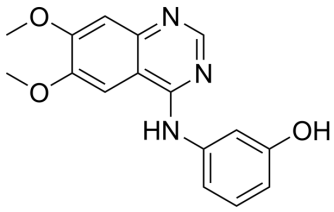
WHI-P180

Cat. No.:	HY-15769
CAS No.:	211555-08-7
Molecular Formula:	$C_{16}H_{15}N_3O_3$
Molecular Weight:	297.31
Target:	RET; VEGFR; EGFR
Pathway:	Protein Tyrosine Kinase/RTK; JAK/STAT Signaling
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 2 years -20°C 1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : 25 mg/mL (84.09 mM; Need ultrasonic)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	3.3635 mL	16.8175 mL	33.6349 mL
5 mM	0.6727 mL	3.3635 mL	6.7270 mL
10 mM	0.3363 mL	1.6817 mL	3.3635 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 50% PEG300 >> 50% saline
   Solubility: 10 mg/mL (33.63 mM); Suspended solution; Need ultrasonic
2. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (8.41 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (8.41 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

WHI-P180 (Janex 3) is a multi-kinase inhibitor; inhibits RET, KDR and EGFR with IC_{50}s of 5 nM, 66 nM and 4 μM, respectively.

IC_{50} & Target

EGFR	KDR	RET
4 μM (IC_{50})	66 nM (IC_{50})	5 nM (IC_{50})

In Vivo

WHI-P180 is also an active inhibitor of IgE-mediated mast cell responses. The elimination half-life of WHI-P180 in CD-1 mice (BALB/c mice) following i.v., i.p., or p.o. administration is less than 10 min. Systemic clearance of WHI-P180 is 6742 mL/h/kg

in CD-I mice and 8188 mL/h/kg in BALB/c mice. Notably, WHI-P180, when administered in two consecutive nontoxic i.p. bolus doses of 25 mg/kg, inhibits IgE/antigen-induced vascular hyperpermeability in a well-characterized murine model of passive cutaneous anaphylaxis[3].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]

Inhibitors (WHI-P180) are pre-incubated in the plate for 15 min with 5 μL kinase and assay buffer at the following concentrations; 13 pM RET and 150 pM KDR. The reaction is initiated by the addition of 5 μL ATP and substrate at 2×final reaction concentrations. For RET, this is 18 μM and 2 μM; for KDR, this is 16 μM and 1 μM, respectively. Reactions are performed at ATP Km for each target. The assay is allowed to proceed at room temperature for 20 min before terminating with the addition of 10 μL HTRF detection buffer containing EDTA supplemented with TK-antibody labelled with Eu3+-Cryptate (1:100 dilution) and streptavidin-XL665 (128 nM). Following incubation at room temperature for 1 h, FRET signal is measured[1].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Cell Assay [1]

IL3-dependent BaF3 cells are modified to express an activated recombinant kinase. Following removal of IL3, the modified cells are dependent on the activity of the recombinant kinase for survival and proliferation. The BaF3 cell lines, expressing KIF5B-RET and KDR are maintained in RPMI-1640 media containing 10% FBS and appropriate antibiotics. Non-modified BaF3 cells (WT) are maintained in RPMI-1640 media containing 10% FBS and supplemented with 10 ng/mL recombinant mouse IL3. For assessment of compound IC_{50}, cells are plated into 384-well plates at 1500 or 3000 cells per well in 30 μL culture medium and compounds dispensed using an acoustic liquid handling platform. Following incubation of the cells for 48 h at 37 °C in a humidified 5% CO_2 atmosphere, viability is determined by addition of 10 μL CellTiter-Glo reagent and measurement of luminescence[1].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal Administration [3]

Mice: A high performance liquid chromatography (HPLC)-based quantitative detection method is used to measure plasma WHI-P180levels in mice. The plasma concentration-time data is fit to a single compartment pharmacokinetic model by using the WinNonlin program to calculate the pharmacokinetic parameters. A cutaneous anaphylaxis model is used to examine the pharmacodynamic effects of WHI-P180 on anaphylaxis-associated vascular hyperpermeability[3].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Newton R, et al. The discovery of 2-substituted phenol quinazolines as potent RET kinase inhibitors with improved KDR selectivity. Eur J Med Chem. 2016 Apr 13;112:20-32.

[2]. Ghosh S, et al. 4-[3-Bromo-4-hydroxyphenyl)amino]-6,7-dimethoxyquinazolin-1-ium chloride methanol solvateand 4-[(3-hydroxyphenyl)amino]-6,7-dimethoxy-1-quinazolinium chloride. Acta Crystallogr C. 2001 Jan;57(Pt 1):76-8.

[3]. Chen CL, et al. Pharmacokinetics and biologic activity of the novel mast cell inhibitor, 4-(3-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline in mice. Pharm Res. 1999 Jan;16(1):117-22.

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