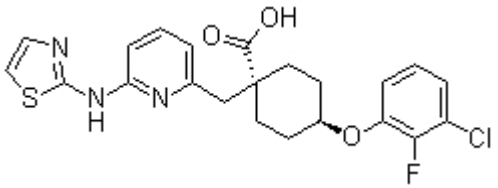
Product Introduction

MK-5108 (VX-689)

MK-5108 (VX-689) is a highly selective **Aurora A** inhibitor with **IC50** of 0.064 nM and is 220- and 190-fold more selective for Aurora A than Aurora B/C, while it inhibits TrkA with less than 100-fold selectivity. Phase 1.

Technical Data:

Molecular Weight (MW):	461.94	
Formula:	$C_{22}H_{21}ClFN_3O_3S$	
Solubility (25°C) * <1 mg/ml means slightly soluble or insoluble:	DMSO 92 mg/mL	
	Water <1 mg/mL	
	Ethanol <1 mg/mL	
Purity:	>98%	
Storage:	3 years -20℃Powder	
	6 months-80℃in DMSO	
CAS No.:	1010085-13-8	

Biological Activity

MK-5108 inhibits Aurora-A activity in an ATP-competitive manner. MK-5108 shows robust selectivity against the other family kinases Aurora-B (220-fold) and Aurora-C (190-fold) in the biochemical assay. MK-5108 also reveals high selectivity for Aurora-A over other protein kinases. MK-5108 inhibits only one kinase (TrkA) with <100-fold selectivity. MK-5108 may be more Aurora-A selective than MLN8054.

Consistent with the induction of pHH3-positive cells, MK-5108 induces accumulation of cells in the G2-M phase. MK-5108 inhibits the proliferation of tumor cells including HCC1143, AU565, MCF-7, HCC1806 and CAL85-1 with an IC50 of 0.42 μM, 0.45 μM, 0.52 μM, 0.56μM and 0.74 μM, respectively. [1] MK-5108 decreases cell viability in a dose-dependent fashion in all three cell lines including LEIO285, LEIO505 and SK-LSM1 cells with an IC50 of approximately 100 nM. Incubation with MK-5108 in LEIO285 increases the proportion of cells in G2/M at 48 and 72 hours post-treatment. MK-5108 significant increases in Caspase 3/7 activity when compared to DMSO-treated control cultures at both time points. In LEIO505 cells, MK-5108 leads to more cells accumulating at G2/M phases at 24 hours but not 48 hours or 72 hours. MK-5108 arrests ULMS cell lines at M phase MK-5108 decreases the IC50 of gemcitabine in LEIO285 cells, but increases IC50 of gemcitabine in LEIO505 and SK-LMS1 cells. [2]

MK-5108 induces pHH3-positive cells at doses of 16 mg/kg and 32 mg/kg. Plasma concentration of MK-5108 at 8 mg/kg and 16 mg/kg are 1.7 μM and 4.4 μM, respectively. MK-5108 treatment results in the induction of pHH3 in tumor and skin tissues, which starts at 2 hours and reachs a maximum at 4 hours. MK-5108 treatments at 15 mg/kg and 30 mg/kg results in significant tumor growth inhibition with the change in mean tumor volume for the treatment group as a percentage of the mean change in the control group (%T/C) of 10% and −6% at day 11, and 17% and 5% at day 18, respectively. MK-5108 is well tolerated at both doses, with minimal reduction in body weight. MK-5108 also exhibits significant antitumor activity through intermittent dosing in nude rats bearing SW48 tumors, MK-5108 at 15 mg/kg and 45 mg/kg causes dose-dependent tumor growth inhibition with a %T/C of 35% and 7% at day 10, and 58% and 32% at day 27, respectively. [1]

References

[1] Shimomura T, et al. Mol Cancer Ther. 2010, 9(1), 157-166.
[2] Shan W, et al. Clin Cancer Res. 2012, 18(12), 3352-3365.

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