



γ -Secretase Modulators (GSM) for the potential treatment of Alzheimer's disease (AD) & novel phenyl bioisosteres

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Abstract

γ -Secretase (GS) is a key target for the potential treatment of Alzheimer's disease. While inhibiting GS led to serious side effects, its modulation holds a lot of potential to deliver a safe treatment. Herein, we report the discovery of a potent and selective gamma secretase modulator (GSM) (S)-3 (RO7185876), belonging to a novel chemical class, the triazolo-azepines. This compound demonstrates an excellent in-vitro and in-vivo DMPK profile. Furthermore, based on its in-vivo efficacy in a pharmacodynamic mouse model and the outcome of the dose range finding (DRF) toxicological studies in two species, this compound was selected to undergo entry in human enabling studies (e.g. GLP toxicology and scale up activities). Furthermore, we will present a novel saturated phenyl bioisostere used in this compound design and compare its properties versus the now more standard BCP and related derivatives.

Biography

H. Ratni is an Distinguished Scientist, Medicinal Chemistry, at F. Hoffmann-La Roche Ltd., Basel, Switzerland. He successfully, bring from early research to the clinic 6 molecules, one already successfully launched.

He received his PhD at the University of Geneva and did a post-doc at Tokyo University before joining F. Hoffmann-La Roche Ltd in 2001. His research has mainly been devoted to the areas of neuroscience (e.g. V1a receptor antagonist, in human clinical trials, phase 3, for autism). In 2005, he participated in a secondment within the Roche group at Chugai Pharmaceutical Co. Ltd, Gotemba Japan. He was the chemistry discovery project leader of the SMN program for the treatment of spinal muscular atrophy, and inventor of Risdiplam (Evrysdi) launched in 2020. His current focus is on gamma secretase modulator for Alzheimer disease.

He is an author or co-author of more than 115 patents and publications and received the following awards:

- 2021: Drug Discovery of the Year Award, by The Society of Medicines Research
- 2020: Senior Industrial Science Award, by the Swiss Chemical Society (SCS)
- 2020: Roche CEO Award, for Excellence
- 2019: Paper of the year award, by the Society of Toxicology (DDTSS)
- 2016: Gold medal at the Roche Patent Inventor's recognition event.
- 2014: Roche Leo Sternbach Award for Innovation in Chemistry

Recent Publications

1. Ratni H, et al (2020) Discovery of RO7185876, a Highly Potent γ Secretase Modulator (GSM) as a Potential Treatment for Alzheimer's Disease. ACS Med Chem Letters 11:1257-1268.
2. Ratni H, et al (2021) Phenyl bioisosteres in medicinal chemistry: discovery of novel γ secretase modulators as a potential treatment for Alzheimer's disease. RSC Medicinal Chemistry 12:758.

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