monitor

MOLECULES

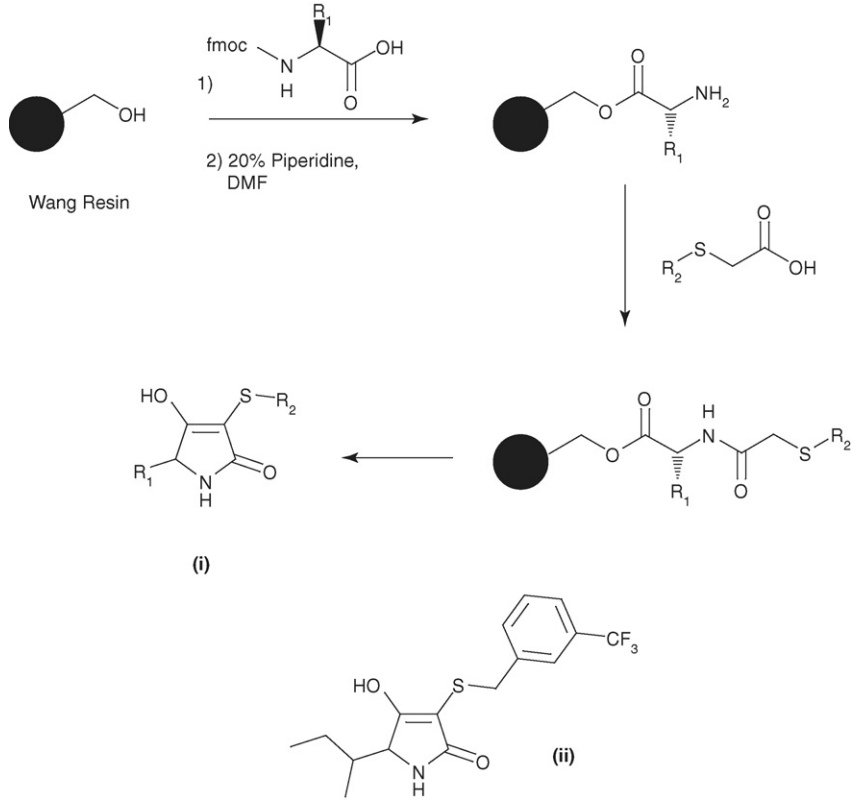
Tetramic and tetronic acids as β-secretase inhibitors

Alzheimer's disease (AD) is a common age-related neurodegenerative disorder affecting ~2% of the population in industrialized countries. One in ten individuals over the age of 65, and nearly half of those over the age of 85, are likely to develop the disease, for which there is currently no cure. Investigation by the scientific community has provided insight into the biology of the disease and revealed several options for treatment.

Brains of patients affected by AD are characterized by two structural features: amyloid plaques and neurofibrillary tangles [1]. β -Amyloid plaques are specific for AD, whereas tangles are also found in other disorders, such as Parkinson's disease [2]. The 'amyloid hypothesis' assigns a central role to the accumulation of β-amyloid peptide (Aβ) in the brain for the development of the pathology [3]. Aβ peptides derive from the abnormal cleavage of the β-amyloid precursor protein (β-APP). β-Secretase (BACE-1) is a member of the pepsin family of aspartyl proteases and has a crucial role in this amyloid cascade. Recent reports have demonstrated a direct correlation between increased BACE-1 activity and Aβ production in AD brain tissue [4]. Because aspartic protease inhibitors have been previously developed, BACE-1 inhibition has been recognized as a tractable target from a drug-development perspective. Most of the BACE-1 inhibitors published to date share a peptidic character and mimic the scissile amide bond of the natural substrate by a non-cleavable transition state isostere. As a consequence, they display low oral bioavailability and poor blood-brain barrier permeation. Therefore, non-peptidic BACE-1 inhibitors are of great interest for AD drug development.

Recent efforts [5], using a solid phase synthesis approach on Wang resin, have identified tetronic, tetramic and N-substituted tetramic acids that can inhibit BACE-1. In this work, compounds such as the tetramic acids were synthesized from loading of Fmoc-protected amino acids onto Wang resin, followed by N-deprotection, amidation and base-catalyzed cleavage from resin with concomitant cyclisation to deliver compounds of general structure **(i)**, as depicted in the Scheme. In this way, a small library was synthesized as singletons and compounds screened in a FRET assay for BACE-1 inhibition. One of the most potent compounds isolated was **(ii)**, which had an IC_{50} of 60 μM for BASE-1 inhibition.

This work has identified a novel series of tetramic acid BACE-1 inhibitors that have low molecular weight. Thus, these are amenable to optimization to provide compounds with the potential for good oral bioavailability. They therefore serve as a useful starting point for further optimization.



1359-6446/06/$ - see front matter © 2005 Elsevier Ltd. All rights reserved. doi:10.1016/j.drudis.2007.02.005

1 LaFerla, F.M. and Oddo, S. (2005) Alzheimer's disease: Aβ, tau and synaptic dysfunction. *Trends Mol. Med.* 11, 170–176
2 Joachim, C.L. and Selkoe, D.J. (1992) The seminal role of beta-amyloid in the pathogenesis of Alzheimer disease. *Alzheimer Dis. Assoc. Disord* 6, 7–34
3 Selkoe, D.J. (1999) Translating cell biology into therapeutic advances in Alzheimer's disease. *Nature* 399, A31–A32
4 Li, R. *et al.* (2004) Amyloid β peptide load is correlated with increased β-secretase activity in sporadic Alzheimer's disease patients. *Proc. Natl. Acad. Sci. U. S. A.* 101, 3632–3637
5 Larbig, G. and Schmidt, B. (2006) Synthesis of tetramic and tetronic acids as β-secretase inhibitors. *J. Comb. Chem.* 8, 480–490

Paul Edwards
mepauledwards@fsmail.net