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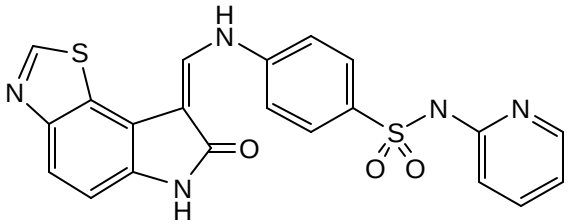
ProductInformation

GW8510

Product Number **G 7791**
Storage Temperature RT

Cas #: 222036-17-1
Synonyms: 4-{[(7-Oxo-6,7-dihydro-8H-[1,3]thiazolo[5,4-e]indol-8-ylidene)methyl]amino}-N-(2-pyridinyl)-benzenesulfonamide



Product Description

Molecular formula: $C_{21}H_{15}N_5O_3S_2$
Molecular weight: 449.51
Supplied as an yellow solid
Purity: approximately 98% (HPLC)

GW8510 is an inhibitor of cyclin-dependent kinase-2 (CDK2). CDKs are serine-threonine kinases crucial for cell cycle progression. They function as kinases only in complex with cyclins. Within the complexes, the cyclin molecule serves a regulatory role, whereas the CDK has the catalytic activity. To date, a total of 14 CDKs and 34 cyclins have been identified. In human cells nine CDKs (CDK1 – CDK9), and 11 cyclins have been found. Progression through the four phases of the cell division cycle (G_1, S, G_2 and M) is controlled by the formation and degradation of CDK-cyclin complexes.[1]

Endogenous inhibitors of CDKs are divided into two categories: one type binds only to cyclins, and the other type binds to CDK/cyclin complexes. The first group, the Ink family, has been identified only in higher eukaryotic cells. The second group is found in all eukaryocytes and is reponsible for the arrest of the cell cycle in G_1 and G_1/S phases. CDK2, the best studied cyclin kinase, is a positive regulator of eukaryotic cell-cycle progression and is mainly responsible for progression of the cell cycle from late G1 through S to late G_2.[2]

GW 8510 is a substituted analog of 3-(benzylidene)-indolin-2-one. Members of this family inhibit receptor tyrosine kinases, such as epidermal growth factor receptor and Her-2 receptor kinases, by competitively blocking the adenosine triphosphate (ATP) binding site.[3,4] GW8510 selectively inhibits CDK2 (IC_{50} = 10 nM). It inhibits CDK1 and CDK4 with IC_{50}s of 110 nm and 130 nM, respectively. GW 8510 blocks the G_1 to S transition. Treatment of cultured diploid fibroblasts with GW8510 reduced BrdU incorporation and inhibited the phosphorylation of Rb protein, a CDK2 substrate. GW8510 also reduced the cytotoxicity of a variety of anticancer agents such as paclitaxel, etoposide, cisplatin, doxorubicin, and 5-fluorouracil. Topical application of GW8510 on neonatal rats reduced etoposide-induced hair loss at the site of application in approximately 50% of the animals. Compared to the untreated sites, the treated sites had an increased number of viable hair follicles and dermal papilla, reduced inflammation, decreased cellular damage to the epithelium, reduced thickening of the epidermis, and a decreased number of apoptotic cells in the hair follicle matrix.[5]

Preparation Instructions

GW8510 is soluble in DMSO at 18 mg/ml.

Storage/Stability

Store tightly sealed at room temperature.

Sold for research purposes under agreement from Glaxo Wellcome Inc. and Glaxo Group Limited.

References

1. Alberts, B., et al., Molecular Biology of the Cell. 4th ed., Garland Publishing, Chapter 17, 990-996 (2002).
2. Sielecki, T. M., et al., Cyclin-dependent kinase inhibitors: useful targets in cell cycle regulation. J. Med. Chem., **43**, 1-18 (2000).

3. Sun, L., et al., Synthesis and biological evaluations of 3-substituted Indolin-2-ones: a novel class of tyrosine kinase inhibitors that exhibit selectivity toward particular receptor tyrosine kinases. J. Med. Chem., **41**, 2588-2603 (1998).
4. Mohammadi, M., et al., Structures of the tyrosine kinase domain of fibroblast growth factor receptor in complex with inhibitors. Science, **276**, 955-959 (1997).
5. Davis, S.T., et al. Prevention of chemotherapy-induced alopecia in rats by CDK inhibitors. Science, **291**, 134-137 (2001).

AH/LY 5/2002