Design and biological characterization of novel Antiatherogenic Tocopherol analogs - Nitric oxide donors

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Low density lipoprotein (LDL) oxidation has been proposed as an early event in the development of atherosclerosis. a-Tocopherol (Vitamin E) represents a major lipophilic antioxidant in LDL due to its reactive oxygen and nitrogen scavenging properties. Nitric oxide (·NO) is also a potent inhibitor of lipid oxidation processes in LDL because its ability to diffuse and concentrate in the hydrophobic core of the particle, reacting at diffusion-limited rates with lipid radicals to form nitrogen-containing products. Herein, we report the design, synthesis and biological properties of novel tocopherol analogs - ·NO donors. These hybrid compounds were designed to share ·NO releasing properties (due to the presence of a furoxan substructure) and LDL incorporation capacity, depending on the tocopherol substructure. They were effectively incorporated into human LDL and released fluxes of ·NO, inhibiting platelet aggregation and having endothelium-dependent vasorelaxation and antioxidant properties. The ·NO-releasing properties as well as the LDL incorporation and antioxidant capacities of these agents reinforce the importance of the site-specific release of ·NO in the cascade of events involve in the inhibition of LDL oxidation, offering a novel approach for the prevention of atherosclerosis and related disorders that involve reactive oxygen and nitrogen species.