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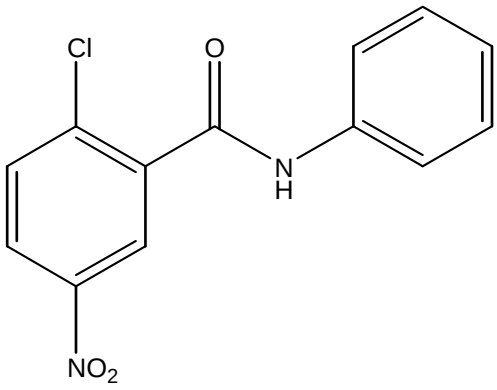
ProductInformation

GW9662

Product Number **M 6191**
Storage Temperature: 2-8 °C

CAS #: 22978-25-2
Synonyms: 2-Chloro-5-nitro-N-phenyl-benzamide



Product Description
Molecular Formula: C_{13} H9 N_2 O_3 Cl
Molecular Weight:: 276.67
Appearance: white solid
Purity: >98% by HPLC

The peroxisome proliferator-activated receptors (PPARs) are members of the nuclear hormone receptor subfamily of transcription factors related to retinoid, steroid and thyroid hormone receptors. PPARs play important role in many cellular functions including lipid metabolism, cell proliferation and differentiation, adipogenesis and inflammatory signaling.[1,2] Three known distinct subtypes of PPARs, designated PPARα, PPARβ (also known as PPARδ) and PPARγ, are the products of different genes. The PPARγ subtype is a ligand-dependent nuclear receptor, highly conserved across all the species. It is expressed predominantly in adipose tissue, macrophages, colon epithelium and also in small intestine and skeletal muscle. PPARγ is a critical transcription factor in the terminal differentiation of white and brown adipose tissue, which induces expression of genes involved in lipid hemostasis, glucose metabolism and macrophage development and function. PPARγ is also expressed in significant levels in human primary and metastatic breast carcinoma, which suggest that the PPARγ transcriptional pathway can induce terminal differentiation of malignant breast epithelial cells.

GW9662 is an irreversible PPARγ antagonist identified in a competition-binding assay against the human ligand-binding domain (region E/F). GW9662 binds PPARγ with IC_{50} in nanomolar range, and is 10- and 600-fold less potent in binding PPARα and PPARδ, respectively. The functional activity of GW9662 as an antagonist of PPARγ was confirmed in an assay of adipocyte differentiation. GW9662 did not affect transcription of full-length PPARδ and PPARα.[4,5] The antagonistic effect of GW9662 was also measured by the inhibition of CD36 expression in peritoneal macrophages stimulated with Interleukin 4 (IL-4) and various other ligands, including BRL49653. CD36 functions in macrophages as a scavenger receptor for oxidized LDL and PPARγ promotes CD36 expression. GW9662 at the concentration of 1 μM inhibited CD36 induction by IL-4 and antagonized PPARγ activation of the transfected $(AOx)_3$-TK-Luc promoter gene by BRL49653 in a dose-dependent manner.[6,7] Recently, PPARγ has been implicated in the development and progression of atherosclerosis. PPARγ ligands, GW7845, ciglitazone and troglitazone, tested on human aortic smooth muscle cells (HASMC) inhibit osteoprotegerin (OPG) expression. The GW9662 completely abolishes effect of GW7845 and ciglitazone on OPG expression. In addition, PPARγ activation inhibits OPG promoter activity. [8]

It is known that early atherosclerotic plagues are full of inflammatory cells which leads to overproduction of transforming growth factor β (TGFβ). TGFβ initiates PPARγ gene expression, which in turn inhibits TGFβ and connective tissue growth factor (CTGF). However, pretreatment of human aortic smooth muscle cells with GW9662 at concentration of one μM/L prior to the addition of ligands, reverses ligand-dependent production of CTGF and slows the lesion-forming process.[9] In summary, GW9662 is a potent and irreversible antagonist of PPARγ, which does not loose its activity in cell cultures and is a valuable tool for determining specific PPARγ receptor-mediated functions in different biological systems.

Preparation Instructions
GW9662 is soluble in DMSO at 26 mg/ml and insoluble in water.

Storage/Stability
Store tightly sealed at 2-8 °C.

Sold for research purposes only, pursuant to an agreement with SmithKline Beecham Corporation and Glaxo Group Limited

References

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9. Fu, M., et al., J. Biol. Chem. 276, 45888-45894 (2001).

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