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Substituted dithiazole piperazine benzamides as novel amyloid beta peptide reducing agents

Hongjie Wang, Ruizhi Wang, Madepalli K. Lakshmana, Adel Nefzi *

Torrey Pines Institute for Molecular Studies, Port Saint Lucie, FL 34987, United States

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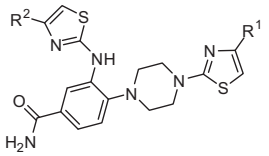
ABSTRACT

Alzheimer's disease is a persistent neurodegenerative disorder of elderly characterized clinically by irreversible loss of memory due to accumulation of amyloid beta peptides within the amyloid plaques. We report the parallel synthesis and screening results of diverse substituted di-thiazole piperazine benzamides. A new compound **TPI-1917-49** was identified as a promising amyloid reducing agent by lowering the levels of Aβ at least in two cell types and in vivo.

Alzheimer's disease (AD) is a devastating and persistent neurodegenerative disorder of elderly characterized by cognitive decline and memory loss resulting in personality changes and ultimately leading to a total dependence on nursing care. It is now estimated that nearly 35.6 million patients are affected by AD worldwide and that about 4.6 million new cases are added up each year causing enormous social and economic burden.[1] Accumulation of amyloid plaques made up of amyloid β peptide (Aβ), derived from amyloid precursor protein (APP) by consecutive actions of β- and γ-secretases is a major hallmark of AD. Current therapy that are based on either AChE inhibition or NMDA receptor antagonism can neither slow nor reverse the disease progression as they do not treat the underlying cause of AD. About 1064 clinical trials have been attempted throughout the world to bring an effective therapy for AD based on all possible mechanisms of action including in most recent years both β- and γ-secretase inhibitors. However, all these attempts to develop disease-modifying therapy have so far failed. It is also highly significant that Aβ has been implicated to play a vital role in the pathogenesis of not only Alzheimer's disease but also traumatic brain injury (TBI),[2] cerebral amyloid angiopathy (CAA)[3] and Glaucoma.[4] Like Alzheimer's disease, there are no effective prevention or treatment strategies for CAA and TBI. Therefore, invention of any anti-amyloid drug would have wider clinical applications especially for disease modifying therapies.

Small molecules containing thiazole moiety has been demonstrated to possess drug like properties against varieties of diseases[5] resulting in so far 17 FDA-approved drugs containing the thiazole ring.[6] The indications to which thiazole derivatives are prescribed include asthma (Cinalukast), bacterial infections (Ceftizoxime), diarrhea (Nitazoxanide), myelogenous leukemia (Dasatinib), pain (Meloxicam), duodenal ulcers (famotidine), anthelmintics (thiabendazole) and as vitamin (thiamine). Among these riluzole is an important and the only thiazole derivative approved by the FDA for CNS disorders and it is both neuroprotective and anticonvulsant.[7] Thus, although the thiazole ring is an important and highly reactive scaffold it is not well exploited for CNS disorders. More recent investigations have developed potent γ-secretase inhibitors[8] and cdk5/p25 inhibitors[9] as a potential treatment for AD based on the fact that cdk5/p25 hyperphosphorylate tau. Additionally, Thioflavin T is a benzothiazole dye that binds amyloid beta peptide of AD and therefore used in the diagnosis of amyloid fibrils both ex vivo and in vitro.[10] In



TPI-1917

substituted di-thiazole piperazine benzamides

(25 compounds)

Scheme 1. Thiazole library screened against AD.

* Corresponding author. Tel.: +1 (772)345 4739; fax: +1 (772)345 3649.
E-mail address: adeln@tpims.org (A. Nefzi).

