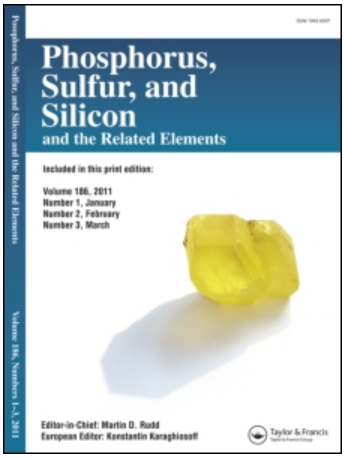

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Amidothionophosphates: Novel Antioxidant Molecules

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AMIDOTHIONOPHOSPHATES: NOVEL ANTIOXIDANT MOLECULES.

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This work describes the synthesis and characterization of a new family of antioxidants. The molecules have the same active group, but different oil-to-water and octanol-to-water partition coefficients due to different substituents. Three new molecules were synthesized based on the chemical structure of the primary amide attached to a thiophosphate group forming an amidothionophosphate. The amidothionophosphate molecules were exposed to the oxidative stress of hydrogen peroxide and sodium hypochlorite, and the chemical changes following the exposure were monitored by ^{31}P NMR. The reaction constants with reactive oxygen species such as hydroxyl radical and superoxide radical were also calculated and found to be $1.5*10^9$ $M^{-1}S^{-1}$ and $8.1*10^2$ $M^{-1}S^{-1}$, respectively. In order to elucidate the ability of amidothionophosphates to act as antioxidants in protecting lipids and proteins, we examined damage prevention in Bovine serum albumin, egg phosphatidyl choline liposomes and lipid emulsions following oxidative stress.Amidothionophosphate showed unique protection properties in these models. In contrast to other antioxidant molecules (ascorbic acid, cystine, and a-tocopherol) the new group did not have any pro-oxidative effects as measured by oxygen consumption from buffer solutions containing amidothionophosphates and cupric sulfate as a redox-active metal. Amidothionophosphates reduced significantly and in a dose-dependent manner the oxidative burst in human neutrophils as measured by luminol-dependent chemiluminescence, and they also markedly depressed the killing of human fibroblasts by mixtures of glucose oxidase and streptolysin S. The toxicity of these molecules was tested by i.p. injection of up to 1000 mg/kg to white Sabra mice. No mortality was observed 30 days after administration of up to 500 mg/kg.