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Conferencia: Discovery of potent and orally bioavailable BACE-1 inhibitors for the treatment of Alzheimer's disease

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Aula de Seminarios do CIQUS

10:15 h

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Andrés A. Trabanco obtained his PhD in Organic Chemistry from the *Universidad de Oviedo* under the supervision of Profs. José Barluenga and Josefa Flórez. During his PhD thesis he worked in the field of Fischer carbene complexes and their application in stereoselective synthesis. In 1999 he joined Prof. Anthony Barrett's group at Imperial College of Science Technology and Medicine in London, where he worked in the synthesis of novel porphyrazines as potential agents for the treatment and diagnosis of cancer. He joined the Neuroscience Medicinal Chemistry Team at Janssen in 2000 and in 2005 was promoted to the position of Medicinal Chemistry Team Leader. In 2008 he was appointed as head of the Neuroscience Hit Generation Team and since 2009 he also acts as Neuroscience External-Chemistry Coordinator. He has been chemistry team leader and active team member for several programs in the areas of schizophrenia, depression, anxiety and cognition which have delivered various clinical candidates. He is an inventor in 39 patent applications and has about 40 publications in peer reviewed journals.

Discovery of potent and orally bioavailable BACE-1 inhibitors for the treatment of Alzheimer's disease

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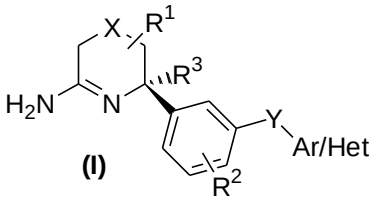
Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common form of dementia. The societal burden of AD is vast: the cost of treatment, care and loss of productivity is estimated at US$300 billion per year; in 2010 there were 454000 new cases of Alzheimer's in the US alone and the number of people with dementia is expected to double in the next 20 years.[1] The cause of AD is unclear but Tau fibrils and amyloid beta (Aβ) deposits are characteristic neuropathological hallmarks and may be associated with disease pathogenesis.[2] The insoluble plaques are predominantly aggregates of Aβ peptides of 39–43 amino acids formed via the sequential cleavage of β-amyloid precursor protein (APP) by aspartyl proteases, β- and γ-secretase.[3] The inhibition of β-secretase (BACE) may therefore represent a potential disease modifying treatment forAD.[4]

Herein we report on the discovery and synthesis of potent amidine-like BACE-1 inhibitors (**I**) which reduce the formation of Aβ peptides in mice and dog models after oral administration.



(I)

References

(1) Brody, H. *Nature* **2011**, *475*, Suppl, S1. (2) Hardy, J., Selkoe, D. J., *Science* **2002**, 5580, 353. (3) Selkoe, D. *J. Physiol. Rev.* **2001**, *81*, 741. (4) De Strooper, B., Vassar, R., Golde, T., *Nature Rev. Neurol.* **2010**, *6*, 99.