ACS Medicinal Chemistry Letters

PATENT HIGHLIGHT

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5-Aryl-1-imino-1-oxo-[1,2,4]thiadiazines

Benjamin Blass*

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

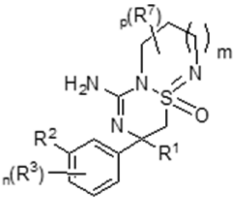
Title:	5-Aryl-1-imino-1-oxo-[1,2,4]thiadiazines		
Patent Application Number:	WO2015091595A1	**Publication date:**	June 25, 2015
Priority Application:	EP13198700.0	**Priority date:**	December 20, 2013
Inventors:	Guba, W.; Happ, W.		
Assignee Company:	Hoffmann-La Roche AG		
Disease Area:	Alzheimer's disease	**Biological Target:**	β-secretase 1 (BACE-1, also known as β-APP cleaving enzyme)

Summary:

Alzheimer's disease is a progressive neurodegenerative disease that impacts approximately 36 million patients globally. The number of afflicted individuals is expected to increase as the population ages. Initial symptoms include memory loss, which eventually progresses to severe cognitive impairment, altered behavioral patterns, and decreased motor functions. Alzheimer's disease is the most common form of dementia and the third leading cause of death. The toll on caregivers and family members is also very high, as eventually patients become unable to care for themselves. To date, clinical options, therapies, and biomarkers remain elusive despite decades and research and billions of dollars invested.

Although a full understanding of disease progression in Alzheimer's disease has not been established, several lines of evidence have implicated β-APP cleaving enzyme (BACE-1), also known as β-secretase 1, as a key player in the pathology of this disease. Specifically, post-mortem histopathological examination of patient brain tissue has revealed a significant increase in neuritic plaques and neurofibrillary tangles.These plaques consist primarily of β-amyloid peptides, which are formed in a stepwise process. Initial proteolytic cleavage of amyloid precursor protein (APP) by BACE-1 is followed by γ-secretase processing. The resulting Aβ-42 amyloid segments form the plaques that are typically found in patient brains. Although it has as yet to be determined if the presence of Aβ-42 amyloid plaques is causative in Alzheimer's disease, significant research efforts have been devoted to the development of BACE-1 inhibitors as potential therapeutic agents for the treatment of this disease. The present disclosure describes compounds capable of inhibiting BACE-1 that may be useful as therapeutic interventions capable of halting disease progression in Alzheimer's disease patients.

Important Compound Classes:



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Definitions:

R^1 is selected from the group consisting of
- i) C_{1-6}−alkyl and
- ii) halogen−C_{1-6}−alkyl;

R^2 is selected from the group consisting of
- i) hydrogen,
- ii) halogen,
- iii) −NH−C(═O)−R^4,
- iv) aryl,
- v) aryl, substituted by 1−3 substituents individually selected from cyano, C_{1-6}−alkyl, halogen−C_{1-6}−alkyl, and halogen,
- vi) heteroaryl,
- vii) heteroaryl, substituted by 1−3 substituents individually selected from R^6, and
- viii) −C═C−R^5;

R^3 is halogen;

R^4 is selected from the group consisting of
- i) heteroaryl, and
- ii) heteroaryl, optionally substituted by 1−3 substituents individually selected from R^6;

R^5 is selected from the group consisting of
- i) aryl,
- ii) aryl, optionally substituted by 1−3 substituents individually selected from cyano, C_{1-6}-alkyl, halogen-C_{1-6}-alkyl and halogen
- iii) heteroaryl, and
- iv) heteroaryl, optionally substituted by 1−3 substituents individually selected from cyano, C_{1-6}−alkyl, halogen−C_{1-6}−alkyl, and halogen;

R6 is selected from the group consisting of
- i) cyano,
- ii) halogen,
- iii) C_{1-6}−alkyl,
- iv) halogen−C_{1-6}−alkyl,
- v) C_{2-6}−alkynyl−O−,
- vi) heteroaryl, and
- vii) heteroaryl, optionally substituted by 1−3 substituents individually selected from cyano, C_{1-6}−alkyl, C_{1-6}−alkoxy, halogen−C_{1-6}−alkyl, halogen−C_{1-6}−alkoxy, and halogen;

