

Product Data Sheet

Product Name: Selitrectinib (LOXO-195)

Cat. No.: GC32808

Chemical Properties

Cas. No. 2097002-61-2

SMILES FC1=CN=C(CC[C@H](N2)C)C([C@](CCC3([H])N3C(C=CN4N=C5)=NC4=C5C2=O)=C1

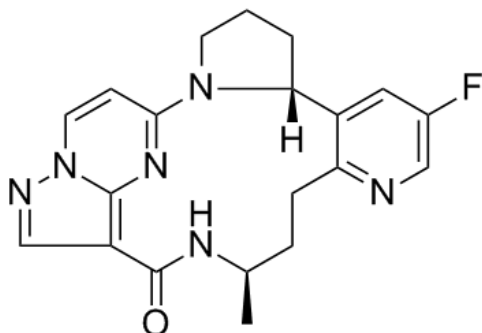
Formula $C_{20}H_{21}FN_6O$ M.Wt 380.42

Solubility DMSO : 62.5 mg/mL (164.29 mM) Storage Store at -20°C

General tips For obtaining a higher solubility , please warm the tube at 37 °C and shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.

Shipping Condition Evaluation sample solution : ship with blue ice All other available size: ship with RT , or blue ice upon request.

Structure



Protocol

Caution: Product has not been fully validated for medical applications. For research use only.

Tel: (909) 407-4943 Fax: (626) 353-8530 E-mail: tech@glpbio.com

Address: 10292 Central Ave. #205, Montclair, CA, USA

Product Data Sheet

Cell experiment: For assessment of cellular inhibition potency, cells are harvested per a standard protocol, counted and added to flat-bottom, collagen I-coated 96-well assay plates at 3×10^4 cells/well (wild-type cell line) or 5×10^4 cells/well (mutant cell lines) in 100 μ L/well of DMEM growth medium containing 10% FBS. Plates are then incubated at room temperature for 30 minutes prior to an overnight incubation at 37°C with 5% CO₂. Next, cells are treated for 1 hour at 37°C, 5% CO₂ with TRK inhibitor compounds (e.g., Selitrectinib (LOXO-195)). Control wells contain either 0.25% DMSO alone or 1 μ M larotrectinib or LOXO-195. Following compound incubation, growth medium is discarded and cells are lysed by addition of 60 μ L/well of ice-cold lysis buffer containing protease and phosphatase inhibitors[1].

Animal experiment: Mice[1]The Δ TRKA, Δ TRKA-G595R, and Δ TRKA -G667C NIH-3T3 tumor cell lines ($\sim 2\text{--}3 \times 10^6$ cells) and KM12 cells (5×10^6 cells) are injected subcutaneously into the right flank of female nu/nu NCr mice. Tumors are allowed to grow to $\sim 100\text{--}200$ mm³ or ~ 500 mm³, and animals are randomized by tumor size into dosing groups of 5 (KM12), 7 (NIH 3T3 Δ TRKA variants) or 3-4 (for PK-PD) animals. Animals are dosed by oral gavage with vehicle, Selitrectinib (LOXO-195) in 1% carboxymethylcellulose/0.5% Tween-80 or larotrectinib in 100% Labrafac lipophile. All animals are obtained at 6-8 weeks of age, housed in groups of 5 and allowed a one-week acclimation period before cancer cell injection. Animals are dosed with vehicle twice daily, Selitrectinib (LOXO-195) at 30 mg/kg, 100 mg/kg and 300 mg/kg twice daily and larotrectinib at 60 mg/kg daily for 9-12 days. Body weight and tumor size are monitored after cell implantation and at regular intervals during dosing[1].

References:

[1]. Drilon A, et al. A Next-Generation TRK Kinase Inhibitor Overcomes Acquired Resistance to Prior TRK Kinase Inhibition in Patients with TRK Fusion-Positive Solid Tumors. Cancer Discov. 2017 Sep;7(9):963-972.

Caution: Product has not been fully validated for medical applications. For research use only.

Tel: (909) 407-4943 Fax: (626) 353-8530 E-mail: tech@glpbio.com

Address: 10292 Central Ave. #205, Montclair, CA, USA

Product Data Sheet

Background

Selitrectinib (LOXO-195) is a next-generation TRK kinase inhibitor (TKI), with IC₅₀s of 0.6 nM, <2.5 nM for TRKA and TRKC respectively.

Selitrectinib (LOXO-195) demonstrates strong binding to the wild-type TRKA, TRKB and TRKC kinase domains. Selitrectinib (LOXO-195) has potent (IC₅₀<1 nM) inhibitory activity in kinase enzyme assays. Importantly, Selitrectinib (LOXO-195) achieves low nanomolar inhibitory activity against TRKA G595R, TRKC G623R, and TRKA G667C, with IC₅₀s ranging from 2.0-9.8 nM. 228 individual kinases in vitro are profiled at a Selitrectinib (LOXO-195) concentration of 1 μM, which is ~1667-fold higher than its IC₅₀ for TRKA (0.6 nM). Selitrectinib (LOXO-195) is more than 1000-fold selective for 98% of non-TRK kinases tested. Selitrectinib (LOXO-195) demonstrates potent inhibition of cell proliferation in TRK fusion-containing KM12, CUTO-3, and MO-91 cell lines (IC₅₀≤5 nM)[1].

Stably transfected NIH-3T3 δTRKA and δTRKA-G595R cells are implanted subcutaneously into the flanks of nude mice. Both larotrectinib and Selitrectinib (LOXO-195) are effective at reducing phosphorylated TRKA in tumors driven by δTRKA. In contrast, only Selitrectinib (LOXO-195) strongly suppresses phospho-TRKA in δTRKA-G595R cells in a dose-dependent manner. Selitrectinib (LOXO-195) also causes inhibition of tumor growth relative to vehicle at all doses in four TRKA-dependent tumor models (δTRKA, δTRKA-G595R, δTRKAG667C, and TPM3-NTRK1 fusion-positive KM12 colorectal cancer cells. Larotrectinib inhibits KM12 and NIH 3T3-δTRKA tumors to a similar degree. Group mean body weight loss does not exceed 5% for any agent. Selitrectinib (LOXO-195) displays high selectivity for the TRK proteins[1]

[1]. Drilon A, et al. A Next-Generation TRK Kinase Inhibitor Overcomes Acquired Resistance to Prior TRK Kinase Inhibition in Patients with TRK Fusion-Positive Solid Tumors. Cancer Discov. 2017 Sep;7(9):963-972.

Caution: Product has not been fully validated for medical applications. For research use only.

Tel: (909) 407-4943 Fax: (626) 353-8530 E-mail: tech@glpbio.com

Address: 10292 Central Ave. #205, Montclair, CA, USA