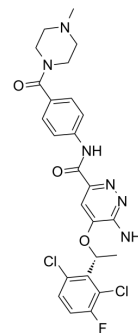


X-376

Cat. No.:	HY-16590		
CAS No.:	1365267-27-1		
Molecular Formula:	C ₂₅ H ₂₅ Cl ₂ FN ₆ O 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 Concentration	Mass		
		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

- 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
- 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
- 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) (IC₅₀=0.61 nM). X-376 is a less potent inhibitor of MET (IC₅₀=0.69 nM). X-376 displays potent anti-tumor activity^[1].

IC₅₀ & Target

ALK
0.61 nM (IC₅₀)

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 (IC₅₀: 77 nM). X-376 is also potent in H2228 lung cancer cells harboring EML4-ALK E6a/b; A20 (IC₅₀: 57 nM). Furthermore, X-376 is potent in SUDHL-1 lymphoma cells harboring NPM-ALK (IC₅₀: 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 IC₅₀s 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 hexuplicate replicates and are performed at least two independent times. IC₅₀s 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 mm³, 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 kinase inhibitors. 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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