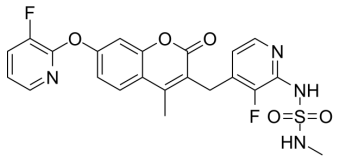
NST-628

Cat. No.:	HY-158115
CAS No.:	3002056-30-3
Molecular Formula:	$C_{22}H_{18}F_2N_4O_5S$
Molecular Weight:	488.46
Target:	Molecular Glues; Raf; MEK
Pathway:	PROTAC; MAPK/ERK Pathway
Storage:	Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description

NST-628 is a brain-permeable MAPK pathway molecule glue that inhibits RAF phosphorylation and MEK activation. NST-628 also binds RAF and prevents the formation of BRAF-CRAF and BRAF-ARAF heterodimers, effectively inhibiting the RAS-MAPK pathway. NST-628 inhibits RAS- and RAF-driven cancers and demonstrated potent inhibition in mutant KRAS, NRAS, BRAF class II/III, and NF1-mutant tumors[1].

In Vitro

NST-628 (100 nM; 2 h) has higher antiproliferative activity in BRAF class II/III mutant cell models compared to other RAF and MEK inhibitors, and it does not promote the formation of BRAF and CRAF heterodimers[2].

NST-628 (4-100 nM; 48 h) increases the levels of early and late apoptotic cells and reduces the number of live cells in a dose-dependent manner in NRAS mutant IPC-298 and SK-MEL-2, NF1 mutant MeWo, and KRAS mutant HCT116 cell lines[2].

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

Apoptosis Analysis[2]

Cell Line:	NRAS mutant IPC-298 and SK-MEL-2, NF1 mutant MeWo, and KRAS mutant HCT116 cell
Concentration:	4, 20, 100 nM
Incubation Time:	48 h
Result:	100 nmol/L NST-628 induced the highest level of apoptosis. Equivalent to the MEK inhibitor Trametinib (HY-10999) and showed greater potency than the MEK inhibitor Cobimetinib (HY-13064), the RAF-MEK inhibitor Avutometinib (HY-18652) and the type II RAF inhibitors Belvarafenib (HY-109080) and Tovorafenib (HY-15246).

In Vivo

qd: once daily ; b.i.d: twice daily

NST-628 (p.o.; 3 mg/kg; qd, 5 mg/kg; qd, or 1.5 mg/kg; b.i.d) can significantly slow tumor growth in mouse models with KRAS and NRAS mutations. NST-628 also leads to tumor regressions in the SK-MEL-2-luc model[2].

NST-628 (i.g.; 0.3-3 mg/kg; qd; 18-20 days) inhibites the RAS-MAPK pathway in mice in a dose-dependent manner. NST-628 also exhibites strong antitumor activity in the MeWo-luc model[2].

NST-628 (i.g.; 2 mg/kg; qd; 26 days) slows tumor growth and effectively inhibits the RAS–MAPK pathway in NCI-H23 KRASG12C-mutant lung adenocarcinoma model[2].

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

Animal Model:	mouse models with KRAS and NRAS mutations [2]
Dosage:	3 mg/kg; qd, 5 mg/kg; qd, and 1.5 mg/kg; b.i.d
Administration:	p.o.
Result:	Significantly inhibited MEK and ERK phosphorylation in tumor tissues. Demonstrated superior anti-tumor efficacy and better tolerability than existing MEK inhibitors (e.g. Cobimetinib (HY-13064)) and RAF inhibitors (e.g. Belvarafenib (HY-109080)).

Animal Model:	NCI-H23 KRASG12C-mutant lung adenocarcinoma model [2]
Dosage:	2 mg/kg; 26 days
Administration:	i.g.; qd
Result:	The combination of NST-628 and sotorasib resulted in deep tumor regressions that were durable for the 40-day study duration.The combination led to a significant decrease in phospho-ERK levels.

REFERENCES

[1]. Ryan M B, et al. Abstract ND10: NST-628 is a novel, potent, fully brain-penetrant MAPK pathway molecular glue that inhibits RAS-and RAF-driven cancers[J]. Cancer Research, 2024, 84(7_Supplement): ND10-ND10.

[2]. Meagan B et al. The Pan-RAF–MEK Nondegrading Molecular Glue NST-628 Is a Potent and Brain-Penetrant Inhibitor of the RAS–MAPK Pathway with Activity across Diverse RAS- and RAF-Driven Cancers. Cancer Discov 2024

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