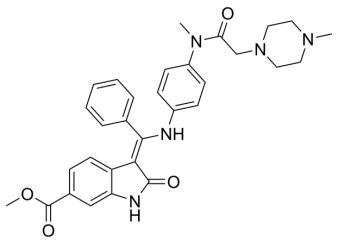
Nintedanib

Cat. No.:	HY-50904
CAS No.:	656247-17-5
Molecular Formula:	$C_{31}H_{33}N_5O_4$
Molecular Weight:	539.62
Target:	PDGFR; VEGFR; FGFR
Pathway:	Protein Tyrosine Kinase/RTK
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 6 months -20°C 1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : 11.36 mg/mL (21.05 mM; ultrasonic and warming and heat to 60°C)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.8532 mL	9.2658 mL	18.5316 mL
	5 mM	0.3706 mL	1.8532 mL	3.7063 mL
	10 mM	0.1853 mL	0.9266 mL	1.8532 mL

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

In Vivo

1. Add each solvent one by one: 1% CMC >> 0.5% Tween-80
   Solubility: 10 mg/mL (18.53 mM); Suspended solution; Need ultrasonic
2. Add each solvent one by one: 50% PEG300 >> 50% saline
   Solubility: 10 mg/mL (18.53 mM); Suspended solution; Need ultrasonic

BIOLOGICAL ACTIVITY

Description

Nintedanib (BIBF 1120) is a potent triple angiokinase inhibitor for VEGFR1/2/3, FGFR1/2/3 and PDGFRα/β with IC_{50}s of 34 nM/13 nM/13 nM, 69 nM/37 nM/108 nM and 59 nM/65 nM, respectively.

IC_{50} & Target

VEGFR1 34 nM (IC_{50})	VEGFR2 13 nM (IC_{50})	VEGFR3 13 nM (IC_{50})	FGFR1 69 nM (IC_{50})
FGFR2 37 nM (IC_{50})	FGFR3 108 nM (IC_{50})	PDGFRα 59 nM (IC_{50})	PDGFRβ 65 nM (IC_{50})

In Vitro

Nintedanib (BIBF 1120) binds to the ATP-binding site in the cleft between the amino and carboxy terminal lobes of the kinase

	domain. Nintedanib (BIBF 1120) inhibits proliferation of PDGF-BB stimulated BRPs with EC_{50} of 79 nM in cell assays. Nintedanib (BIBF 1120) (100 nM) blocks activation of MAPK after stimulation with 5% serum plus PDGF-BB. Nintedanib (BIBF 1120) prevents PDGF-BB stimulated proliferation with an EC_{50} of 69 nM in cultures of human vascular smooth muscle cells (HUASMC)[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Nintedanib (BIBF 1120) (25-100 mg/kg daily p.o.) is highly active in all tumor models, including human tumor xenografts growing in nude mice and a syngeneic rat tumor model. This is evident in the magnetic resonance imaging of tumor perfusion after 3 days, reducing vessel density and vessel integrity after 5 days, and profound growth inhibition[1]. Nintedanib (BIBF 1120) is orally available and displays encouraging efficacy in in vivo tumor models while being well tolerated[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [2]	Enzyme activity is assayed in the presence or absence of serial dilutions of BIBF1120 performed in 25% DMSO. Each microtiter plate contains internal controls such as blank, maximum reaction, and historical reference compound. All incubations are conducted at room temperature on a rotation shaker. 10 µL of each BIBF1120 dilution is added to 10 µL of diluted kinase (0.8 µg/mL VEGFR2, 10 mM Tris pH 7.5, 2 mM EDTA, and 2 mg/mL BSA) and preincubated for 1 hour. The reaction is started by addition of 30 µL of substrate mix containing 62.4 mM Tris pH 7.5, 2.7 mM DTT, 5.3 mM $MnCl_2$, 13.3 mM Mg-acetate, 0.42 mM ATP, 0.83 mg/mL Poly-Glu-Tyr(4:1), and 1.7 µg/mL Poly-Glu-Tyr(4:1)-biotin and incubated for 1 hour. The reaction is stopped by addition of 50 µL of 250 mM EDTA, 20 mM HEPES, pH 7.4. 90 µL of the reaction mix is transferred to a streptavidin plate and incubated for 1-2 hours. After three washes with PBS the EU-labeled antibody, PY20 is added (recommended dilution 1:2000 of 0.5 mg/mL labeled antibody in DELFIA assay buffer). Excessive detection antibody is removed by three ishes of DELFIA washing buffer. Then 10 minutes before measurement on the multilabel reader, each well is incubated with 100 µL of DELFIA enhancement solution. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Five-week-old to 6-wk-old athymic NMRI-nu/nu female mice (21-31 g) are used for the assay. After acclimatization, mice are inoculated with 1 to 5×10^6 (in 100 µL) FaDu, Caki-1, SKOV-3, H460, HT-29, or PAC-120 cells s.c. into the right flank of the animal. After acclimatization, F344 Fischer rats are injected with 5×10^6 (in 100 µL) GS-9L cells s.c. into the right flank of the animal. For pharmacokinetic analysis, blood is isolated at indicated time points from the retroorbital plexus of mice and plasma is analyzed using high performance liquid chromatography-mass spectrometry methodology. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Nature Machine Intelligence. 2020 Jun.
- Sci Transl Med. 7 Jul 2022.
- Sci Transl Med. 2018 Jul 18;10(450):eaaq1093.
- Sci Adv. 2022 Jun 17;8(24):eabn4564.
- Br J Cancer. 2020 Mar;122(7):986-994.

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REFERENCES

[1]. Hilberg F, et al. BIBF 1120: triple angiokinase inhibitor with sustained receptor blockade and good antitumor efficacy. Cancer Res, 2008, 68(12), 4774-4782.

[2]. Roth GJ, et al. Design, synthesis, and evaluation of indolinones as triple angiokinase inhibitors and the discovery of a highly specific 6-methoxycarbonyl-substituted indolinone (BIBF 1120). J Med Chem, 2009, 52(14), 4466-4480.

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