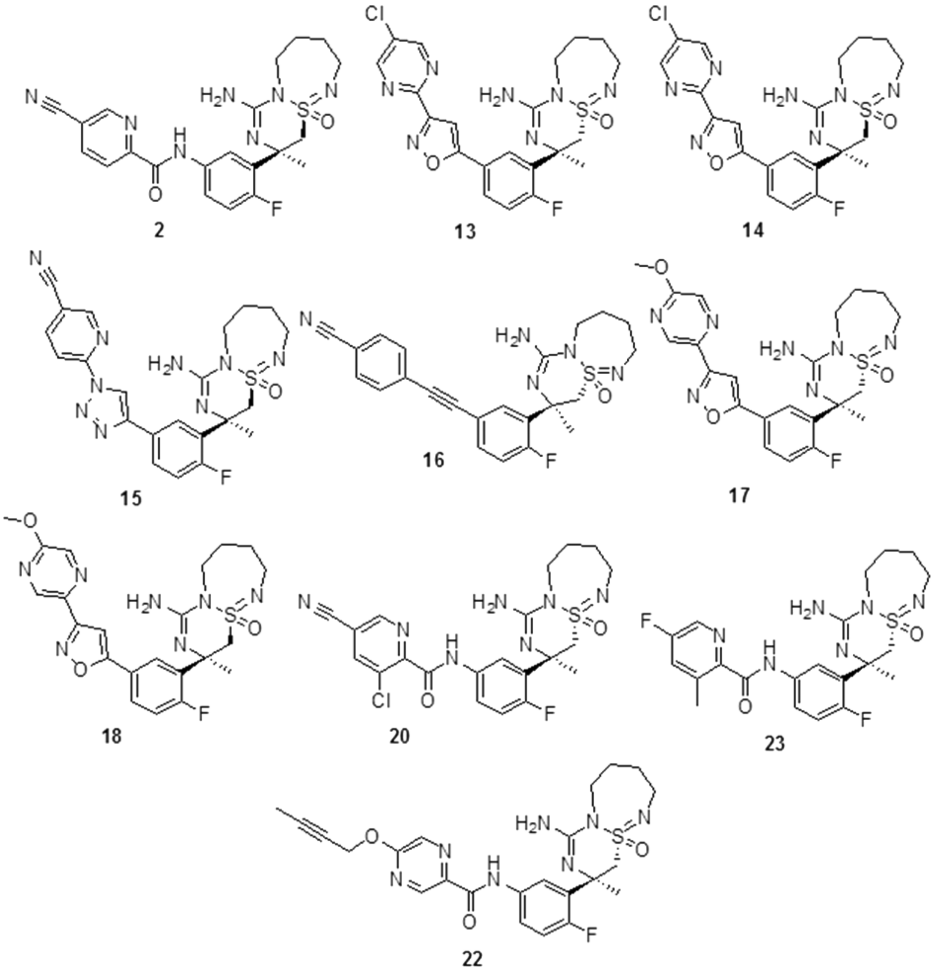
R^7 is selected from the group consisting of
- i) halogen, and
- ii) halogen−C_{1-6}−alkyl;

m is 1 or 2;

n is 0 or 1; and

p is 0, 1, or 2.

Key Structures:



Recent Review Articles:

Ghosh, A. K.; Osswald, H. L. BACE1 (β-secretase) inhibitors for the treatment of Alzheimer's disease. *Chem. Soc. Rev.* **2014**, *43* (19), 6765−813.

Yan, R.; Vassar, R. Targeting the β secretase BACE1 for Alzheimer's disease therapy. *Lancet Neurol.* **2014**, *13* (3), 319−329.

Vassar, R. BACE1 inhibitor drugs in clinical trials for Alzheimer's disease. *Alzheimer's Res. Ther.* **2014**, *6*, 89.

Biological Assay:

Cellular Aβ lowering assay: The HEK293 APP cells were seeded in 96-well Microtiter plates in cell culture medium (Iscove's, plus 10% (v/v) fetal bovine serum, penicillin/streptomycin) to about 80% confluency, and the compounds were added at a 3× concentration in 1/3 volume of culture medium (final DMSO concentration was kept at 1% v/v). After 18−20 h incubation at 37 °C and 5% CO_2 in a humidified incubator, the culture supernatants were harvested for the determination of Aβ40 concentrations using Perkin−Elmer Human Amyloid beta 1−40 (high specificity) Kit (Cat# AL275C).

In a Perkin−Elmer White Optiplate-384 (Cat# 6007290), 2 μL of culture supernatants were combined with 2 μL of a 10× AlphaLISA Anti-hAβAcceptor beads + Biotinylated Antibody AntiAβ 1−40 Mix (50 μL/mL/5 nM). After 1 h room temperature incubation, 16 μL of a 1.25× preparation of Streptavidin (SA) Donor beads (25 μL/mL) were added and incubated for 30 min in the dark. Light emission at 615 nm was then recorded using EnVision-Alpha Reader. Levels of Aβ40 in the culture supernatants were calculated as percentage of maximum signal (cells treated with 1% DMSO without inhibitor). The IC_{50} values were calculated using the Excel XLfit software.

Biological Data:

Entry	IC_{50} (μm)	Entry	IC_{50} (nm)
2	0.002	17	0.009
13	0.012	18	0.694
14	0095	20	0.001
15	0095	22	0.0002
16	0.021	23	0.0015

Claims:	19 Total claims
	13 Composition of matter claims
	6 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.