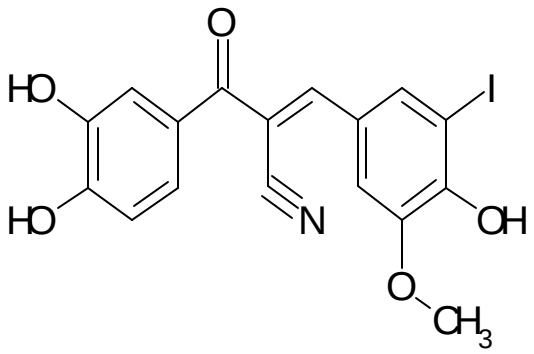
3050 Spruce Street
Saint Louis, Missouri 63103 USA
Telephone (800) 325-5832 (314) 771-5765
Fax (314) 286-7828
email: techserv@sial.com
sigma-aldrich.com

ProductInformation

TYRPHOSTIN I-OMe-AG 538

Product Number **T7697**
Storage Temperature: 0 °C

CAS #: 133550-18-2
Synonyms: α-Cyano-(3-methoxy, 4-hydroxy, 5-iodo) cinnamoyl-(3',4'-dihydroxyphenyl)ketone



Product Description
Molecular Formula: $C_{17}H_{12}INO_5$
Molecular Weight: 437.08
Supplied as an orange powder.
Purity: Approximately 99% (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 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 the common *cis*-benzylidenemalononitrile moiety. In one group of tyrphostins the phenolic moiety of *cis*-benzylidene-malononitrile 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), was detected using conjugated anti-phosphotyrosine. Tyrphostin I-OMe-AG 538 inhibits IGF1R autophosphorylation with an IC_{50} of approximately 3.4 µM. It inhibited the phosphorylation of poly(Glu,Tyr) with an IC_{50} of approximately 2 µM. Compared to its parent tyrphostin AG 538, I-OMe-AG 538 is more hydrophobic which allows it to penetrate more readily into cells. It is also less vulnerable to oxidation than AG538. In intact cells, both AG 538 and I-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). The superiority of I-OMe-AG 538 in cellular systems is perhaps due to its enhanced stability and hydrophobicity.[4]

Preparation Instructions
I–OMe–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 alpha-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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