■ NEUROPROTECTIVE BCHE INHIBITORS

IC$_{50}$ (BChE) = 60 nM / K$_C$ = 13 nM, no inhibition of AChE at 100 μM.
R = H (formed after carbamoylation of BChE's active site): strongly reduced ROS-mediated cytotoxicity on hippocampal neuronal cells (HT-22)
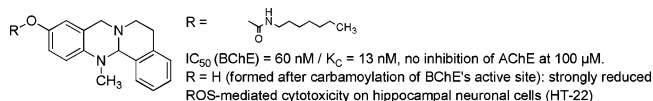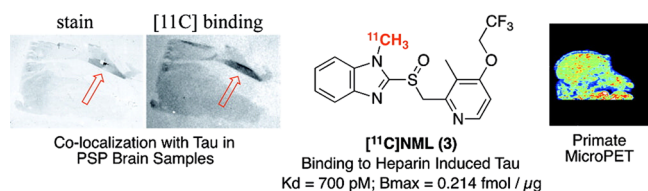
Alzheimer's disease is a distressing neurodegenerative disorder, is the most common cause of dementia, and affects millions of older people around the world. While researchers worldwide continue to aggressively pursue a cure, the cause of this disease is still unknown, and the need for therapeutics remains unmet.

In this Special Issue, Darras et al. (DOI: 10.1021/ml3001825) describe the design and synthesis of a set of compounds that are able to inhibit the butyrylcholinesterase enzyme, which has drawn a lot of attention from the community of drug developers working on Alzheimer's disease, since its inhibition might be more effective in improving cognitive deficits of patients when compared with the currently available drugs inhibiting acetylcholinesterase. The compounds in this study not only show high potency by an irreversible mode of action but also show remarkable selectivity toward butyrylcholinesterase. Additionally, these compounds are able to reduce the amount of reactive oxygen species (ROS) and to protect neuronal cells from cell death induced by ROS, the formation of which is strongly associated with Alzheimer's disease. Such structures could open the way to a more than purely symptomatic treatment of this devastating disease.

■ NEW PET IMAGING TECHNIQUE FOR DETECTING TAU NEUROFIBRILLARY TANGLES

stain   [11C] binding

Co-localization with Tau in PSP Brain Samples

[^{11}C]NML (3)
Binding to Heparin Induced Tau
Kd = 700 pM; Bmax = 0.214 fmol / μg

Primate MicroPET

PET imaging of Alzheimer's disease is an aggressive area of research with much effort to date focusing upon targeting amyloid plaques. This led to the first radiopharmaceutical approved by the FDA this year. However, whereas imaging amyloid is of enormous value, it has been shown that tau burden, rather than amyloid, correlates with cognitive decline in Alzheimer's disease. Currently, there has only been limited success in the development of tau imaging agents. As such, development of a radiopharmaceutical for tau is of the utmost importance to Alzheimer's disease research.

Here, Shao et al. (DOI: 10.1021/ml300216t) report the development of a radiopharmaceutical based upon lansoprazole, a compound with an affinity for tau neurofibrillary tangles. The authors offer a robust, reliable method for carrying out fast and efficient production of [^{11}C]N-methyl lansoprazole and describe their initial efforts at validating this radiopharmaceutical to translate it into clinical use. This study could provide further insight in the development of tau imaging agents for detecting Alzheimer's disease as well as detecting various forms of tauopathies.

■ LYSOSOMAL MODULATORS AS NOVEL TREATMENT FOR ALZHEIMER'S DISEASE
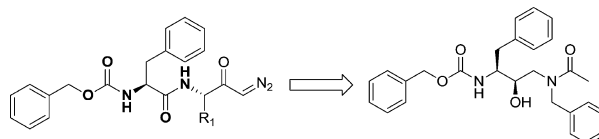
Non-peptidic Lysosomal Modulator

Lysosomes are the cellular components involved in removing misfolded or aggregating proteins, but with aging and disease, lysosomes can become less effective at clearing toxic accumulations that are linked to dementia. Several studies now indicate that lysosomal enzymes can be up-regulated to offset age-related deficits in proteolytic clearance that constitute a risk factor for Alzheimer's disease. Positive modulators of the lysosomal system, for instance, Z-Phe-Ala-diazomethylketone (PADK), enhance lysosomal cathepsin levels to elicit protective clearance of toxic proteins in the brain. Therefore, synthesis of compounds targeting lysosomal modulation serves as an innovative approach for treating Alzheimer's disease.

In this Special Issue, Viswanathan et al. (DOI: 10.1021/ml300197h) describe the synthesis and activity of two first-in-class lysosomal modulators that were developed based initially on the PADK structure. The novel compounds exhibit improved modulation as compared to PADK but without the weak enzyme inhibitory properties characteristic of PADK. One compound is notable as a drug development candidate. Developing this class of modulatory agents could accelerate drug discovery efforts to protect against the protein accumulation pathology believed to underlie cognitive dysfunction, perhaps as a route to prevent or slow the progression of Alzheimer's disease.