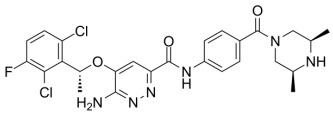
Ensartinib

Cat. No.:	HY-103714
CAS No.:	1370651-20-9
Molecular Formula:	$C_{26}H_{27}Cl_2FN_6O_3$
Molecular Weight:	561.44
Target:	ALK; c-Met/HGFR
Pathway:	Protein Tyrosine Kinase/RTK
Storage:	Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description	Ensartinib (X-396) is a potent and dual ALK/MET inhibitor with IC_{50}s of <0.4 nM and 0.74 nM, respectively.
IC_{50} & Target	MET 0.74 nM (IC_{50})
In Vitro	The ability of Ensartinib (X-396) to inhibit the growth of different cancer cell lines harboring ALK fusions or point mutations is tested. Ensartinib is potent in H3122 lung cancer cells harboring EML4-ALK E13;A20 (IC_{50}: 15nM). Ensartinib is also potent in H2228 lung cancer cells harboring EML4-ALK E6a/b; A20 (IC_{50}: 45 nM). Furthermore, X-376 is potent in SUDHL-1 lymphoma cells harboring NPM-ALK (IC_{50}: 9 nM). X-376 also inhibits SY5Y neuroblastoma cells harboring ALK F1174L, MKN-45 gastric carcinoma cells harboring MET dependent, HepG2 cells and PC-9 lung cancer cell lines harboring EGFR exon 19 del with IC_{50} s of 68 nM, 156 nM, 9.644 μM and 2.989 μM, respectively[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	The effects of Ensartinib (X-396) in vivo against H3122 xenografts are examined. A pharmacokinetic study reveals that Ensartinib shows substantial bioavailability and moderate half-lives in vivo. Nude mice harboring H3122 xenografts are treated with Ensartinib at 25mg/kg bid. Ensartinib significantly delays the growth of tumors compared to vehicle alone. In the xenograft experiments, Ensartinib appears well-tolerated in vivo. Mouse weight is unaffected by Ensartinib treatment. Drug-treated mice appear healthy and do not display any signs of compound related toxicity. To further assess potential side effects of Ensartinib, additional systemic toxicity and toxico-kinetic studies are performed in Sprague Dawley (SD) rats. Following 10 days of repeated oral administration of Ensartinib at 20, 40, 80 mg/kg in SD rats, all animals survive to study termination. The no significant toxicity (NST) levels are determined to be 80mg/kg for Ensartinib. At NST levels, Ensartinib achieves an AUC of 66 μM×hr and a C_{max} of 7.19 μM[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	For viability experiments, cells are seeded in 96-well plates at 25%-33% confluency and exposed to drugs.The human lung adenocarcinoma cell lines H3122 and H2228 are treated with Ensartinib (10, 30, 100, 300 and 1000 nM). SUDHL-1 lymphoma cells are treated with Ensartinib (5, 10, 30, 100 and 300 nM). SY5Y neuroblastoma cells are treated with Ensartinib (30, 100, 300 and 1000 nM). At 72 hours post Ensartinib addition, Cell Titer Blue Reagent is added and fluorescence is measured on a Spectramax spectrophotometer. All experimental points are set up in hextuplicate replicates and are performed at least two

	independent times. IC_{50}s are calculated using GraphPad Prism version 5 for Windows. The curves are fit using a nonlinear regression model with a log (inhibitor) vs. response formula[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice[1] Nude mice (nu/nu) are injected with H3122 cells. Once tumors reach an average volume of 450 mm^3, a total of 27 athymic mice harboring H3122 tumors are randomized and dosed via oral gavage with 25mg/kg Ensartinib (X-396) or the control vehicle. Two, five, and fifteen hours after the single treatment (3 tumors/timepoint/group), mice are sacrificed and serum is collected for assessment of drug concentration using an LC-MS based bioanalytical method. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Cancers. 2020 Mar 28;12(4):813.
- Drug Des Dev Ther. 2020 Nov 30;14:5259-5273.

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REFERENCES

[1]. Lovly CM, et al. Insights into ALK-driven cancers revealed through development of novel ALK tyrosine kinaseinhibitors. Cancer Res. 2011 Jul 15;71(14):4920-31.

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