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Novel Edaravone Derivatives as Neuroprotective Agents for the Treatment of ALS

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Abstract

Background: Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disease (ND) with limited treatment options [1]. Although with some drawbacks, Edaravone is one of the available drugs for ALS that targets oxidative stress (OS), a key factor in the pathophysiology of this disease [1]. **Objective:** This work aimed to evaluate the cytotoxic effects and neuroprotective potential of a new series of Edaravone derivatives (MS's), designed to target mitochondria and enhance its biological activity, against OS inducers and mitochondrial disruptors. **Methods:** Cholinergically differentiated SH-SY5Y cells were treated with MS's (0–100 µM) for 24h to assess their cytotoxicity using the NR uptake and MTT reduction assays. To evaluate the potential neuroprotective effects of MS's, SH-SY5Y cells were simultaneously exposed to *tert*-Butyl Hydroperoxide (*t*-BHP, 0–40 µM), Iron(III) (0–1000 µM, in the form of a FeNTA complex) or Phenazine Methosulfate (PMS, 0–5 µM), in the presence and absence of non-cytotoxic concentrations of MS's (0–25 µM). Cellular viability was then assessed by the NR uptake assay, 24h after exposure. The production of reactive oxygen/nitrogen species (RS) was also measured in SH-SY5Y cells upon exposure to *t*-BHP, Iron(III) or PMS, in the presence and absence of MS's for 24h, using the DCFH-DA probe. In all assays, edaravone was used as a model drug. **Results:** The novel edaravone derivatives generally exhibited no significant cytotoxicity at concentrations below 50 µM. Under OS conditions induced by *t*-BHP, all test compounds significantly reduced RS production. However, only four compounds significantly reduced *t*-BHP-induced cytotoxicity. In the presence of Iron(III) or PMS, six of the nine developed MS compounds notably reduced RS overproduction and significantly reduced both Iron(III)- and PMS-induced cytotoxicity, with three MS compounds showing more pronounced cytoprotective effects, with greater increase in cell viability observed for all tested concentrations and in a concentration-dependent manner. **Conclusions:** These Edaravone derivatives showed promising neuroprotective properties, exhibiting enhanced antioxidant activity compared to the parent compound. Given these findings, these innovative derivatives hold significant potential for further studies to assess their applicability in the treatment of ND, particularly ALS.

Keywords: Amyotrophic Lateral Sclerosis; Oxidative Stress; Neuroprotection

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