ACS Chemical Neuroscience

In This Issue

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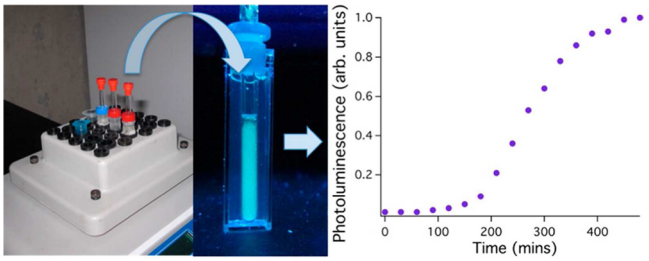
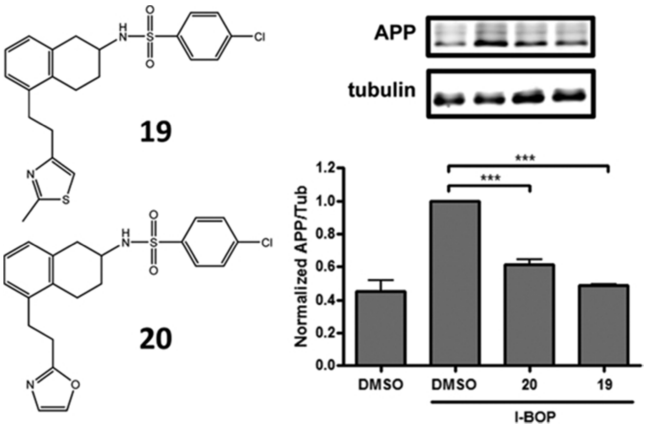
A LOW-COST METHOD FOR MONITORING FIBRILLIZATION OF Aβ PEPTIDE



The transition of monomeric amyloid-β (Aβ) to aggregate forms such as fibrils is linked to the progression of Alzheimer's disease (AD). Many techniques have been developed to quickly monitor the transition from primarily monomeric peptide into fibrils; however, they require specialized equipment such as microplate readers. In the current issue, Cook and Martí (DOI: 10.1021/cn300135n) report a novel methodology for growing and monitoring amyloid proteins in a reproducible way without the need for expensive or specialized instrumentation.

The authors developed a relatively simple technique for incubating and monitoring Aβ aggregation. The methodology involves the use of modified NMR tubes, a microtube thermoshaker, and a fluorescence or UV−vis spectrometer. The described approach presents a practical and reliable way to track Aβ fibrilization using fluorescence or turbidity assays.

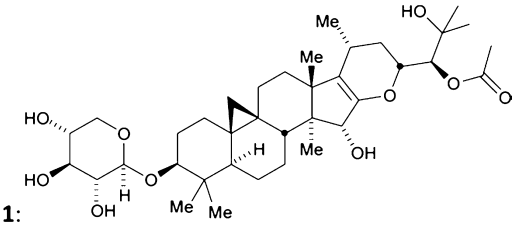
A NEW CLASS OF PROMISING ALZHEIMER'S DISEASE THERAPEUTICS



Recent work reveals that the Alzheimer's disease (AD) brain is under oxidative stress. Nonenzymatic lipid oxidation products, known as isoprostanes, have been reported to be elevated in the AD brain and cerebrospinal fluid. More specifically, isoprostane 2αIII (iP2αIII) is an agonist of the thromboxane A2-prostanoid (TP) receptor, which increases production of Aβ peptides found within AD plaques. Therefore, TP receptor antagonists may serve as therapeutic agents for AD. In the current issue, Soper et al. (DOI: 10.1021/cn3000795) develop a new class of brain-penetrating compounds that antagonize the TP receptor.

The authors modified the previous TP receptor antagonists that were unable to cross the blood-brain barrier. Replacing the carboxylic acid moiety of a known TP receptor antagonist with heterocyclic bioisosteres permitted permeability across the blood-brain barrier. The modification resulted in a potent TP receptor antagonist which inhibited TP receptor-dependent Aβ release.

GAMMA-SECRETASE MODULATORS FOR ALZHEIMER'S DISEASE TREATMENT



Compound **1**:

Aβ is produced through the sequential action of proteases on amyloid precursor protein (APP), an integral transmembrane protein. Gamma-secretase is one such protease which cleaves APP to produce Aβ, which is associated with the onset of Alzheimer's disease (AD). Thus, the direct involvement in Aβ formation has made gamma-secretase a prime drug target. In this issue, Findeis et al. (DOI: 10.1021/cn3000857) isolate a natural product with gamma-secretase modulating properties.

The authors describe the characterization of a novel gamma-secretase modulator (GSM) derived from the black cohosh plant. The structure of the putative active moiety of the compound is described after isolation, purification, and validation. Indeed, this compound lowers levels of Aβ42 and increases shorter Aβ peptides, such as Aβ37 and Aβ39 with only minor reduction in Aβ40 levels. This profile of modulating the production of Aβ toward shorter forms while sparing the processing of other important substrates is believed to be potentially useful for the treatment of AD.

Special Issue: Alzheimer's Disease

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