ACS Medicinal Chemistry Letters

PATENT HIGHLIGHT

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Imidazo[2,1]thiazol-3-one Derivatives Useful as Diagnostic Agents for Alzheimer's Disease

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Title:	Imidazo[2,1]thiazol-3-one derivatives useful as diagnostic agents for Alzheimer's disease		
Patent/Patent Application Number:	WO2014/026881	**Publication date:**	February 20th, 2014
Priority Application:	EP 12180367.0	**Priority date:**	August 14th, 2012
Inventors:	Gobbi, Luca; Knust, Henner; Koblet, Andreas		
Assignee Company:	Hoffmann-La Roche Inc.		
Disease Area:	Alzheimer's disease	**Biological Target:**	Tau aggregates A-β aggregates

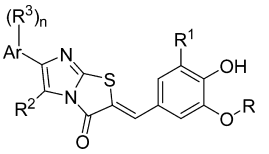
Summary:

According to Alzheimer's Disease International, there are nearly 36 million Alzheimer's patients worldwide. As the global population ages, the number of patients impacted by this progressive neurodegenerative disease is expected to increase substantially. Clinical manifestations of this disease include cognitive decline, disorientation, language impairment, and permanent memory loss. In the final stages of Alzheimer's disease, patients are often totally dependent on custodial care and severely cognitively impaired.

The root cause of Alzheimer's disease has as yet to be determined, but post-mortem studies of Alzheimer's disease patient's brains have revealed the presence of large numbers of plaques composed of both β-amyloid peptides and neurofibrillary tangles composed of hyperphosphorylated tau protein filaments. Under normal circumstances, the tau protein is expressed in neurons and plays an important role in the formation of the neuronal microtubule network. Much like the formation of β-amyloid plaques, the mechanism that caused tau hyperphosphorylation, aggregation, and subsequent plaque formation is unknown.

It has been suggested that it may be possible to track the progression of Alzheimer's disease by monitoring plaque formation in patients. In addition, if it could be demonstrated that the plaques appear in asymptomatic patients, it may be possible to identify at risk patients prior to the onset of symptoms. Currently, however, the only method of detecting tau aggregates requires histological analysis of biopsy or autopsy samples. The present disclosure describes compounds that may be useful as in vivo imaging agents capable of detecting tau and β-amyloid plaques in patients.

Important Compound Classes:



Definitions:

Ar is phenyl, pyridinyl, 2,3-dihydro-benzo[I,4]dioxinyl, 1,3-dihydro-indol-2-one, pyrazinyl, isoxazol-3-yl, imidazolyl, thiophenyl, or pyrimidinyl;

R is lower alkyl or lower alkyl substituted by halogen;

R^1 is hydrogen, halogen, hydroxy, lower alkoxy, lower alkyl, and lower alkoxy substituted by halogen;

R^2 is hydrogen, lower alkyl;

R^3 is hydrogen, halogen, lower alkyl, lower alkyl substituted by halogen, lower alkoxy, lower alkoxy substituted by halogen, $O(CH_2)_mO(CH_2)_mO$—lower alkyl substituted by halogen, cyano, lower alkoxy substituted by hydroxy, lower alkenyloxy, C(O)OH, heterocycloalkyl selected from morpholinyl, pyrrolidinyl, or pyrrolidin-2-one, or is heteroaryl selected from imidazolyl substituted by lower alkyl, or

$NR'R''$ and R'/R'' are independent from each others' hydrogen or lower alkyl or —C(O)— lower alkyl; or is $-C(O)NR^4R^5$ and

R^4 is hydrogen or lower alkyl and

R^5 is hydrogen, lower alkyl, lower alkenyl, $-(CH_2)_mO$—lower alkyl substituted by halogen, lower alkyl substituted by halogen, $-(CH_2)_n$—phenyl optionally substituted by halogen, $-(CH_2)_mNHC(O)$—lower alkyl, or $-(CH_2)_mNH_2$, or

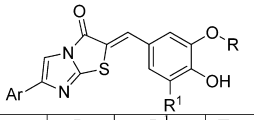
R^4 and R^5 may form together with the N atom to which they are attached a piperidine or azetidine ring, which may be substituted by halogen; or is —C(O)O—lower alkyl substituted by halogen;

n is 1 or 2;

m is 1, 2, or 3.

Received: April 11, 2014
Published: April 28, 2014

Key Structures:



Entry	Ar	R	R^1	Tau IC_{50} (nM)	A-β IC_{50} (nM)
1	4-Py	CH_3	OCH_3	5	93
2	4-Cl-Phenyl	CH_3	OCH_3	2	7
6	4-Cl-Phenyl	CH_3	Cl	2	32
7	4-Cl-Phenyl	CH_3	Br	2	18
8	4-Cl-Phenyl	CH_3	OH	5	18
12	3-CH_3-4-Py	CH_3	H	79	>10,000
16	3-CH_3-4-Py	CH_3	OCH_3	8	32
21	3-Cl-Phenyl	CH_3	OCH_3	1	6
24	3-CF_3-Phenyl	CH_3	Cl	3	123
35	3-OCF_3-Phenyl	CH_3	F	13	>10,000

Recent Review Articles:

1. Pooler, A. M.; Noble, W.; Hanger, D. P. A role for tau at the synapse in Alzheimer's disease pathogenesis. *Neuropharmacology* **2014**, *76* (PA), 1−8.
2. Anand, R.; Gill, K. D.; Mahdi, A. A. Therapeutics of Alzheimer's disease: Past, present and future. *Neuropharmacology* **2014**, *76* (PA), 27−50.
3. Jensen, J. R.; Cisek, K.; Funk, K. E.; Naphade, S.; Schafer, K. N.; Kuret, J. Research toward tau imaging. *J. Alzheimer's Dis.* **2011**, *26* (S3), 147−157.
4. Villemagne, V. L.; Furumoto, S.; Fodero-Tavoletti, M.; Harada, R.; Mulligan, R. S.; Kudo, Y.; Masters, C. L.; Yanai, K.; Rowe, C. C.; Okamura, N. The challenges of tau imaging. *Future Neurol.* **2012**, *7* (4), 409−421.

Biological Assay: Thiazin-red R displacement fluorescence assay

Biological Data:

Entry	Tau IC_{50} (nM)	A-β IC_{50} (nM)	Entry	Tau IC_{50} (nM)	A-β IC_{50} (nM)
1	5	93	12	79	>10,000
2	2	7	16	8	32
6	2	32	21	1	6
7	2	18	24	3	123
8	5	18	35	13	>10,000

Claims:

26 Total claims
19 Composition of matter claims
7 Method of use claims

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Notes

The authors declare no competing financial interest.