

Product Information

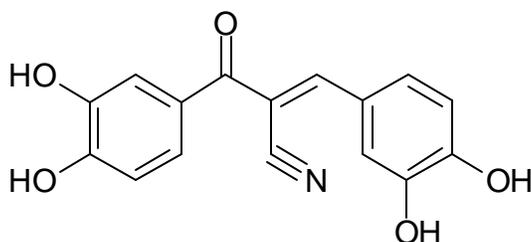
TYRPHOSTIN AG 538

Product Number **T7822**

Storage Temperature: 0 °C

CAS#: 133550-18-2

Synonyms: (αE)- α -[(3,4-Dihydroxyphenyl)methylene]-3,4-dihydroxy- β -oxo-benzenepropanenitrile, α -Cyano-(3,4-dihydroxy)cinnamoyl-(3',4'-dihydroxyphenyl)ketone



Product Description

Molecular Formula: C₁₆H₁₁N O₅

Molecular Weight: 297.28

Supplied as a yellow powder

Purity: Approximately 98% (HPLC)

Among growth factor receptors implicated in the regulation of neoplastic cell growth are members of the class I receptor tyrosine kinase family, the epidermal growth factor (EGF) receptor family, (EGFR/erbB1, HER2/Neu /erbB2, erbB3, and erbB4), the insulin-like growth factor 1 receptor (IGF1R), and the insulin receptor (IR). IGF1R and IR are two structurally related glycoproteins in which receptor occupation induces the autophosphorylation required for catalytic activity. These receptors, their ligands, and the proteolytic enzymes that degrade these proteins constitute an important regulatory system for both normal and neoplastic cell growth.^{1,2}

In many tumors, such as lung cancer, colon carcinoma, cervical cancer, and central nervous system tumors, growth factor signaling is enhanced due to the overexpression of growth factor receptor tyrosine kinases. Synthetic protein tyrosine kinase inhibitors (tyrphostins) selectively inhibit the activity of these growth factors receptors.² Some tyrphostins target

multiple receptors and exert complex effects on cell growth and proliferation. Tyrphostins are classified based on modifications to a common *cis*-benzylidene-malononitrile backbone. In one group of tyrphostins the phenolic moiety of *cis*-benzylidenemalononitrile is replaced by a substituted benzene or by a heteroaromatic ring. A second group of tyrphostins comprises a series of conformationally constrained derivatives in which the malononitrile moiety is fixed relative to the aromatic ring(s). Finally, there are two groups of tyrphostins in which the position *trans* to the *cis*-benzenemalononitrile moiety has been substituted with a ketone and amide.³

The inhibition of IGF1R kinase activity by tyrphostins was measured in two cell-free ELISA assays. In the first method, the autophosphorylation of bound IGF1R was detected using conjugated anti-phosphotyrosine. In the second method, the phosphorylation of a bound substrate, poly(Glu,Tyr), by IGF1R was detected using conjugated anti-phosphotyrosine. Tyrphostin AG 538 was the most potent inhibitor of the IGF1R autophosphorylation sites, Tyr¹¹⁵⁸ and Tyr¹¹⁶² where it competes for binding with the IGF1R substrate and inhibition is independent of ATP concentration. The IC₅₀ for inhibition of autophosphorylation was approximately 400 nM, while the IC₅₀ for inhibition of poly(Gly,Tyr) phosphorylation was approximately 61 nM in the presence of 20 μ M ATP. AG 538 also inhibits EGFR kinase activity, however the potency of this inhibition is 10-fold lower. In intact cells, AG 538 and its cell-permeable analog L-OME-AG 538 demonstrated dose-dependent inhibition of IGF1R autophosphorylation and of the activation of the downstream targets, protein kinase B (PKB/Akt) and mitogen-activated protein kinase (ERK2).⁴

Preparation Instructions

Tyrphostin AG 538 is soluble in DMSO at 50 mg/ml.

Storage/Stability

Store at 0°C tightly sealed under argon, and protected from light.

References

1. Hernandez-Sanchez, C., et al., The role of the tyrosine kinase domain of the insulin-like growth factor-I receptor in intracellular signaling, cellular proliferation, and tumorigenesis. *J. Biol. Chem.*, **270**, 29176-29181 (1995).
2. Osherov, N., et al., Selective inhibition of the epidermal growth factor and HER2/neu receptors by tyrphostins. *J. Biol. Chem.*, **268**, 11134-11142 (1993).
3. Gazit, A., et al., Tyrphostins. 2. Heterocyclic and α -substituted benzylidenemalononitrile tyrphostins as potent inhibitors of EGF receptor and ErbB2/neu tyrosine kinases. *J. Med. Chem.*, **34**, 1896-1907 (1991).
4. Blum, G., et al., Substrate competitive inhibitors of IGF-1 receptor kinase. *Biochemistry*, **39**, 15705-15712 (2000).

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