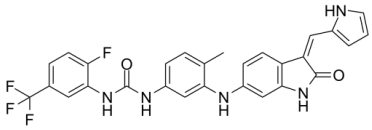
Data Sheet

Product Name:	GNF-5837
Cat. No.:	CS-1728
CAS No.:	1033769-28-6
Molecular Formula:	C28H21F4N5O2
Molecular Weight:	535.49
Target:	Trk Receptor
Pathway:	Neuronal Signaling; Protein Tyrosine Kinase/RTK
Solubility:	DMSO : ≥ 32 mg/mL (59.76 mM); H2O : < 0.1 mg/mL (insoluble)



BIOLOGICAL ACTIVITY:

GNF-5837 is a potent, selective, and orally bioavailable pan-**tropomyosin receptor kinase (TRK)** inhibitor which display antiproliferative effects in cellular Ba/F3 assays (**IC_{50}** values of 7 nM, 9 nM and 11 nM for cells containing the fusion proteins **Tel-TrkC**, **Tel-TrkB** and **Tel-TrkA**, respectively) [1]. **In Vitro:** GNF-5837 (0.1-500 nM; 72-144 hours; GOT1 cells) treatment decreases cell viability in a time- and dose-dependent manner in GOT1 cells[2].

GNF-5837 (5-500 nM; 24 hours; GOT1 cells) causes downregulation of PI3K-Akt-mTOR signaling, Ras-Raf-MEK-ERK signaling[2].

GNF-5837 (5-500 nM; 72 hours; GOT1 cells) treatment induces G1 cell cycle arrest[2].

GNF-5837 (500 nM; 144 hours; GOT1 cells) treatment increases apoptotic cell death[2]. **In Vivo:** GNF-5837 (25-100 mg/kg; oral administration; once daily; for 10 days; mice) treatment inhibits tumor growth in a mouse xenograft model derived from RIE cells expressing both TRKA and NGF[1].

PROTOCOL (Extracted from published papers and Only for reference)

Cell assay [1] GNF-5837 was tested for their ability to inhibit the proliferation of wt Ba/F3 cells and Ba/F3 cells transformed with constitutively expressed luciferase reporter and BCR-ABL or Tel-KDR or other Tel fusion kinases. Parental Ba/F3 cells were maintained in media containing recombinant mouse IL3 and the kinase transformed Ba/F3 cells were maintained in media without IL-3. 7.5 nL of compounds were spotted to each well of 1536-well assay plates by Liquid handling System Echo 555. 700 cells were then plated into each well of the assay plates in 7 uL culture media per well and compounds were tested at 0.17 nM to 10 uM in 3-fold serial dilutions. The cells were then incubated for 48 hours at 37°C. 3 uL of Bright-Glo was added to each well and the plates were read using ViewLux. Animal administration [1] 3 x 106 of Rie cells expressing TrkA and NGF were implanted with a subcutaneous injection into the right hind flank of a Balb/c nude mouse. After implant, once tumors became palpable, animals were dosed with the vehicle, 25 mg/Kg, 50 mg/Kg, or 100 mg/Kg of GNF-5837 using oral gavages once a day for 10 days. Tumor volumes were measured by a caliper 3 times per week and were calculated using (L x W x H)/2.

References:

[1]. Albaugh, P. et al. Discovery of GNF-5837, a Selective TRK Inhibitor with Efficacy in Rodent Cancer Tumor Models. ACS MEDICINAL CHEMISTRY LETTERS, 2012; 3 (2): 140

[2]. Aristizabal Prada ET, et al. Tropomyosin receptor kinase: a novel target in screened neuroendocrine tumors. Endocr Relat Cancer. 2018 May;25(5):547-560.

CAIndexNames:

Urea, N-[3-[[2,3-dihydro-2-oxo-3-(1H-pyrrol-2-ylmethylene)-1H-indol-6-yl]amino]-4-methylphenyl]-N'-[2-fluoro-5-(trifluoromethyl)phenyl]-

SMILES:

O=C(NC1=CC(C(F)(F)F)=CC=C1F)NC2=CC=C(C)C(NC3=CC(NC/4=O)=C(C=C3)C4=C\C5=CC=CN5)=C2

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