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PATENT HIGHLIGHT

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Fused Morphlinopyrimidines and Methods of Use Thereof

Benjamin Blass*

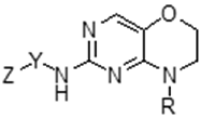
Temple University School of Pharmacy, 3307 North Broad Street, Philadelphia, Pennsylvania 19140, United States

Title:	Fused Morphlinopyrimidines and Methods of Use Thereof		
Patent/Patent Application Number:	WO2015066696A1	**Publication date:**	May 7th, 2015
Priority Application:	US 62/047,215	**Priority date:**	September 8, 2014
	US 61/899,616		November 4, 2013
Inventors:	Burnett, D. A.; Bursavich, M. G.; Mcriner, A. J.		
Assignee Company:	Forum Pharmaceuticals, Inc.		
Disease Area:	Alzheimer's disease	**Biological Target:**	γ-Secretase modulation

Summary:

Alzheimer's disease is a progressive, neurodegenerative disease that impacts the lives of over 45 million people globally. In the absence of effective treatments, it is expected that the patient population will exceed 75 million by 2030 and increase to over 135 million by 2050. Despite decades of research, the underlying causes of Alzheimer's disease remain a mystery and efforts to develop novel therapies for this debilitating condition have been largely unsuccessful. A major area of research has been and continues to be the formation of senile plaques and neurofibrillary tangles in the cortical and subcortical regions of the brain. These features are associated with the degeneration and loss of neurons, and are known to contain β-amyloid and tau proteins, respectively. It has been theorized that preventing the formation and/or clearing these material from the brain will arrest the progression of Alzheimer's disease. Previous reports have demonstrated that β-amyloid plaques are formed from the Aβ42 protein, a cleavage product of the amyloid precursor protein (APP). This protein is produced from APP as a result of sequential cleavage of APP by β-secretase and γ-secretase. Initial cleavage of APP by β-secretase produces soluble β-APP and a membrane bound fragment designated C-99. Further processing of C-99 by γ-secretase cleaves this protein and releases Aβ42, which has a high propensity to aggregate and is the main component of senile plaques. The present application discloses a series of compounds that selectively inhibit γ-secretase and are potentially useful for the treatment of Alzheimer's disease.

Important Compound Classes:



Definitions:

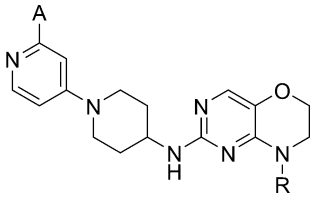
R is phenyl, $-C_1-C_4$ alkylene-phenyl or $-C_1-C_6$ alkyl, each of which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of −halo, −CN, $-NH_2$, $-C_1-C_4$alkyl, halo-substituted C_1-C_4alkyl, amino-substituted C_1-C_4alkyl, $-NH-C_1-C_4$alkyl, $-NHC(O)-C_1-C_4$alkyl, $-C(O)N(C_1-C_4alkyl)_2$, $-C(O)NH-C_1-C_4$alkyl, $-C(O)N(C_1-C_4alkyl)_2$, hydroxy-substituted C_1-C_4alkyl, $-S(O)_2-C_1-C_4$alkyl, $-S(O)_2$-halosubstituted C_1-C_4alkyl, $-S(O)_2-NH-C_1-C_4$alkyl, $-S(O)_2-N(C_1-C_4alkyl)_2$, $-NH-S(O)_2-C_1-C_4$alkyl, $-N(C_1-C_4alkyl)-S(O)_2-C_1-C_4$alkyl, $-C_1-C_4$alkoxy, halo-substituted C_1-C_4alkoxy, 3- to 7-membered monocyclic heterocycle, C_3-C_8 monocyclic cycloalkyl, and $-C(O)NH_2$;

Y is 4- to 6-membered nitrogen-containing nonaromatic heterocycle, each of which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of −halo, oxo, $-C_1-C_4$alkoxy, halo-substituted C_1-C_4alkoxy, $-C_1-C_4$alkyl, halo-substituted C_1-C_4alkyl, amino-substituted C_1-C_4alkoxy, −CN, $(C_1-C_4alkyl)_2N-C_1-C_4$alkoxy, $-NH-C_1-C_4$alkyl, −OH, and $-NH_2$;

Z is 5- to 6-membered nitrogen-containing heterocycle, which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of −halo, $-NH_2$, −OH, $-C_1-C_4$alkyl, halo-substituted C_1-C_4alkyl, $-C_1-C_4$alkoxy, and 3- to 7-membered monocyclic heterocycle.

