Aminoflavone Analog, L-Lysyl Prodrug, Dimethanesulfonate Salt  
(NSC 710464, AFP 464)  
ADME-PK and Biochemical Pharmacology Summary  
Division of Cancer Treatment and Diagnosis  
National Cancer Institute

The lysyl prodrug of aminoflavone is rapidly converted to the parent compound after administration to animals as the either the HBr (NSC 702295) or the dimethanesulfonate (NSC 710464; AFP464) salt. The elimination of aminoflavone (NSC 686288) is rapid after administration of the parent compound or the prodrug (terminal half-life ranged from 18 min to 4.8 hours after i.v. administration to rodents, dogs, and non-human primates). The clearance was similar in mice and rats on a body surface area basis (9.7 - 14 L/hr/m$^2$) but more rapid in dogs (74 – 127 L/hr/m$^2$) and cynomolgus monkeys (39 – 79 L/hr/m$^2$). Clearance of the drug was increased upon repeated administration - modestly in the rat and markedly in the dog, but not significantly in the monkey. It is likely that NSC 686288 induces it own metabolism though an AhR-CYP1A1-dependent pathway.

NSC 686288 is extensively metabolized in vitro by CYP1A enzymes, producing multiple hydroxylated compounds. In the rat, N-acetylation is also a prominent pathway for metabolism of NSC 686288. The oxidative metabolism of NSC 686288 is postulated to produce reactive products that covalently bind DNA and other macromolecules. Recent studies suggest that N-hydroxyl species (hydroxylamines) produced by CYP1A1 are substrates for further bioactivation by sulfotransferases (e.g., SULT1A1). It is postulated that the resulting N-sulfoxy-groups can be further converted to nitrenium ions that form adducts with DNA and proteins.

The covalent binding of NSC 686288 metabolites to macromolecules induces DNA damage and apoptosis through a p53/p21 dependent mechanism as evidenced by the presence of DNA-protein crosslinks, γ-H2AX foci, and S-phase arrest in treated cells. These effects were highest in tumor cell lines that were most sensitive to NSC 686288 and much lower in resistant cell lines. Further studies demonstrated that NSC 686288 induced CYP1A1, CYP1B1 and SULT1A1 expression in sensitive cells subsequent to translocation of AhR to the nucleus. Studies using renal cancer cell lines showed that NSC 686288 increased CYP1A1 mRNA expression in sensitive cell lines. Experimental data from renal cell isolates from 13 patients with renal cell carcinoma found that drug-sensitive isolates had increased binding of aminoflavone metabolites when compared with resistant isolates.

Thus it is postulated that sensitivity of tumor cells to NSC 686288 is dependent upon an interaction of the compound with Ah receptors, followed by induction of CYP1A and SULT1A1 gene expression and subsequent activation of the compound to DNA-interactive metabolites. Assessment of appropriate endpoints along this pharmacodynamic-metabolic cascade (e.g., CYP1A1 and SULT1A1 induction, DNA binding, apoptosis) may provide suitable biomarkers for correlation with AFP 464 dose/exposure, toxicity, and clinical response. Further validation of a responsive biomarker may ultimately allow pre-selection of patients most likely to benefit from treatment with AFP 464.
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References


Loaiza-Perez, AI; Kenney, S; Hose, C; et al. CYP1A1 and CYP1B1 induction and high covalent binding of metabolites are markers to predict sensitivity to aminoflavone in breast and renal cancer cells. Cancer Epidemiology Biomarkers & Prevention, 11 (10): A224 Part 2, 2002.


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