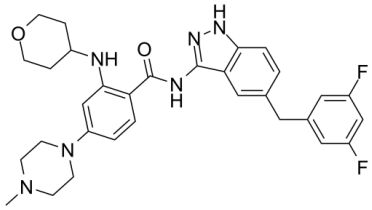
Data Sheet

Product Name:	Entrectinib
Cat. No.:	CS-4343
CAS No.:	1108743-60-7
Molecular Formula:	C31H34F2N6O2
Molecular Weight:	560.64
Target:	ALK; Autophagy; ROS; Trk Receptor
Pathway:	Autophagy; Neuronal Signaling; Protein Tyrosine Kinase/RTK
Solubility:	DMSO : ≥ 31 mg/mL (55.29 mM)



BIOLOGICAL ACTIVITY:

Entrectinib (NMS-E628) is a potent, orally available, and CNS-active **pan-Trk**, **ROS1**, and **ALK** inhibitor. Entrectinib inhibits TrkA, TrkB, TrkC, ROS1 and ALK with **IC_{50}** values of 1, 3, 5, 12 and 7 nM, respectively. Antitumor activity. IC50 & Target: IC50: 1 nM (TrkA), 1 nM (TrkB), 1 nM (TrkC), 1 nM (ROS1),1 nM (ALK)[1] **In Vitro:** Entrectinib (NMS-E628) is found to be exquisitely active in inhibiting the proliferation of a limited number of cell lines: the TRKA-driven colorectal carcinoma cell line KM12 (IC_{50} of 17 nM), the ALK-dependent ALCL cell lines SU-DHL-1, Karpas-299, SUP-M2 and SR-786 (IC_{50} of 20, 31, 41, and 81 nM, respectively), the ALK-dependent NSCLC cell line NCI-H2228 (IC_{50} of 68 nM) and the FLT3-dependent AML cell line MV-4-11 (IC_{50} of 81 nM). Entrectinib potently blocks proliferation of Ba/F3-TEL-TRKB (IC_{50} of 2.9 nM), Ba/F3-TEL-TRKC (IC_{50} of 3.3 nM), and Ba/F3-TEL-ROS1 (IC_{50} of 5.3 nM) cells, with a high degree of selectivity versus parental Ba/F3 cells or those transformed by nontargeted kinases such as ABL and RET, which are inhibited with IC_{50}s in the range of 2 to 3 μM[1]. Entrectinib significantly inhibits the growth of TrkB-expressing NB cells in vitro, and it significantly enhances the growth inhibition of Irino-TMZ when used in combination[2]. **In Vivo:** Oral administration of entrectinib to tumor-bearing mice induces regression in relevant human xenograft tumors, including the TRKA-dependent colorectal carcinoma KM12, ROS1-driven tumors, and several ALK-dependent models of different tissue origins, including a model of brain-localized lung cancer metastasis[1]. Single agent therapy results in significant tumor growth inhibition in animals treated with entrectinib compared to control animals[2].

PROTOCOL (Extracted from published papers and Only for reference)

Cell Assay: [2]NLF, NLF-TrkB, SY5Y or SY5Y-TrkB cells are plated in 96 well plates, and they are exposed to drug at different concentrations (1, 5, 10, 20, 30, 50 and 100 nM of entrectinib, 1.5 μM Irino and 50 μM TMZ, respectively) for one hr followed by addition of 100 ng/mL of BDNF. Plates are harvested at 24, 48, and 72 hr following addition of drug. The plates are processed and cell viability is analyzed using a standard SRB assay protocol[2]. **Animal Administration:** [2]Mice: Entrectinib is reconstituted in 0.5% methylcellulose containing 1% Tween 80 at a final dosing volume of 10 mL/kg (e.g., 0.2 mL for a 20 gm mouse). Treatment with entrectinib, Irino and TMZ started about 15–17 days after tumor inoculation when the average tumor size is 0.2 cm^3. Mice are sacrificed when tumor volume reached 3 cm^3. Tumors are harvested and flash frozen on dry ice for analysis of protein expression[2].

References:

[1]. Ardini E, et al. Entrectinib, a Pan-TRK, ROS1, and ALK Inhibitor with Activity in Multiple Molecularly Defined Cancer Indications. Mol Cancer Ther. 2016 Apr;15(4):628-39.

[2]. Iyer R, et al. Entrectinib is a potent inhibitor of Trk-driven neuroblastomas in a xenograft mouse model. Cancer Lett. 2016 Mar 28;372(2):179-86.

CAIndexNames:

Benzamide, N-[5-[(3,5-difluorophenyl)methyl]-1H-indazol-3-yl]-4-(4-methyl-1-piperazinyl)-2-[(tetrahydro-2H-pyran-4-yl)amino]-

SMILES:

O=C(NC1=NNC2=C1C=C(CC3=CC(F)=CC(F)=C3)C=C2)C4=C(NC5CCOCC5)C=C(N6CCN(C)CC6)C=C4

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