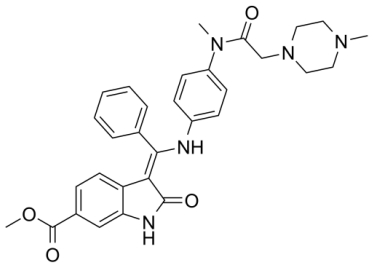
Data Sheet

Product Name:	Nintedanib
Cat. No.:	CS-0104
CAS No.:	656247-17-5
Molecular Formula:	$C_{31}H_{33}N_5O_4$
Molecular Weight:	539.62
Target:	FGFR; PDGFR; VEGFR
Pathway:	Protein Tyrosine Kinase/RTK
Solubility:	DMSO : 11.5 mg/mL (21.31 mM; Need ultrasonic)



BIOLOGICAL ACTIVITY:

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. IC50 & Target: IC50: 34 nM (VEGFR1), 13 nM (VEGFR2), 13 nM (VEGFR3), 69 nM (FGFR1), 37 nM (FGFR1), 108 nM (FGFR1), 59 nM (PDGFRα), 65 nM (PDGFRβ) **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]. **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].

PROTOCOL (Extracted from published papers and Only for reference)

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 Each microtiter plate contains internal controls such as blank, maximum reaction, and historical reference compound.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. **Animal Administration:** BIBF 1120 is formulated in a 0.5 % Natrosol solution.[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.

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.

CAIndexNames:

(Z)-methyl 3-(((4-(N-methyl-2-(4-methylpiperazin-1-yl)acetamido)phenyl)amino)(phenyl)methylene)-2-oxoindoline-6-carboxylate

SMILES:

O=C1NC2=CC(C(OC)=O)=CC=C2/C1=C(NC3=CC=C(N(C(CN4CCN(C)CC4)=O)C)C=C3)\C5=CC=CC=C5

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