X-376

Cat. No.: HY-16590

CAS No.: 1365267-27-1

Molecular Formula: $C_{25}H_{25}Cl_2FN_6O_3$

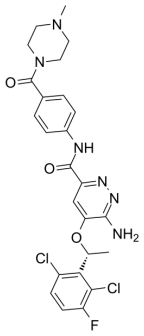
Molecular Weight: 547.41

Target: Anaplastic lymphoma kinase (ALK); c-Met/HGFR

Pathway: Protein Tyrosine Kinase/RTK

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	2 years
	-20°C	1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : 100 mg/mL (182.68 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.8268 mL	9.1339 mL	18.2678 mL
	5 mM	0.3654 mL	1.8268 mL	3.6536 mL
	10 mM	0.1827 mL	0.9134 mL	1.8268 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (4.57 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (4.57 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (4.57 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

X-376 is a potent and highly specific ALK tyrosine kinase inhibitor (TKI) (IC_{50}=0.61 nM). X-376 is a less potent inhibitor of MET (IC_{50}=0.69 nM). X-376 displays potent anti-tumor activity[1].

IC_{50} & Target

ALK
0.61 nM (IC_{50})

In Vitro

The ability of X-376 to inhibit the growth of different cancer cell lines harboring ALK fusions or point mutations is tested. X-

	376 is potent in H3122 lung cancer cells harboring EML4-ALK E13;A20 (IC_{50}: 77 nM). X-376 is also potent in H2228 lung cancer cells harboring EML4-ALK E6a/b; A20 (IC_{50}: 57 nM). Furthermore, X-376 is potent in SUDHL-1 lymphoma cells harboring NPM-ALK (IC_{50}: 32 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 142 nM, 150 nM, 15.137 μM and 3.062 μM, respectively[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	The effects of X-376 in vivo against H3122 xenografts are examined. A pharmacokinetic study reveals that X-376 shows substantial bioavailability and moderate half-lives in vivo. Nude mice harboring H3122 xenografts are treated with X-376 at 50 mg/kg bid. X-376 significantly delays the growth of tumors compared to vehicle alone. In the xenograft experiments, X-376 appears well-tolerated in vivo. Mouse weight is unaffected by X-376 treatment. Drug-treated mice appear healthy and do not display any signs of compound related toxicity. To further assess potential side effects of X-376, additional systemic toxicity and toxico-kinetic studies are performed in Sprague Dawley (SD) rats. Following 10 days of repeated oral administration of X-376 at 25, 50, 100 mg/kg in SD rats, all animals survive to study termination. The no significant toxicity (NST) levels are determined to be 50 mg/kg for X-376. At NST levels, X-376 achieves an AUC of 41 μM×hr and a C_{max} of 5.04 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 X-376 (10, 30, 100, 300 and 1000 nM). SUDHL-1 lymphoma cells are treated with X-376 (5, 10, 30, 100 and 300 nM). SY5Y neuroblastoma cells are treated with X-376 (30, 100, 300 and 1000 nM). At 72 hours post X-376 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 50 mg/kg X-376 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

- RSC Adv. 2020, 10(9):5412-5427.

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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.

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

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