CNB-001 - a novel synthetic pyrazole derivative of curcumin with neuroprotective, anti-oxidant and anti-inflammatory action

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Technology description

INVENTION

Investigators at the Salk Institute have designed, synthesized and optimized a novel pyrazole derivative of curcumin. CNB-001 displays much improved potency and metabolic stability over curcumin and is neuroprotective in multiple neurotoxicity assays in which curcumin is inactive while retaining anti-oxidant and anti-inflammatory actions.

Background:

Numerous studies have reported the anti-oxidant, anti-inflammatory and anti-amyloid effects of curcumin. However, its poor stability has led researchers at the Salk to design and develop curcuminoid derivatives with improved potency and pharmacokinetic properties. CNB-001 has been extensively investigated in models of traumatic brain injury (TBI), Alzheimer's disease (AD), lung inflammation and stroke. The stroke models include the rabbit small clot embolic stroke model (RSCEM)- the same model used in the development of tPA. The primary endpoint of this model is behavior based upon motor function components of the NIH Stroke Scale for human stroke. CNB-001 was found to be effective in protecting neurons in the in vitro stroke models through maintenance of ATP levels and prevention of nerve cell death. The compound significantly reduced stroke-induced behavioral deficits when given as a single subcutaneous dose of 100mg/kg, 1-hour post embolism in the rabbit model. These studies also demonstrated that the activity of CNB-001 in vivo is mediated through the maintenance of the PI3K-Akt kinase pathway and ATP levels, and the modulation of calcium-calmodulin-dependent protein kinase IIa. Additional work in models of AD has shown that CNB-001 normalizes several markers for synapse loss and oxidative stress in the hippocampus caused by AD and increases levels of BDNF and the transcription of some BDNF-responsive genes in both normal rats and AD mice. Importantly, CNB-001 clears intracellular amyloid and other aggregated proteins in the brain that accumulate with old age. Total Abeta and plaque loads are not significantly reduced in treated AD mice, but CNB-001 reduces the more toxic soluble Abeta1-42. Two studies showed that CNB-001 is very effective in treating rodent models of TBI. As CNB-001 is a potent 5 lox inhibitor, it was tested and shown to have therapeutic efficacy in a rodent model of airway inflammation and remodeling.

Keywords

Alzheimer's Disease
Asthma
Calcium Signaling
Drug Discovery
Neurodegenerative Disorders
Oxidative Stress
Parkinson's
Phosphatidylinositol 3'-kinase
Schubert5-lipoxygenase (5-LOX)
Anti-oxidant
tPA
Traumatic Brain Injury (TBI)
StrokeAmyloid-beta

Application area

Stroke, Alzheimer's disease, Parkinson's disease, Traumatic Brain Injury, and Lung inflammation (asthma)

Advantages

Potent inhibitor of 5-lipoxygenase (IC50~70 nM)
More potent than Zileuton which is FDA approved for the prophylaxis and chronic treatment of asthma
Compound profile: MW, 440; cLogP, 4.67; tPSA, 74.52
Well tolerated in animal models with no reported adverse effects
Orally bioavailable
No predicted toxicity in CeeTOX assay for membrane integrity, mitochondrial function, cell proliferation, apoptosis, oxidative stress, and solubility
EC50: Between 500 and 1000 nM in cell culture assays. As low as 10 mg/kg in a rodent object recognition memory assay
Crosses blood-brain-barrier (by gavage) at high levels with a plasma half-life of over 2hrs

Institution

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