Synthesis of Cytochrome P450 Inhibitors of Vitamin E Metabolism

by

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Abstract:

Vitamin E is a group of eight different tocopherols and tocotrienols distinguished by the degree of methylation of the aromatic ring. The North American diet contains more γ-tocopherol than the more biologically active α-tocopherol. γ-Tocopherol has recently been shown to have several advantages over its more heavily studied α-analogue such as the trapping of electrophilic mutagens such as peroxynitrite. Cytochrome P450 preferentially metabolizes γ-tocopherol over all other tocopherols beginning with an ω-hydroxylation on the phytol side chain. Whether a single enzyme (CYP4F2) or several isozymes (such as the CYP3A family) are responsible for this action has remained controversial. We herewith report the synthesis of a highly potent inhibitor of the oxidative metabolism of tocopherols and tocotrienols and the subsequent biological testing in human cell lines to determine the active enzyme of vitamin E metabolism.