Syntheses of Dihydronicotinamide Riboside Derivatives and Their Use in Disease Conditions

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Technology description

This invention provides methods of synthesizing new types of nicotinamide riboside derivatives, called dihydronicotinamide riboside derivatives, and methods of using the derivatives to increase NAD concentrations in cells and tissues in order to treat disease states in situations where enhancement of NAD concentration could be efficacious.

Technology Overview

Increasing mammalian cell and tissue NAD production has been shown to provide a number of health benefits in animal models of human disease. Examples include protection from neurodegeneration caused by Alzheimer’ s disease, resistance to toxic effects of high fat diets, improvement in mitochondrial densities, improvements in insulin sensitivity and exercise endurance, improvement in muscle function in muscular dystrophy patients, and reversal of fatty liver disease. Enhancing NAD could also protect from neurotrauma, such as blast injury and noise induced hearing loss.

Nicotinamide riboside has been shown to increase NAD production and NAD levels in mammalian cells. The Sauve laboratory has developed efficient synthetic methods to produce NR, which is currently used for commercial production of NR at low cost.

Dihydronicotinamide riboside derivatives are new types of NR derivatives, incorporating reduction of the nicotinamide ring to the dihydro-nicotinamide riboside structure. The inventors have achieved synthesis of dihydronicotinamide riboside derivatives using NR and NR esters as starting points and the synthetic and isolated yields are very high. The inventors demonstrated that the dihydronicotinamide riboside derivatives are robust enhancers of NAD concentration in cultured mammalian cells (ranges of NAD increase were 200-1000% of untreated controls). No apparent toxicity was observed with these compounds. Instead, the compounds were shown to enable cells to resist toxicity caused by hydrogen peroxide and a DNA-damaging carcinogenic agent, demonstrating efficacy in cell protection.

The compounds could be used for enhancing NAD concentrations in biological systems, including humans. They could be used in the treatment of disease states where enhancement of NAD concentration could be efficacious, such as neurotrauma, neurodegenerative states and states characterized by high ROS toxicity and genotoxic stress.

Application area

Reagents for enhancing NAD concentrations in biological systems
Therapeutic agents for treating disease states where enhancement of NAD concentration could be efficacious, such as neurotrauma, neurodegenerative states and states characterized by high ROS toxicity and genotoxic stress
PCT Application: Syntheses, activities, and methods of use of dihydronicotinamide riboside derivatives

Advantages

The dihydronicotinamide riboside derivatives are strong enhancers for increasing NAD concentrations
No apparent toxicity in mammals
Enhanced lipophilicity for improved drug behavior, such as drug absorption and penetration of blood-brain barrier

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