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Patent Highlight
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Bridged Piperidine Derivatives Useful as γ-Secretase Inhibitors for the Treatment of Alzheimer's Disease

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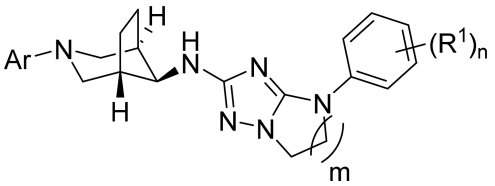
Important Compound Classes.



Title. Bridged piperidine derivatives

Patent Application Number. WO 2018060300A1

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Priority Application. EP16191512.9

Priority Date. September 29th, 2016

Inventors. Bartels, B.; Jakob-Roetne, R.; Linberg, A.; Neidhart, W.; Ratni, H.; Reutlinger, M.; Sarie, J. C.; Vastakaite, G.

Assignee Company. Pharmascience, Inc.

Disease Area. Alzheimer's disease

Biological Target. γ-Secretase

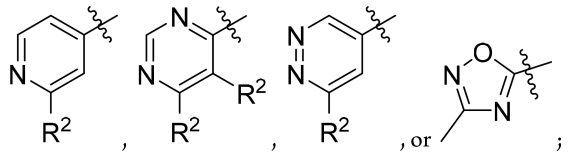
Summary. Despite decades of research, effective therapies for Alzheimer's disease remain elusive. The current U.S. patient population exceeds 5 million and is expected to rise to 16 million by 2050 (https://www.alz.org/facts/). This progressive neurodegenerative disorder has been linked to β-amyloid plaques and neurofibrillary tangles in the cortical and subcortical regions of the brain. Further, the formation of these features is associated with the degeneration and loss of neurons. They contain β-amyloid and tau proteins, respectively. It has been hypothesized that prevention or elimination of this material from the brain will arrest and possibly reverse the progression of Alzheimer's disease. β-Amyloid plaques are formed from the Aβ42 protein, a cleavage product of the amyloid precursor protein (APP). Initial β-secretase mediated cleavage of APP produces a soluble fragment (β-APP) and a membrane bound portion (C-99). γ-Secretase then cleaves C-99, which produces Aβ42, a protein that forms insoluble aggregates that are the main component of β-amyloid plaques. In theory, inhibition of either β-secretase or γ-secretase would prevent the formation of Aβ42, prevent the formation of the associated plaques, and arrest Alzheimer's disease progression. The present application discloses a series of compounds that selectively inhibit γ-secretase and are potentially useful for the treatment of Alzheimer's disease.

Definitions. R^1 is hydrogen, lower alkyl, lower alkyl substituted by halogen, halogen, lower alkoxy or lower alkoxy substituted by halogen; R^1 may be the same or different, if $n = 2$ or 3;

n is 1, 2, or 3;

m is 1, 2, or 3;

Ar is a five- or six-membered heteroaryl group, selected from



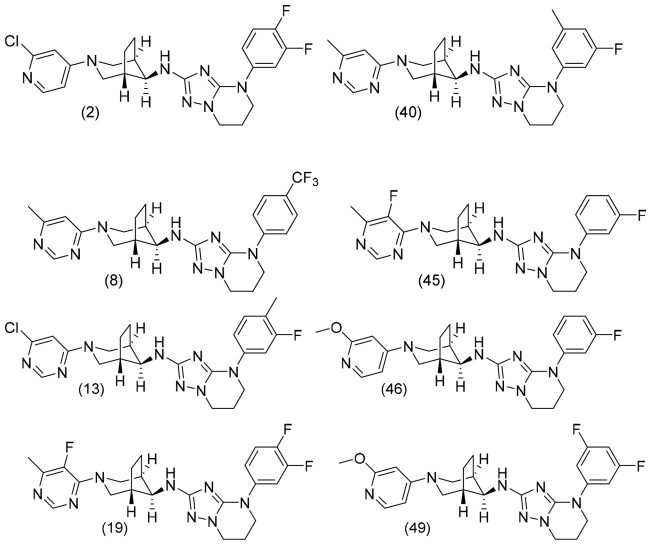
wherein

R^2 is hydrogen, lower alkyl, lower alkyl substituted by halogen, halogen or lower alkoxy;

R^3 is hydrogen or halogen;

$-()_m-$ is $-(CH_2)_m-$.

Key Structures.



Biological Assay. Cellular γ-secretase assay with quantification of secreted Aβ42 by the means of an AlphaLisa assay kit (Human Amyloid beta 1−42 Kit: Cat# AL203C, PerkinElmer).

Biological Data.

Entry	EC_{50} Aβ42 (nM)	Entry	EC_{50} Aβ42 (nM)
2	0.0059	40	0.0092
8	0.0117	45	0.013
13	0.0114	46	0.0103
19	0.0139	49	0.0064

Claims. Nineteen total claims.

Thirteen composition of matter claims.

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One process claim.
Five method of use claims.

Recent Review Articles.

1. Johnson, D. S.; Pettersson, M. γ-Secretase modulators as Aβ42-lowering pharmacological agents to treat Alzheimer's disease. *Topics in Medicinal Chemistry* **2017**, *24*, 87−118.
2. Kumar, D.; Ganeshpurkar, A.; Kumar, D.; Modi, G.; Gupta, S. K.; Singh, S. K. Secretase inhibitors for the treatment of Alzheimer's disease: Long road ahead. *European Journal of Medicinal Chemistry* **2018**, *148*, 436−452.
3. Tan, Y.; Zhang, Q.; Wong, S. G.; Hua, Q. Anti-Alzheimer therapeutic drugs targeting γ-secretase. *Current Topics in Medicinal Chemistry* **2016**, *16* (5), 549−557.

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Notes

The author declares no competing financial interest.

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