-secretase modulator, reduces Aβ42 and Aβ40 secretion, with an IC50 of 3.6 and 18.4 μM, respectively.</td>
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<tr>
<td>Purity: &gt;98.0%</td>
<td>Clinical Data: Phase 1</td>
<td>Size: 10 mM × 1 mL, 5 mg, 10 mg, 50 mg, 100 mg</td>
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<tr>
<td>L-685458 (L-685,458)</td>
<td>HY-19369</td>
<td>L-685458 is a potent inhibitor of Amyloid β-Protein precursor γ-secretase activity with IC50 of 17 nM, shows greater than 50-100-fold selectivity over other aspartyl proteases tested. IC50 value: 17 nM Target: γ-secretase in vitro: L-685458 is a Notch inhibitor.</td>
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<tr>
<td>Purity: 99.78%</td>
<td>Clinical Data: No Development Reported</td>
<td>Size: 10 mM × 1 mL, 1 mg</td>
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<tr>
<td>LY-411575</td>
<td>HY-50752</td>
<td>LY-411575 is a potent γ-secretase inhibitor with IC50 of 0.078 nM/0.082 nM (membrane/cell-based), and also inhibits Notch S3 cleavage with IC50 of 0.39 nM.</td>
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<tr>
<td>Purity: 99.20%</td>
<td>Clinical Data: No Development Reported</td>
<td>Size: 10 mM × 1 mL, 5 mg, 10 mg, 50 mg, 100 mg</td>
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</tr>
<tr>
<td>LY-411575 isomer 1</td>
<td>HY-50752A</td>
<td>LY-411575 isomer 1 is an isomer of LY411575, which is a potent γ-secretase inhibitor.</td>
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<tr>
<td>Purity: 99.51%</td>
<td>Clinical Data: No Development Reported</td>
<td>Size: 10 mM × 1 mL, 1 mg</td>
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</tr>
<tr>
<td>LY-411575 isomer 2</td>
<td>HY-50752B</td>
<td>LY-411575 isomer 2 is an isomer of LY411575, which is a potent γ-secretase inhibitor.</td>
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</tr>
<tr>
<td>Purity: 99.84%</td>
<td>Clinical Data: No Development Reported</td>
<td>Size: 10 mM × 1 mL, 1 mg</td>
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<tr>
<td>MK-0752</td>
<td>HY-10974</td>
<td>MK-0752 is a moderately potent γ-secretase inhibitor, which reduces Aβ40 production with IC50 of 5 nM.</td>
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<tr>
<td>Purity: 98.00%</td>
<td>Clinical Data: Phase 2</td>
<td>Size: 10 mM × 1 mL, 5 mg, 10 mg, 50 mg, 100 mg</td>
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<tr>
<td>NGP555</td>
<td>HY-108714</td>
<td>NGP555 is a γ-secretase modulator.</td>
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<tr>
<td>Purity: 98.64%</td>
<td>Clinical Data: No Development Reported</td>
<td>Size: 10 mM × 1 mL, 5 mg, 10 mg, 25 mg, 50 mg, 100 mg</td>
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<tr>
<td>Nirogacestat (PF-3084014; PF-03084014)</td>
<td>HY-15185</td>
<td>Nirogacestat (PF-3084014) is a reversible, noncompetitive, and selective γ-secretase inhibitor with IC50 of 6.2 nM.</td>
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<tr>
<td>Purity: 99.95%</td>
<td>Clinical Data: Phase 2</td>
<td>Size: 10 mM × 1 mL, 5 mg, 10 mg, 50 mg, 100 mg</td>
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<tr>
<td><strong>Cat. No.</strong></td>
<td><strong>Name</strong></td>
<td><strong>Cat. No.</strong></td>
<td><strong>Name</strong></td>
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<tr>
<td>HY-120789</td>
<td>PF-06648671</td>
<td>HY-11102</td>
<td>RO4929097 (RG-4733)</td>
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<tr>
<td>HY-10009</td>
<td>Semagacestat (LY450139)</td>
<td>HY-B1786</td>
<td>Sulindac sulfide (cis-Sulindac sulfide)</td>
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<tr>
<td>HY-13526</td>
<td>YO-01027 (Dibenzazepine; DBZ)</td>
<td>HY-12465</td>
<td>Z-Ile-Leu-aldehyde (Z-IL-CHO; GSI-XII; γ-Secretase inhibitor XII)</td>
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<tr>
<td>HY-128581</td>
<td>γ-Secretase modulator 4</td>
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</tr>
</tbody>
</table>

**PF-06648671**

PF-06648671 is a novel, brainpenetrable, and orally active γ-secretase modulator (GSM). PF-06648671 reduces Aβ42 and Aβ40, with concomitant increases in Aβ37 and Aβ38 in vitro. PF-06648671 is used for the study of Alzheimer’s disease.

- **Purity:** >98%
- **Clinical Data:** No Development Reported
- **Size:** 1 mg, 5 mg

**RO4929097 (RG-4733)**

RO4929097 (RG-4733) is a γ secretase inhibitor with IC\(_{50}\) of 4 nM, inhibiting cellular processing of Aβ40 and Notch with EC\(_{50}\) of 14 nM and 5 nM, respectively.

- **Purity:** 98.29%
- **Clinical Data:** Phase 2
- **Size:** 10 mM × 1 mL, 5 mg, 10 mg, 50 mg, 100 mg

**Semagacestat (LY450139)**

Semagacestat is a γ-secretase inhibitor, inhibits β-amyloid (Aβ42, Aβ38 and Aβ40 with IC\(_{50}\) of 10.9, 12 and 12.1 nM, respectively; also inhibits Notch signaling with IC\(_{50}\) of 14.1 nM.

- **Purity:** 98.83%
- **Clinical Data:** Phase 3
- **Size:** 10 mM × 1 mL, 5 mg, 10 mg, 50 mg, 100 mg

**Sulindac sulfide (cis-Sulindac sulfide)**

Sulindac sulfide is a noncompetitive γ-secretase inhibitor, with an IC\(_{50}\) of 20.2 μM for V\(_{12}\)-secretase activity.

- **Purity:** >98%
- **Clinical Data:** No Development Reported
- **Size:** 1 mg, 5 mg

**YO-01027 (Dibenzazepine; DBZ)**

YO-01027 (Dibenzazepine;DBZ) is a potent γ-secretase inhibitor with IC\(_{50}\) values of 2.92 and 2.64 nM for Notch and APPL cleavage, respectively.

- **Purity:** 99.23%
- **Clinical Data:** No Development Reported
- **Size:** 10 mM × 1 mL, 2 mg, 5 mg, 10 mg, 25 mg

**Z-Ile-Leu-aldehyde (Z-IL-CHO; GSI-XII; γ-Secretase inhibitor XII)**

Z-Ile-Leu-aldehyde (Z-IL-CHO) is a potent and competitive peptide aldehyde inhibitor of γ-secretase and notch.

- **Purity:** 98.10%
- **Clinical Data:** No Development Reported
- **Size:** 10 mM × 1 mL, 5 mg, 10 mg

**γ-Secretase modulator 4**

γ-Secretase modulator 4 is a potent γ-secretase modulator, reduces the Aβ42 level with IC\(_{50}\) of 0.014 μM and 0.017 μM in human and mouse, respectively.

- **Purity:** >98%
- **Clinical Data:** No Development Reported
- **Size:** 1 mg, 5 mg