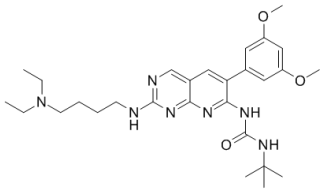
Data Sheet

Product Name:	PD173074
Cat. No.:	HY-10321
CAS No.:	219580-11-7
Molecular Formula:	$C_{28}H_{41}N_7O_3$
Molecular Weight:	523.67
Target:	FGFR; VEGFR
Pathway:	Protein Tyrosine Kinase/RTK
Solubility:	DMSO: ≥ 52 mg/mL



BIOLOGICAL ACTIVITY:

PD173074 is a potent **FGFR1** inhibitor with **IC_{50}** of 25 nM and also inhibits **VEGFR2** with **IC_{50}** of 100-200 nM, 1000-fold selective for FGFR1 than PDGFR and c-Src.

IC50 & Target: IC50: 25 nM (FGFR1), 100-200 nM (VEGFR2)

In Vitro: PD 173074 inhibits autophosphorylation of FGFR1 in a dose-dependent manner with an IC_{50} in the range 1-5 nM. PD 173074 is an ATP-competitive inhibitor of FGFR1 with an inhibitory constant (K_i) of 40 nM[1]. PD 173074 and SU 5402 produce concentration-dependent reductions in FGF-2 enhancement of granule neuron survival, with IC_{50} values of 8 nM and 9 μM, respectively. PD 173074 does not inhibit neurotrophic and neuritogenic actions of FGF-2 signalling molecules in cerebellar granule neurons. PD 173074 and SU 5402 concentration-dependently inhibits the neurite growth response, when tested on FGF-2-treated granule neurons growing on polylysine/laminin, with IC_{50}s of 22 nM and 25 μM, respectively[2]. PD173074 effectively antagonizes the effect of FGF-2 on proliferation and differentiation of OL progenitors in culture. Mitogen-activated protein kinase (MAPK) activation, a downstream event after activation of either FGFR or PDGFR, is also blocked by PD173074 in OL progenitors stimulated with FGF-2 but not PDGF[3].

In Vivo: PD 173074 (1 mg/kg, i.p.) exhibits dose-dependent inhibition of FGF-induced neovascularization and angiogenesis in mice[1]. D173074 (25 mg/kg, p.o.) significantly inhibits tumor growth in mice[4].

PROTOCOL (Extracted from published papers and Only for reference)

Cell Assay: [1]An NIH 3T3 cell line overexpressing VEGFR2 (Flk-1) has been described previously. This cell line also expresses FGFR1 endogenously. Cells (1×10^6) in DMEM supplemented with 10% calf serum are seeded in 10 cm^2 dishes and allowed to grow for 48 h. The medium is then removed and the cells are made quiescent in starvation medium (DMEM with 0.1% calf serum). After 18 h, the cells are incubated for 5 min with various concentrations of PD 173074 prepared in starvation medium. The cells are then stimulated with growth factor [VEGF (100 ng/mL) or aFGF (100 ng/mL) and heparin (10 μg/mL)] for 5 min at 37°C. The cells are washed with ice-cold PBS and lysed in 1 mL of lysis buffer (25 mM HEPES pH 7.5, 150 mM NaCl, 1% Triton X-100, 10% glycerol, 1 mM EGTA, 1.5 mM $MgCl_2$, 1 mM PMSF, 10 μg/mL aprotonin, 10 μg/mL leupeptin) containing phosphatase inhibitor (0.2 mM Na_3VO_4). For inhibition studies of FGFR1, cell lysates are immunoprecipitated with antibodies to FGFR1, and then analyzed by SDS-PAGE and immunoblotting with antibodies to phosphotyrosine. For inhibition studies of VEGFR2, cell lysates (20 μL) are analyzed directly by SDS-PAGE and immunoblotted with antibodies to phosphotyrosine. **Animal Administration:** PD173074 is dissolved in 0.05mol/Llactic acid buffer.[4] Six-week-old athymic nude mice are inoculated subcutaneously with 3×10^5 NIH 3T3 cells expressing Y373C FGFR3 and Ras V12. Intraperitoneal injections of either 20 mg/kg PD173074 or 0.05 mol/Llactic acid buffer are initiated on the day of tumor injection and continued for 9 days. Ten mice for each experiment are included.

References:

[1]. Mohammadi M, et al. Crystal structure of an angiogenesis inhibitor bound to the FGF receptor tyrosine kinase domain. EMBO J. 1998 Oct 15; 17(20):5896-904.
[2]. Skaper SD, et al. The FGFR1 inhibitor PD 173074 selectively and potently antagonizes FGF-2 neurotrophic and neurotropic effects. J Neurochem. 2000 Oct;75(4):1520-7.
[3]. Bansal R, et al. Specific inhibitor of FGF receptor signaling: FGF-2-mediated effects on proliferation, differentiation, and MAPK activation are inhibited by PD173074 in oligodendrocyte-lineage cells. J Neurosci Res. 2003 Nov 15;74(4):486-93.
[4]. Trudel S, et al. Inhibition of fibroblast growth factor receptor 3 induces differentiation and apoptosis in t(4;14) myeloma. Blood. 2004 May 1; 103(9):3521-8.
[5]. Mahe M, et al. An FGFR3/MYC positive feedback loop provides new opportunities for targeted therapies in bladder cancers. EMBO Mol Med. 2018 Apr; 10(4). pii: e8163.

Tel: 609-228-6898 Fax: 609-228-5909 E-mail: tech@MedChemExpress.com
Address: 1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA