Ferrostatins for therapeutic control of reactive oxygen species in excitotoxic and degenerative diseases

Programmed cell death is essential for homeostasis but may also contribute to disabling neuronal pathologies. Four genetically distinct mechanisms of cell death are known: apoptosis, autophagy, necrosis, and ferroptosis. Ferroptosis has been found to cause excitotoxic and degenerative damage to neurons. Importantly, Ferrostatin-1 (Fer-1) is a potent inhibitor of ferroptosis and has prevented cell death in in vitro models of Huntington’s disease, periventricular leukomalacia and kidney dysfunction. Following this success, analogs of Fer-1 were created, focusing on optimizing the compound’s stability and solubility thereby making it a more viable therapeutic candidate. This technology is a set of Fer-1 derivatives, one of which, SRS 15-72, was found to have physical properties compatible with pharmaceutical preparation, making it a promising therapeutic candidate for pathologies that include ferroptosis.

Stable and soluble ferroptosis inhibitor treats disease by modulating lipid peroxidation

Fer-1 prevents glutamate-induced excitotoxicity in rat brain samples, as well as ferroptotic cell death in cancerous tissue and various neurodegenerative disease models including Huntington’s disease. Structure-activity relationship experiments following Fer-1 led to the synthesis of SRS 15-72 which has comparable potency while exhibiting increased stability and solubility in vitro. Altogether, this technology has the potential to be a potent tool in the fight against degenerative diseases involving lipid peroxidation such as amyotrophic lateral sclerosis, Huntington’s disease, and Parkinson’s disease.

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Applications:

- Small molecule therapeutic for degenerative disease
- Prophylaxis for neurodegeneration
- Probe for studying ferroptosis and neurodegeneration
- Method of modulating ferroptotic activity
- Method of modulating cell life spans
- Method of modulating iron metabolism
- New approach to antioxidant therapy

Advantages:

- Microsomal stability and solubility confirmed in vitro
- Based on compound with demonstrated in vitro effectiveness
- Inhibits ferroptosis, a cell-death mechanism involved in various neurodegenerative diseases.

Patent Information:

Patent Pending (US 20160297748)
Patent Pending (WO/2015/084749)
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Related Publications:


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