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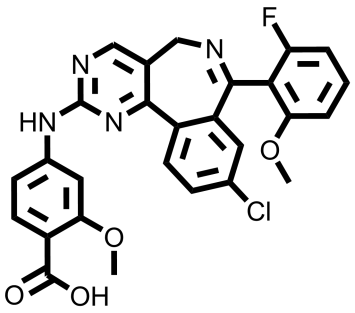
Aurora A inhibitor – MLN8237 (Alisertib)

Chemical Name: 4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzoic acid



Molecular Weight:	518.92
Formula:	$C_{27}H_{20}ClFN_4O_4$
Purity:	≥ 98%
CAS#:	1028486-01-2
Solubility:	DMSO up to 25 mM
Storage	Powder: 4°C 1 year DMSO: 4°C 3 month -20°C 1 year

Biological Activity:

MLN8237 (Alisertib) is a highly potent and selective Aurora A inhibitor with an IC_{50} of 1.2 nM, >200-fold selective towards structurally related Aurora B (IC_{50} of 396.5 nM). It does not have any significant activity against 205 other kinases. MLN8237 treatment inhibits the phosphorylation of Aurora A in MM1.S and OPM1 cells, without affecting the Aurora B mediated histone H3 phosphorylation. MLN8237 significantly inhibits cell proliferation in multiple myeloma (MM) cell lines with IC50 values of 0.003-1.71 μM. MLN8237 treatment also causes the inhibition of colony formation of FLO-1, OE19, and OE33 esophageal adenocarinoma cell lines, and induces a significant increase in the percentage of polyploid cells, and subsequently an increase in the percentage of cells in the sub-G1 phase, which can be further enhanced in combination with cisplatin (2.5 μM).In recent studies, MLN8237 induced polyploidization and expression of mature megakaryocyte markers in acute megakaryocytic leukemia (AMKL) blasts and displayed potent anti-AMKL activity in vivo. MLN8237 is currently in Phase II study for treatment of patients with ovarian, fallopian tube, or peritoneal carcinoma.

How to Use:

In vitro: MLN8237 was used at 0.5-5 μM concentration in vitro and in cellular assays.

In vivo: MLN8237 was dosed to mice orally at 15-30 mg/kg once per day, or in combination with Cisplatin (2 mg/kg) to significantly enhance antitumor activity.

Reference:

1. Görgün G, et al. A novel Aurora-A kinase inhibitor MLN8237 induces cytotoxicity and cell-cycle arrest in multiple myeloma. (2010) Blood. 115(25):5202-13.
2. Kelly KR, et al. The novel Aurora A kinase inhibitor MLN8237 is active in resistant chronic myeloid leukaemia and significantly increases the efficacy of nilotinib. (2011) J Cell Mol Med. 15(10):2057-70.
3. Manfredi MG, et al. Characterization of Alisertib (MLN8237), an investigational small-molecule inhibitor of aurora A kinase using novel in vivo pharmacodynamic assays. (2011) Clin Cancer Res. 17(24):7614-24.
4. Cervantes A, et al. Phase I pharmacokinetic/pharmacodynamic study of MLN8237, an investigational, oral, selective aurora a kinase inhibitor, in patients with advanced solid tumors. (2012) Clin Cancer Res. 18(17):4764-74.
5. Dees EC, et al. Phase I study of aurora A kinase inhibitor MLN8237 in advanced solid tumors:

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safety, pharmacokinetics, pharmacodynamics, and bioavailability of two oral formulations. (2012) Clin Cancer Res. 18(17):4775-84.

6. Wen Q, et al.Identification of regulators of polyploidization presents therapeutic targets for treatment of AMKL. (2012) Cell. 150(3):575-89.