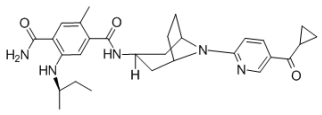
XL888

Cat. No.:	HY-13313
CAS No.:	1149705-71-4
Molecular Formula:	$C_{29}H_{37}N_5O_3$
Molecular Weight:	503.64
Target:	HSP
Pathway:	Cell Cycle/DNA Damage; Metabolic Enzyme/Protease
Storage:	Powder -20°C 3 years In solvent -80°C 6 months -20°C 1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 100 mg/mL (198.55 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Concentration \ Solvent \ Mass	1 mg	5 mg	10 mg
1 mM	1.9855 mL	9.9277 mL	19.8555 mL
5 mM	0.3971 mL	1.9855 mL	3.9711 mL
10 mM	0.1986 mL	0.9928 mL	1.9855 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 (4.96 mM); Clear solution
2. Add each solvent one by one: **10% DMSO >> 90% (20% SBE-β-CD in saline)**
   Solubility: ≥ 2.5 mg/mL (4.96 mM); Clear solution
3. Add each solvent one by one: **10% DMSO >> 90% corn oil**
   Solubility: ≥ 2.5 mg/mL (4.96 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

XL888 is a heat shock protein-90 (**HSP90**) inhibitor, with an **IC_{50}** of 24 nM.

IC_{50} & Target

HSP90
24 nM (IC_{50})

In Vitro

XL888 is a heat shock protein-90 (HSP90) inhibitor. Treatment with XL888 leads to dose dependent decreases in the

	growth of all the cell lines with no significant difference in IC_{50} values observed between the naive and resistance pairs of cell lines (t=0.25, p=0.82). Treatment of all of the vemurafenib resistant cell lines with XL888 (300 nM) induces high levels (>66%) of apoptosis, caspase-3 cleavage and loss of mitochondrial membrane potential (TMRM) in every cell line tested. Treatment of cell lines that are naïve, intrinsically resistant and with acquired vemurafenib resistance with XL888 (300 nM) leads to robust time-dependent increases in the expression of HSP70 isoform 1 (HSP71)[2].
In Vivo	Treatment of the established M245 tumors with XL888 (125 mg/kg 3× week) leads to a significant slowing of tumor growth (P=0.017) without any effect upon animal weights. Analysis of xenograft specimens by LC-MRM shows a marked increase in intratumoral HSP70 expression following XL888 treatment[1]. It is noted that the XL888 is well tolerated by the mice, with no significant alterations in body weigh observed over the study period. LC-MRM mediated analysis of xenograft samples following 15-days of XL888 treatment shows a robust (8.6-fold) increase in intratumoral HSP70 expression compare to controls[2].

PROTOCOL

Cell Assay [1]	Cells are plated in 96-well plates at **2×10^4 per well**. Media with vehicle (DMSO) or **XL888** (**10**, **30**, **100** or **300 nM**) is added the following day and replaced twice a week. After 4 weeks the plates are stained with crystal violet[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [2]	**BALB SCID mice** are subcutaneously injected with 2.5×10^6 cells per mouse and grown to approximately 100 mm^3 prior to dosing. Mice are treated with either **XL888 100 mg/kg** (n=5) or an equivalent volume of vehicle (10 mM HCl), 3× per week **by oral gavage**. Mouse weights and tumor volumes ($L\times W^2/2$) are measured 3× per week. Upon completion of the experiment, vehicle and drug treated tumor biopsies are processed for LC-MRM analysi[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- **Theranostics**. 2019 Aug 12;9(20):5769-5783.

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REFERENCES

[1]. Haarberg HE, et al. Inhibition of Wee1, AKT, and CDK4 underlies the efficacy of the HSP90 inhibitor XL888 in an in vivo model of NRAS-mutant melanoma. Mol Cancer Ther. 2013 Jun;12(6):901-12.

[2]. Paraiso KH, et al. The HSP90 inhibitor XL888 overcomes BRAF inhibitor resistance mediated through diverse mechanisms. Clin Cancer Res. 2012 May 1;18(9):2502-14.

[3]. Bussenius J, et al. Discovery of XL888: a novel tropane-derived small molecule inhibitor of HSP90. Bioorg Med Chem Lett. 2012 Sep 1;22(17):5396-404.

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