

EVALUATION OF ANTIMUSCARINIC AND ANTIADRENERGIC EFFECTS OF TROPANE ALKALOIDS OF *ERYTHROXYLUM PERVILLEI*

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In previous work, bioactivity-guided fractionation of a chloroform extract of the roots of *Erythroxylum pervillei* Baillon, collected in southern Madagascar in 1992, led to the isolation of tropane alkaloid esters. Of these substances, pervilleines A-F were found in a small tumor panel to reverse multidrug resistance (MDR) for the KB-V1 vinblastine-resistant oral epidermoid carcinoma cell line in the presence of vinblastine, while being much less cytotoxic for normal KB cells and other cancer cell lines.¹ The parent alkaloid, pervilleine A, was also found to restore the vinblastine sensitivity of CEM/VLB100 (multidrug-resistant human leukemic lymphoblast CEM) cells as well as the chemosensitivity to colchicine of the KB-8-5 cell line. Pervilleine A was shown to be effective as an MDR inhibitory agent in an in vivo hollow fiber assay using KB-V1 cells when co-administered with vinblastine, with this tropane alkaloid postulated to act mechanistically by inhibiting P-glycoprotein mediated drug efflux.² Owing to the promising MDR-inhibitory activities of pervilleines A-C and F, which were comparable in potency to the standard MDR inhibitor, verapamil, these compounds were selected for further development through the RAID (Rapid Access to Invention Development) program of the U.S. National Cancer Institute. Pervilleine A (NSC 687938) was approved by the NCI Biological Evaluation Committee in December, 2004 for evaluation in a MDR xenograft HCT-15 colon cancer model.

Due to the tropane ring similarity of pervilleine alkaloids with that of the well known (-)-hyoscyamine [(-)-cocaine], the antimuscarinic and adrenergic activities of pervilleine A was evaluated. When compared with the potency of (-)-hyoscyamine K_β 1.8 nM, a well-known competitive blocker, in the guinea pig ileum and the rat anococcygeus smooth muscle, pervilleine A exhibited non-competitive inhibition in the guinea pig ileum. Moreover, 100 μM of pervilleine A did not affect the carbachol-induced contraction of the rat anococcygeus smooth muscle. In adrenergic test preparations, pervilleine A blocked nonspecifically the vascular response of (-)-norepinephrine in the rat aorta ring, while the contractile response of rat vas deferens to (-)-norepinephrine was not affected significantly by 100 μM concentration of pervilleine A. These data suggest that pervilleine A has weak nonspecific anticholinergic and vascular antiadrenergic activities.

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