Novel Gamma-Secretase Modulators for the Treatment of Alzheimer's Disease and Related Neurodegenerative Disorders

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BACKGROUND

Thirty million people worldwide are currently living with Alzheimer's disease (AD) and unless the disease can be effectively prevented, this number will balloon in aging populations. For example, in the U.S. the number of people age 65 and older is expected to increase from 39 million in 2008 to 72 million in 2030, with the number of people with AD doubling every 5-year interval over the age of 65.

A key pathological indication of AD is an overabundance of neuritic plaques in regions of the brain participating in memory and cognition. Research has confirmed that Aβ42 forms the "seed" of these amyloid plaques, which gradually accumulate in the brain and induce cell death in the underlying brain tissue. It is widely accepted that all Aβ peptides are derived from proteolytic processing of an amyloid precursor protein (APP). Several drug discovery strategies including inhibition of gamma-secretase have been used to inhibit Aβ42 production from amyloid precursor protein. However, the involvement of gamma-secretase inhibitors in the proteolysis of several other substrates (e.g. Notch receptors) can lead to adverse effects (e.g. triggering goblet cell hyperplasia in the gastrointestinal tract).

Alternatively, gamma-secretase modulators (GSMs), such as those described in U.S. patent 7,244,739, lower the production of toxic, longer forms of Aβ, such as Aβ42, and promote the formation of smaller, less toxic Aβ peptides (Aβ37 and Aβ38) at nanomolar potencies. The design of gamma-secretase modulators for the treatment of AD is rapidly expanding, yet most of the gamma-secretase modulators cited in the literature are non-steroidal anti-inflammatory drugs (NSAIDs) and suffer from poor potency and minimal brain penetration.

TECHNOLOGY DESCRIPTION

Researchers at UC San Diego have developed methods for synthesizing and testing a number of novel gamma-secretase modulators with dramatically improved aqueous solubilities. The enhanced aqueous solubilities of these gamma-secretase modulators are expected to exhibit improved pharmacokinetic and pharmacodynamic properties compared to the 2-aminothiazole GSM compounds previously described in U.S. patent 7,244,739. The present invention is a new class of soluble GSMs that promises to be far more amenable to preclinical and clinical development protocols as a result of their enhanced aqueous solubilities.

SGSM technology covered by this invention may prove useful for treating diseases associated with altered levels of certain Aβ peptide alloforms (i.e., Aβ42 and Aβ40), such as Alzheimer's disease, Down's syndrome, hereditary cerebral hemorrhage with amyloidosis-Dutch Type, cerebral amyloid angiopathy, and mild cognitive impairment, as well as a number of other neurodegenerative proteinopathies (e.g. Creutzfeldt-Jakob disease, frontotemporal dementias, amyotropic lateral sclerosis, Huntington's disease, Parkinson's disease).

INTELLECTUAL PROPERTY INFO

See PCT/US2011/041905 (WO 2011/163636).

PATENT STATUS

Country	Type	Number	Dated	Case
United States Of America	Issued Patent	9,403,815	08/02/2016	2010-246

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OTHER INFORMATION

CATEGORIZED AS
- Medical
  - Disease: Central Nervous System

RELATED CASES
2010-246-0, 2013-201-0

RELATED MATERIALS

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