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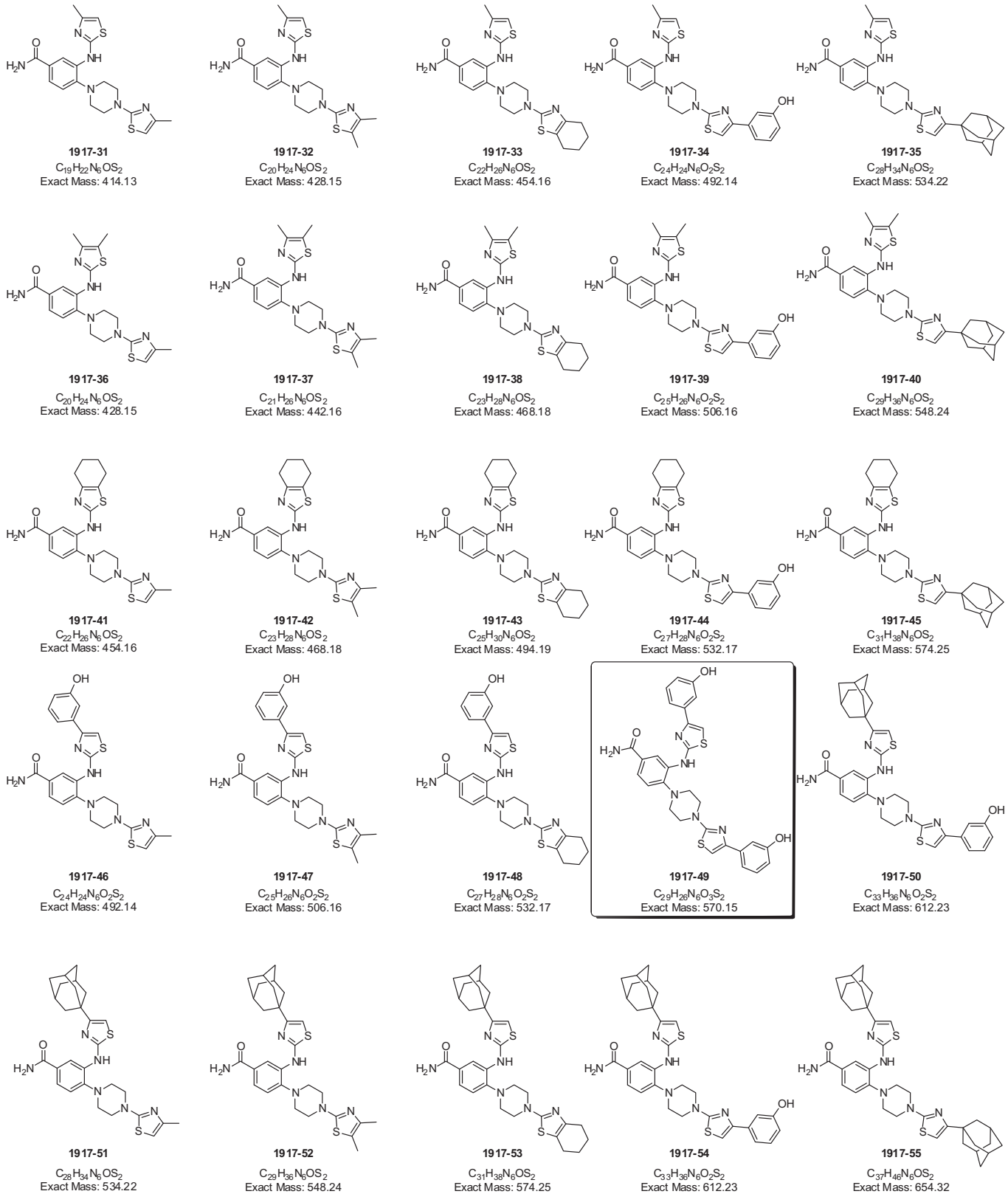

Scheme 2. Structures of the substituted di-thiazole piperazine benzamides screened against AD.

the absence of an effective disease modifying therapy for AD, and also because the thiazole ring is highly reactive and has successfully been derived to make many drugs, we decided to synthesize and characterize a variety of novel derivatives of thiazole and screened them for their effect in lowering Aβ levels in a cell-based assay and identified thiazole compound (**TPI-1917-49**) as potential Aβ lowering small molecule compound with novel mechanism of action.