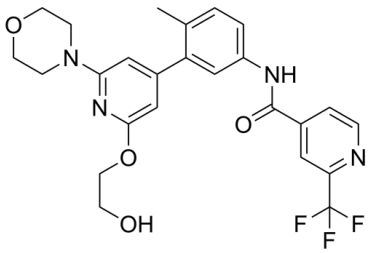
Data Sheet

Product Name:	Naporafenib
Cat. No.:	CS-0043317
CAS No.:	1800398-38-2
Molecular Formula:	$C_{25}H_{25}F_3N_4O_4$
Molecular Weight:	502.49
Target:	Bcr-Abl; p38 MAPK; Raf
Pathway:	MAPK/ERK Pathway; Protein Tyrosine Kinase/RTK
Solubility:	DMSO : 100 mg/mL (ultrasonic)



BIOLOGICAL ACTIVITY:

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]. IC50 & Target:CRAF, BRAF[1] ***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]. ***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].

PROTOCOL (Extracted from published papers and Only for reference)

Animal Administration:90% PEG400 + 10% Tween80[1]Mice[1]

SCID beige female tumor-bearing NCI-H358 mice, n=8 per group, are randomized into 3 groups 14 days post tumor cell inoculation with an average tumor volume range of 259.44- 262.47mm^3. Animals are administered an oral dose of either vehicle, LXH254 at 30mg/kg or 200mg/kg daily for 14 consecutive days at a dosing volume of 10 mL/kg of animal body weight during course of treatment. Tumor volumes are measured by digital caliper 3 times a week and body weights of all animals are recorded through the course of treatment.

Female nude tumor bearing Calu6 mice, n=6 per group are randomized into treatment groups on day 17 following tumor implantation, when the average tumor volume is 180 mm^3. Treatments with LXH254 are initiated on Day 17 and continued for 16 days. Dosing volume is 10 mL/kg. Tumor volumes are collected at the time of randomization and twice weekly thereafter for the study duration.

Nude female mice tumor bearing NCI-H358, n=8 per group, are randomized into 2 groups with an average tumor volume range of

275.74 mm^3. Animals are administered an oral dose of either vehicle or LXH254 at 100 mg/kg daily for 14 consecutive days at a dosing volume of 10 mL/kg of animal body weight during course of treatment. Tumor volumes are measured by digital caliper 3 times a week and body weights of all animals are recorded through the course of treatment[1].

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.

CAIndexNames:

4-Pyridinecarboxamide, N-[3-[2-(2-hydroxyethoxy)-6-(4-morpholinyl)-4-pyridinyl]-4-methylphenyl]-2-(trifluoromethyl)-

SMILES:

CC1=CC=C(NC(C2=CC(C(F)(F)F)=NC=C2)=O)C=C1C3=CC(N4CCOCC4)=NC(OCCO)=C3

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