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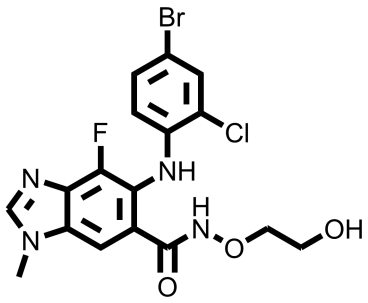
MEK Inhibitor AZD6244 (Selumetinib)

Chemical Name: 6-(4-bromo-2-chlorophenylamino)-7-fluoro-N-(2-hydroxyethoxy)-3-methyl-3H-benzo[d]imidazole-5-carboxamide



Molecular Weight:	457.68
Formula:	$C_{17}H_{15}BrClFN_4O_3$
Purity:	≥98%
CAS#:	606143-52-6
Solubility:	DMSO up to 100 mM
Storage	Powder: 4°C 1 year DMSO: 4°C 3 month -20°C 1 year

Biological Activity:

AZD6244 (Selumetinib, ARRY-142886) is an orally active, highly potent and selective non-ATP competitive MEK inhibitor, inhibiting MEK1 with an IC_{50} of 14 nM. In vitro cell viability inhibition screening of a tumor cell line panel found that cell lines harboring BRAF or RAS mutations were more likely to be sensitive to AZD6244. Treatment of primary HCC cells with AZD6244 led to growth inhibition, caspase-3 and caspase-7 activation, poly(ADP)ribose polymerase cleavage, and inhibition of ERK1/2 and p90RSK phosphorylation. AZD6244 significantly inhibits phosphorylation of ERK1/2 in 2-1318, 5-1318, 26-1004 and 4-1318 xenografts and induces apoptosis in primary 2-1318 cells by activating the caspase pathway. Currently AZD6244 is undergoing Phase II/III clinical trials to treat solid tumors.

How to Use:

In vitro: AZD6244 was used at 5-10 μM final concentration in vitro and in cellular assays.

In vivo: AZD6244 was orally dosed to mice at 25-100 mg/kg once per day, or in combination with Docetaxel (15 mg/kg) or Irinotecan (25 mg/kg) to significantly reduce the tumor volume.

Reference:

1. Yeh TC, et al. Biological characterization of ARRY-142886 (AZD6244), a potent, highly selective mitogen-activated protein kinase kinase 1/2 inhibitor. (2007) Clin Cancer Res. 13(5):1576-83.
2. Davies BR, et al. AZD6244 (ARRY-142886), a potent inhibitor of mitogen-activated protein kinase/extracellular signal-regulated kinase kinase 1/2 kinases: mechanism of action in vivo, pharmacokinetic/pharmacodynamic relationship, and potential for combination in preclinical models. (2007) Mol Cancer Ther. 6(8):2209-19.
3. Dry JR, et al. Transcriptional pathway signatures predict MEK addiction and response to selumetinib (AZD6244). (2010) Cancer Res. 70(6):2264-73.
4. Bhalla S, et al. The novel anti-MEK small molecule AZD6244 induces BIM-dependent and AKT-independent apoptosis in diffuse large B-cell lymphoma. (2011) Blood. 118(4):1052-61.
5. Morelli MP, et al. Preclinical activity of the rational combination of selumetinib (AZD6244) in combination with vorinostat in KRAS-mutant colorectal cancer models. (2012) Clin Cancer Res. 18(4):1051-62.