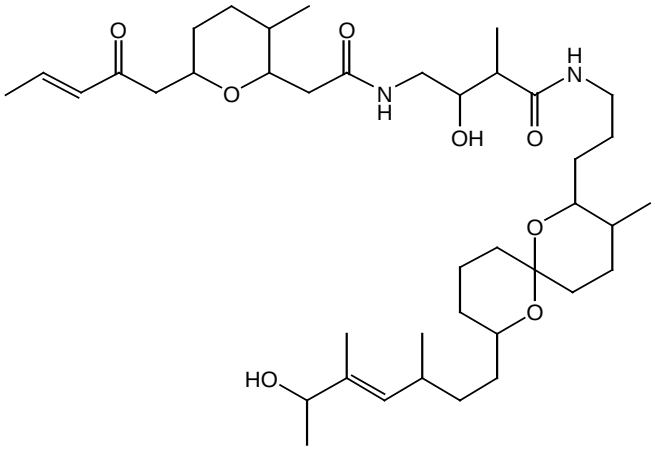
BISTRATENE A

ProductInformation

Product Number **B 5183**
Storage Temperature –20 °C

CAS #: 115566–02–04
Synonyms: Bistramide A; BisA; Tetrahydro-N-[2-hydroxy-4-[[3-[8-(6-hydroxy-3,5-dimethyl-4-heptenyl)-3-methyl-1,7-dioxaspiro[5.5]undec-2-yl]propyl]amino]-3-methyl-4-oxobutyl]-3-methyl-6-(2-oxo-3-pentenyl)-2H-pyran-2-acetamide,



Product Description
Molecular Formula: $C_{40}H_{68}N_2O_8$
Molecular Weight: 704.98
Appearance: oil
Purity: >98% by HPLC

The cyclic polyether toxin bistratene A was originally isolated from the marine ascidian *Lissoclinum bistratum* (sponge), and subsequently synthesized. Bistratene A selectively activates the δ isoform of protein kinase C (PKCδ), induces translocation of PKCδ, and affects cell growth and differentiation in a variety of systems.

The PKC family consists of at least ten distinct kinases that phosphorylate serine and threonine residues in many target proteins that play key roles in cell signaling, cell cycle control, differentiation, and other cellular functions. PKCδ belongs to the novel PKC subfamily (nPKC) of calcium-independent, phorbol ester-responsive isozymes. There is increasing evidence that PKCδ inhibits cell growth/cell cycle progression and induces either cell differentiation or cell death. It also mediates apoptosis induced by chemicals and irradiation.[1,2]

Bistratene A has been used to study cell growth, differentiation and death in several cell culture systems.[3] The signaling pathways activated by bistratene A were investigated in rat IEC–18 cells treated with either 100 nM phorbol myristate acetate (PMA, an activator of PKC α, δ and ε) or 100 nM bistratene A, which selectively activates only PKCδ.[4] Both agents induced translocation/activation of PKC to the cell membrane, with bistratene A translocating only the PKCδ isoform. Treatment with PMA activated PKC α, δ, and ε, leading to transient cell cycle arrest in G_0/G_1 phase. Treatment with Bistratene A produced sustained cell cycle arrest in both G_0/G_1 and G_2/M phases that was not abolished by depletion of PKCα, δ, and ε, and thus appeared to be PKC–independent. Bistratene A also induced PKC–independent apoptosis in this cell line. On the other hand, both bistratene A and PMA activated Erk1/2, linking PKCδ to a PKC-dependent MAPK pathway and confirming that bistratene A is able to stimulate at least two distinct pathways in intestinal epithelial cell, one PKC–independent and one PKC–dependent.[4,5]

Treatment of HL–60 promyeloid leukemia cells with 100 ng/mL bistratene A inhibited cytokinesis but had no effect on DNA synthesis and nuclear division. Thus, the cells became binucleated and contained increased amounts of α–tubulin, indicating that the G_2/M arrest by bistratene A was the result of the inhibition of cytokinesis, perhaps through the control of stathmin.[6] The stathmins comprise a family of soluble proteins that depolymerize tubulin microtubules and are regulated by PKC-mediated phosphorylation. Phosphorylation of nuclear stathmin blocks the destabilization of microbutules and allows mitotic spindle assembly. In contrast the phosphorylation of cytoplasmic stathmin incrases α-tubulin accumulation in the equatorial plane and blocks cell division.[6,7]

Bistratene A also inhibited growth of A549 lung carcinoma cells and MCF–7 breast adenocarcinoma cells. In MM96E melanoma cells bistratene A induced cell cycle arrest in G_2/M, an increase in tyrosinase and melanin content, as well as the phosphorylation of several proteins, including stathmin.[8,9]

Bistratene A is a useful tool for the study of role of PKCδ in the processes controlling cell growth, differentiation and death.

Preparation Instructions
Bistratene A is soluble in DMSO.

Storage/Stability
Store at –20 °C.

References

1. Black, J. D., Protein kinase C-mediated regulation of the cell cycle. Front. Biosci. **5**, D406-D423 (2000).
2. Dempsey, E.C. et al., Protein kinase C isozymes and the regulation of diverse cell responses. Am. J. Physiol. **279**, L429-L438 (2000).
3. Walters, D., The bistratenes: novel tools to study cell growth regulation. Progress Med. Chem. **1**, 319-329 (1996)
4. Frey, M. R., et al., Stimulation of protein kinase C-dependent and -independent signaling pathways by bistratene A in intestinal epithelial cells. Biochem. Pharmacol. **61,** 1093-1100 (2001).
5. Frey, M. R. et al., Protein kinase C signaling mediates a program of cell cycle withdrawal in the intestinal epithelium. J. Cell. Biol. **151**, 763-778 (2000).
6. Johnson, W.E., et al., Bistratene A induces a microtubule-dependent block in cytokinesis and altered stathmin expression in HL–60 cells. Biochem. Biophys. Res. Commun. **260**, 80-88 (1999).
7. Mistry, S.J., and Atweh, G.F., Stathmin inhibition enhances okadaic acid-induced mitotic arrest: a potential role for stathmin in mitotic exit. J. Biol. Chem. **276**, 31209-31215 (2001).
8. Griffiths, G., et al., The polyether bistratene A activates protein kinase C-delta and induces growth arrest in HL60 cells., Biochem. Biophys. Res. Commun. **222**, 802-808 (1996).
9. Watters, D., et al., Stimulation of melanogenesis in a human melanoma cell line by bistratene A. Biochem. Pharmacol. **55**, 1691-1699 (1998).

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