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Discovery and characterization of novel indole and 7-azaindole derivatives as inhibitors of β-amyloid-42 aggregation for the treatment of Alzheimer's disease

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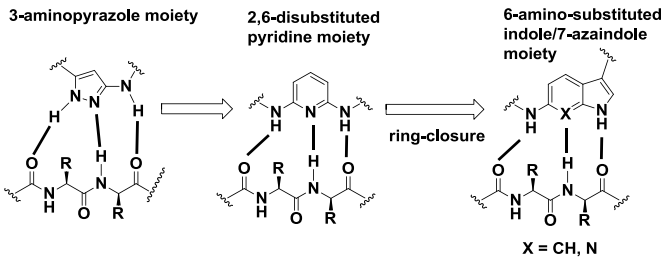
ABSTRACT

The aggregation of amyloid-β peptides into cytotoxic oligomeric and fibrillary aggregates is believed to be one of the major pathological events in Alzheimer disease. Here we report the design and synthesis of a novel series of indole and 7-azaindole derivatives containing, nitrile, piperidine and N-methyl-piperidine substituents at the 3-position to prevent the pathological self-assembly of amyloid-β. We have further demonstrated that substitution of the azaindole and indole derivatives at the 3 positions is required to obtain compounds with improved physicochemical properties to allow brain penetration.

Alzheimer's disease (AD) is a form of senile dementia, characterized by a progressive loss of memory and cognitive function[1-3]. It has been hypothesized that formation of β-amyloid (Aβ) plaques is key to the development and progression of the disease. Present pharmacotherapies with known anti-cholinesterase activity, such as Aricept and Exelon, are only helpful to alleviate some of the symptoms for a limited time period[4]. These agents act to stabilize the remaining neuronal networks and prolong neuronal function until their therapeutic effect diminishes and drug tolerance occurs. The marginal benefits from these therapies emphasize the urgent need to develop alternative and effective disease-modifying agents[5]. Several trends have been emerging using small molecules to target various AD pathological routes such as the amyloidogenic secretases (β/γ- secretase)[6-7], amyloid-β aggregation[8-14], tau phosphorylation and fibrillation[15-17] and metal-ion redox/reactive oxygen species (ROS)[18-22].

Of those, Aβ is one of the most promising targets for the development of new therapies as the substantial data derived from genetics, animal modeling, and biochemical studies support the idea that Aβ, the major component of senile plaques, plays a central role in AD pathophysiology[23-24]. Thus, we have initiated a program aiming to design novel non dye compounds for the inhibition of Aβ aggregation for AD therapeutics. We have previously reported small molecule inhibitors of Aβ based on our rational design, *i.e.* 3-aminopyrazole[24] and 2,6-disubstituted pyridine derivatives[25] which can interact via a donor-acceptor-donor (DAD) hydrogen bond pattern complementary to that of the β-sheet of Aβ[22-24]. However, compounds following this design displayed low metabolic stability and poor PK properties[25]. To overcome these issues, we sought to evaluate whether replacing the 2,6-disubstituted pyridine moiety with 6-amino-substituted indole and 7-azaindole moieties (Fig. 1) would improve metabolic stability and PK properties while maintaining their inhibition of Aβ aggregation properties.



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