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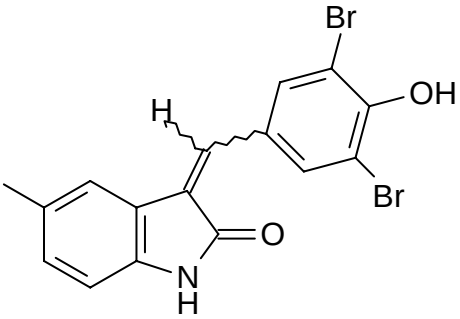
ProductInformation

GW5074

Product Number **G 6416**
Store at Room Temperature

Synonyms: 3-(3,5-Dibromo-4-hydroxybenzylidine-5-iodo-1,3-dihydro-indol-2-one



Product Description
Molecular Formula: $C_{15}H_8Br_2O_2NI$
Molecular Weight: 520.9 (anhydrous)

Supplied as an orange-red solid

The small guanine-nucleotide binding-protein Ras participates in diverse cellular signal transmission processes, such as cellular growth, development, and differentiation. Ras is localized in the plasma membrane and can exist in two conformations: a guanosine triphosphate (GTP)-bound active state and the guanosine diphosphate (GDP)-bound inactive state. The GTP-bound form of Ras signals by binding to several effector molecules, most notably the serine-threonine kinase, c-Raf1. Upon activation c-Raf1 initiates a kinase cascade through MEK (mitogen-activated protein kinase kinase or ERK kinase), a dual-specificity protein kinase that, in turn, phosphorylates ERK (extracellular signal-regulated kinase), another serine-threonine kinase. These kinases convey signals to the nucleus through a directed series of activating phosphorylations.[1,2,3] Mutation and overexpression of *ras* genes play a major role in tumorigenesis. cRaf1 contributes to tumorigenicity by blocking apoptosis through direct interaction with bcl-2 family members.

GW5074 is a benzylidine oxindole derivative that inhibits the Raf/MEK/ERK2 kinase cascade by blocking the kinase activity of c-Raf1. In studies of the structure-activity relationship within a family of benzylidine oxindoles, a significant correlation was found between the acidity of the phenol and the potency of cRaf1 inhibition. Compounds with an acidic phenol and a donor/acceptor binding group (NH-CO) were found to be the most potent cRaf1 kinase inhibitors.[4] GW5074 inhibited the Raf/MEK/ERK2 cascade *in vitro* with an IC_{50} of 9 nM. In cell culture, the addition of 5 μM GW5074 inhibited MAPK activation by 80%.

Preparation Instructions
GW5074 is soluble in DMSO.

Storage/Stability
Store tightly sealed at room temperature.

References
1. Therrien, M., et al., KSR, a novel protein kinase required for RAS signal transduction. Cell, **83**, 879-888 (1995).
2. Zimmermann, S., and Moelling, K., Phosphorylation and regulation of Raf by Akt (protein kinase B). Science, **286**, 1741-1744 (1999).
3. Rommel, C., et al., Differentiation stage-specific inhibition of the Raf-MEK-ERK pathway by Akt. Science, **286**, 1738-1741 (1999).
4. Lackey, K., et al., The discovery of potent cRaf1 kinase inhibitors. Bioorg. Med. Chem. Lett., **10**, 223-226 (2000).

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