Received: June 28, 2015
Published: July 13, 2015

Key Structures:



Entry	A	R
16	OCH_3	3,5-difluorophenyl
19	OCH_3	phenyl
24	Cl	phenyl
25	OCH_3	2-methylpheyl
28	OCH_3	2-chlorophenyl
30	OCH_3	2-trifluoromethoxyphenyl
34	Cl	2-methylphenyl
61	OCH_3	3,4,5-trifluorophenyl
62	OCH_3	2,4-difluorophenyl
63	OCH_3	4-chlorophenyl
65	OCH_3	2-trifluoromethyl-4-fluorophenyl
68	OCH_3	4-fluorophenyl

Recent Review Articles:

Hall, A.; Patel, T. R. γ-Secretase modulators: current status and future directions. *Prog. Med. Chem.* **2014**, *53*, 101−145.

Wolfe, M. S.; Selkoe, D. J. γ-Secretase: A horseshoe structure brings good luck. *Cell* **2014**, *158* (2), 247−249.

Gertsik, N.; Chiu, D.; Li, Y. M. Complex regulation of γ-secretase: from obligatory to modulatory subunits. *Front. Aging Neurosci.* **2014**, *6* (342), 1−10.

Mikulca, J. A.; Nguyen, V.; Gajdosik, D. A.; Teklu, S. G.; Giunta, E. A.; Lessa, E. A.; Tran, C. H.; Terak, E. C.; Raffa, R. B. Potential novel targets for Alzheimer pharmacotherapy: II. Update on secretase inhibitors and related approaches. *J. Clin. Pharm. Ther.* **2014**, *39* (1), 25−37.

Biological Assay:

In vitro cell screening and quantification of Aβ(1−x) and Aβ (1−42) Peptides:

Human neuroglioma H4 cells were transfected with a pcDNA3.1 plasmid expressing human wild type APP751 cDNA, and a stable cell line was generated using G418 selection. Cells are plated at 15,000 cells/well in Costar 96-well plates and placed at 37 °C and 5% CO_2. Six hours after plating, cells are washed three times with Pro293 chemically defined medium, followed by addition of compounds (0.003−10 μM, final DMSO concentration of 0.33%). Plates were incubated overnight (16−18 h), and supernatant was removed for quantification of Aβ peptides by sandwich ELISA.

ELISA measurements of Aβ peptides:

Aβ peptide levels were quantified by sandwich ELISA. Ninety six-well plates are coated with C-terminal specific Aβ antibodies recognizing either Aβ 37, Aβ 38, Aβ 40, Aβ 42, Aβ 43, or an N-terminal specific Aβ antibody to detect Aβ 1−x. Plates are then blocked overnight at 4 °C with 1% bovine serum albumin (BSA) in PBS-T. Plates are washed, and 100 III of cultured cell supernatant or synthetic Aβ peptide standards and a detection antibody (4G8-HRP) are applied to the blocked plate and incubated overnight at 4 °C. The next day, wells are washed before the addition of detection substrate (TMB peroxidase). Plates are then read for absorbance at 450 nm on a Molecular Devices SpectraMax M5e Microplate Reader.

Biological Data:

Entry	IC50 (nM)	Entry	IC50 (nM)
16	25.6	34	90
19	25.2	61	56
24	54.3	62	72.4
25	58.5	63	25.4
28	54.8	65	11.9
30	20.8	68	30.5

Claims:

49 Total claims

40 Composition of matter claims

9 Method of use claims

AUTHOR INFORMATION

Corresponding Author

*Tel: 215-707-1085. E-mail: benjamin.blass@temple.edu.

Notes

The authors declare no competing financial interest.