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SZABO-SCANDIC HandelsgmbH

Quellenstraße 110, A-1100 Wien

T. +43(0)1 489 3961-0

F. +43(0)1 489 3961-7

mail@szabo-scandic.com

www.szabo-scandic.com

linkedin.com/company/szaboscandic

Naporafenib

Cat. No.: HY-112089

CAS No.: 1800398-38-2

Molecular Formula: $C_{25}H_{25}F_3N_4O_4$

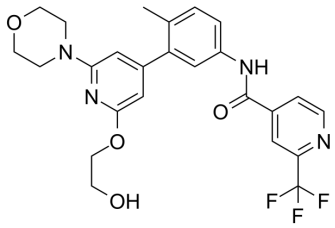
Molecular Weight: 502.49

Target: Raf; p38 MAPK; Bcr-Abl

Pathway: MAPK/ERK Pathway; Protein Tyrosine Kinase/RTK

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	1 year
	-20°C	6 months



SOLVENT & SOLUBILITY

In Vitro

DMSO : 100 mg/mL (199.01 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.9901 mL	9.9504 mL	19.9009 mL
	5 mM	0.3980 mL	1.9901 mL	3.9802 mL
	10 mM	0.1990 mL	0.9950 mL	1.9901 mL

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

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (4.98 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (4.98 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (4.98 mM); Clear solution
4. Add each solvent one by one: 5% DMSO >> 40% PEG300 >> 5% Tween-80 >> 50% saline
   Solubility: 2.5 mg/mL (4.98 mM); Suspended solution; Need ultrasonic

BIOLOGICAL ACTIVITY

Description

Naporafenib (LXH254) is a potent, selective, orally active, type II BRAF and CRAF inhibitor, with IC_{50} values of 0.072 and 0.21 nM against CRAF and BRAF, respectively[1][2].

IC_{50} & Target				
	CRAF	Braf	ARAF	p38α
	0.072 nM (IC_{50})	0.21 nM (IC_{50})	6.4 nM (IC_{50})	2.1 μM (IC_{50})

	Abl1 4.9 μM (IC_{50})

In Vitro

Naporafenib (Compound A) is an adenosine triphosphate (ATP)-competitive inhibitor of BRAF (also referred to herein as b-RAF or b-Raf) and CRAF (also referred to herein as c-RAF or c- Raf) protein kinases. Throughout the present disclosure, Naporafenib is also referred to as a c-RAF (or CRAF) inhibitor or a C-RAF/c-Raf kinase inhibitor. In cell-based assays, Naporafenib has demonstrated anti-proliferative activity in cell lines that contain a variety of mutations that activate MAPK signaling. Moreover, Naporafenib is a Type 2 ATP -competitive inhibitor of both B-Raf and C-Raf that keeps the kinase pocket in an inactive conformation, thereby reducing the paradoxical activation seen with many B-Raf inhibitors, and blocking mutant RAS-driven signaling and cell proliferation[1].
Naporafenib (0-10 μM, 1 h) inhibits both monomeric and dimeric RAF and promotes RAF dimer formation[2].
Naporafenib has reduced ability to suppress MAPK signaling driven by ARAF and further that the contribution of ARAF to MAPK signaling increases in the absence of CRAF expression[2].
Naporafenib shows more sensitivity when cells lack ARAF[2].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Western Blot Analysis[2]

Cell Line:	HCT116, MEL-JUSO, Mia PaCa-2, A375($BRAF^{V600E}$), and HCT116 ($KRAS^{G13D}$)
Concentration:	0-10 μM
Incubation Time:	1 h
Result:	Promoted B/CRAF heterodimer formation. Displayed similar inhibition of monomeric $BRAFV^{600}$ and wild-type dimeric RAF (IC_{50} for p-ERK levels of 59 and 78 nmol/L in A-375 and HCT 116 cells, respectively).

Cell Proliferation Assay[2]

Cell Line:	Two NRAS-mutant melanoma cell lines (MEL-JUSO and SK-MEL-30), three KRAS-mutant cell lines (COR-L23, MIA PaCa-2, and HCT116), and derived variants lacking expression of either ARAF, BRAF, or CRAF.
Concentration:	0-10 μM
Incubation Time:	24 h
Result:	The sensitivity was increased relative to parental cell lines in all models tested by loss of ARAF expression.

In Vivo

Treatment with Naporafenib (Compound A) generates tumor regression in several KRAS-mutant models including the NSCLC-derived Calu-6 (KRAS Q61K) and NCI-H358 (KRAS G12C). Naporafenib exhibits efficacy in numerous MAPK-driven human cancer cell lines and in xenograft tumors representing model tumors harboring human lesions in KRAS, NRAS and BRAF oncogenes[1].
Naporafenib shows significant antitumor activity in models harboring BRAF mutations either alone or coincident with either activated NRAS or KRAS, and RAS mutants lacking ARAF are more sensitive to Naporafenib[2].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal Model:	Outbred athymic (nu/nu) female mice and SCID Beige mice; BRAF-, NRAS-, and KRAS-mutant xenograft models, as well as a RAS/RAF wild-type model[2]
Dosage:	100 mg/kg
Administration:	Orally, daily

Result:	Significantly decreased tumor volume in models harboring BRAF mutations either alone or coincident with either activated NRAS or KRAS, slightly decreased tumor volume in KRAS model.

CUSTOMER VALIDATION

- Biomed Chromatogr. 2021 Feb;35(2):e4968.
- Research Square Print. October 27th, 2022.

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REFERENCES

[1]. CAPONIGRO, Giordano, et al. THERAPEUTIC COMBINATIONS COMPRISING A RAF INHIBITOR AND A ERK INHIBITOR. WO 2018051306 A1 20180322

[2]. Kelli-Ann Monaco, et al. LXH254, a Potent and Selective ARAF-Sparing Inhibitor of BRAF and CRAF for the Treatment of MAPK-Driven Tumors. Clin Cancer Res. 2021 Apr 1;27(7):2061-2073.

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