Inhibitors of cytochrome P-450-dependent arachidonic acid metabolism

Capdevila, Jorge

Gil, Lionel

Orellana, Miriam

Marnett, Lawrence J.

Mason, J. Ian

Yadagiri, Pendri

Falck, J. R.

A new generation of heteroatom analogs of arachidonic acid are documented as powerful and selective inhibitors of the cytochrome P-450-dependent arachidonic acid oxygenase reaction (IC50, 5-10 ?m) with little effect on either cyclooxygenase or soybean lipoxidase at 100 ?m. The imidazole derivatives, ketoconazole and clotrimazole, are potent and selective inhibitors of the arachidonic acid epoxygenase and lipoxidase-like activities of phenobarbital-induced rat liver microsomal fractions (IC50, 2.0 and 0.3 ?m, respectively). In contrast, the ? ?w-1 oxygenase activity of ciprofibrate-induced microsomal fractions was relatively resistant to inhibition by these compounds (IC50, 50 and 25 ?m for ketoconazole and clotrimazole, respectively). Nordihydroguaiaretic acid (NDGA), eicosatetraynoic acid (ETYA), and indomethacin, extensively utilized inhibitors of the cyclooxygenase and lipoxygenase branches of the arachidonate cascade, also inhibit cytochrome P-450-dependent arachidonic acid metabol