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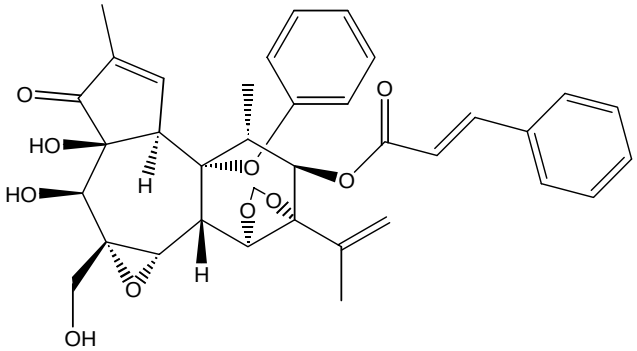
ProductInformation

THYMELEATOXIN

Product Number **T 7068**
Storage Temperature –20 °C

Cas #: 94482-56-1
Synonyms:TXA;
(2S,3aR,3bS,3cS,4aR,5S,5aS,8aR,8bS,9R,10R,10aS)-3a,3b,3c,4a,5,5a,8a,9,10,10a-Decahydro-5,5a-dihydroxy-4a-(hydroxymethyl)-7,9-dimethyl-10a-(1-methylethenyl)-6-oxo-2-phenyl-6H-2,8b-epoxyoxireno[6,7]azuleno[5,4-e]-1,3-benzodioxol-10-yl ester 3-phenyl-2-propenoic acid



Product Description
Molecular Formula: $C_{36}H_{36}O_{10}$
Molecular Weight: 628.68 (anhydrous)
Appearance: a white solid
Purity: 99%

Protein Kinase C (PKC) plays an important role in the regulation of diverse cellular functions. In humans at least 11 different PKC polypeptides have been identified. Each isoform differs in primary structure, tissue distribution, subcellular localization, mode of action *in vitro*, response to extracellular signals, and substrate specificity.[1,2]

Thymeleatoxin (TXA), an analog of mezerein, belongs to tumor-promoting phorbol-esters, which function as activators of PKC, causing translocation and down-regulation of PKC isozymes. All phorbol ester tumor promotors bind to cysteine–rich zink fingers present in the C1 domain of the regulatory region of PKC. TXA was originally introduced as a highly selective activator of PKC alpha, beta I, beta II, and gamma isoforms.[3]

However subsequent binding studies provided evidence that while TXA shows the preference for PKC alpha, beta I, beta II and gamma, it is also capable of inhibiting PKVB. TXA shows 20–fold less affinity for PKC eta and iota than for PKC-βI. Isozyme recognition by phorbolesters depends on the changes in the structure of the lipophilic chain of C12 ester in the phorbol esters. TXA is a poor activator of PKC-δ, and may be used as a tool to explore biological roles of selective PKC isozymes in cellular systems.[4]

In experiments on human lung carcinoma cell line, TXA (0.5 μM) potently inducd MnSOD gene expression and caused translocation of PKC α, β,δ, and η isotypes.[5] Treatment of mesangial cells with the tumor promoters,including TXA, caused translocation and at least partial down-regulation of the PKC-α, β,δ, and ε.[6] Studies of PKC isotypes involved in IFN-γ-induced activation of microglia using BV2 murine cells and induction of nitric oxide (NO) and inducible nitric oxide synthase (iNOS) have shown that in cells pretreated for 48 hours with TXA, NO release and iNOS expression were significantly reduced.[7]

In an *in vitro* model of the intrinsic drug resistance of human colon cancer, the human colonic epithelium was chronically exposed to endogenous PKC stimulatory factors, including TXA. Thymeleatoxin was just as effective in inducing drug resistance in KM12L4a cells as phorbol dibutyrate, a potent activator of all phorbol ester-responsive PKC isozymes. The induction of resistance by TXA was associated with a reduction in cytotoxic drug accumulation in KM12L4a cells. These results are a strong evidence that phorbol-ester activation of cPKC-α is sufficient for the induction of resistance observed in KM12L4a cells.[8]

Preparation Instructions
Thymeleatoxin is soluble in DMSO and ethanol. It is insoluble in water.

Storage/Stability
Store tightly sealed and protected from light at –20 °C.

References

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2. Jaken, S., Current Opinion in Cell Biology, **8,** 168-173 (1996).
3. Ryves, W. J., et al., Activation of the PKC-isotypes α, β,γ, δ, and ε by phorbol esters of different biological activities., FEBS Lett., **288** , 5-9 (1991).
4. Kazanietz, M.G., et al., Characterization of ligand and substrate specificity for the calcium–dependent and calcium–independent Protein Kinase C isozymes., Mol. Pharmacol., **44**, 298-507 (1993).
5. White, C.W., et al., Protein kinase C delta-dependent induction of manganese superoxide dismutase gene expression by microtubule-active anticancer drugs., J. Biol. Chem., **273**, 34639-34645 (1998).
6. Huwiler, A., et al., Comparison of different tumor promoters and bryostatin 1 on protein kinase C activation and down-regulation in rat renal mesangial cells., J. Biochem. Pharmacol., **48,** 689-700 (1994).
7. Kang, J., et al., Identification of protein kinase C isoforms involved in interferon-gamma-induced expression of inducible nitric oxide synthase in murine BV2 microglia., J. Neurosci. Lett., **299**, 205-208 (2001).
8. Gravitt, K.R., et al., Evidence that protein kinase C-alpha activation is a critical event in phorbol ester-induced multiple drug resistance in human colon cancer cells., J. Biochem. Pharmacol., **48,** 375-381 (1994).

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