

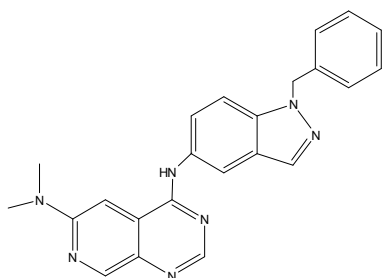
Product Information

GW2974

Catalog Number **G0668**
Store at Room Temperature

CAS RN 202272-68-2

Synonyms: GW974, N⁴-(1-Benzyl-1H-indazol-5-yl)-N⁶,N⁶-dimethyl-pyrido[3,4-d]pyrimidine-4,6-diamine



Product Description

Molecular Formula: C₂₃H₂₁N₇

Formula Weight: 395.46

Appearance: yellow solid

Purity: ≥98% (HPLC)

GW2974 is a dual inhibitor of ErbB-2 and epidermal growth factor receptor (EGFR) tyrosine kinase. Protein tyrosine kinases (PTK) are enzymes that catalyze the phosphorylation of tyrosine residues within proteins. There are two main classes of PTK: receptor PTK, and cellular or non-receptor PTK. These enzymes are involved in cell signaling pathways and regulate key functions such as proliferation, differentiation, apoptosis, and neurite outgrowth. Spontaneous activation of PTK through point mutation or over-expression can lead to various forms of cancer, as well as to benign proliferative conditions. More than 70% of the known oncogenes code for PTK.

The type I receptor PTK constitute a family of transmembrane proteins that possess an extracellular ligand-binding domain and an intracellular catalytic domain. Activation of these kinases through ligand binding to the extracellular domain induces dimerization of the receptor and autophosphorylation of tyrosine residues outside the catalytic domain. The best characterized of the type I receptors are the EGFR and ErbB-2 (HER-2/neu protooncogene).

Using high-throughput screens, researchers identified several indazolylaminoquinazolines and pyrido-[3,4-d]-pyrimidines that inhibit type I receptor tyrosine kinases.¹ These compounds potently and selectively inhibit ErbB-2 and EGFR *in vitro* with IC₅₀ <80 nM and are 50-fold more selective for ErbB-2 and EGFR than for cRaf1, cDK1, cDK2, c-Src, Mek, p38, VEGFR, and cFMS. These compounds also inhibit the proliferation of several ErbB-2- and EGFR-expressing tumor cell lines at concentrations ≤2 μM and cause a reduction of ErbB-2 and EGFR autophosphorylation in tumor fragments from xenograft models.¹

The most potent of these compounds, GW2974, inhibits the proliferation of ErbB-2- and EGFR-expressing tumor cell lines at concentrations <0.5 μM and with a selectivity 75-fold greater for tumor cells than for normal cells. *In vivo* administration of 30 mg/kg of GW2974 inhibits average tumor growth by 95% after 21 days of treatment in tumors over-expressing ErbB-2. Thus, this compound shows the ability to control tumors in xenograft models. GW2974 may have potential use in experimental models of cancer therapy and in studies of the role of EGFR and ErbB-2 in normal cell function.^{2,3}

Precautions and Disclaimer

This product is for R&D use only, not for drug, household, or other uses. Please consult the Material Safety Data Sheet for information regarding hazards and safe handling practices.

Preparation Instructions

GW2974 is soluble in DMSO at ≥20 mg/ml and insoluble in water.

Storage/Stability

Store the product at room temperature.

References

1. Cockerill, S., et al., Indazolylamino quinazolines and pyridopyrimidines as inhibitors of the EGFR and cErbB-2. *Bioorg. Med. Chem. Lett.*, **11**, 1401-1455 (2001).
2. Rusnak, D.W., et al., The characterization of novel, dual ErbB-2/EGFR, tyrosine kinase inhibitors: potential therapy for cancer. *Cancer Res.*, **61**, 7196-7203 (2001).
3. Kastan, M. B., Molecular determinants of sensitivity to antitumor agents. *Biochim. Biophys. Acta*, **1424**, 37-42 (1999).

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