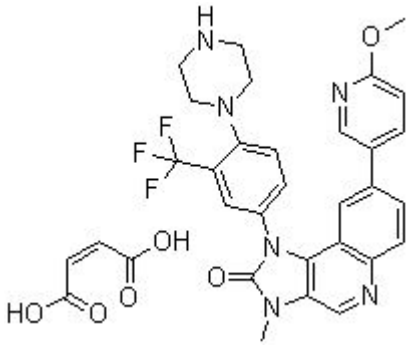
Product Introduction

BGT226 (NVP-BGT226)

NVP-BGT226 is a novel class I **PI3K/mTOR** inhibitor for PI3Kα/β/γ with **IC50** of 4 nM/63 nM/38 nM. Phase 1/2.

Technical Data:

Molecular Weight (MW):	650.6	
Formula:	$C_{28}H_{25}F_3N_6O_2.C_4H_4O_4$	
Solubility (25°C) * <1 mg/ml means slightly soluble or insoluble:	DMSO 30 mg/mL	
	Water <1 mg/mL	
	Ethanol <1 mg/mL	
Purity:	>98%	
Storage:	3 years -20℃Powder	
	6 months-80℃in DMSO	
CAS No.:	1245537-68-1	

Biological Activity

The anti-proliferative and pro-apoptotic effects of NVP-BGT226 are independent of bcr-abl status. The activation of the AKT/mTOR signal cascade is suppressed by NVP-BGT226 in a concentration- and time-dependent manner. Flow cytometric analysis exhibits an accumulation of cells in the G(0)-G(1) phase with concomitant loss in the S-phase. NVP-BGT226 displays potent growth-inhibitory activity against all tested cell lines including SCC4, TU183 and KB cell lines with the IC50 ranging from 7.4 to 30.1 nM. Notably, both Detroit 562 and HONE-1 cells, which express PIK3CA mutation H1047R, are still sensitive to

the growth-inhibitory effect of NVP-BGT226 treatment. In addition, the sensitivity to NVP-BGT226 between HONE-1 cells and its cisplatin-resistant variant is almost identical. Results of the terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL) assay and the analysis of caspase 3/7 and PARP indicates that NVP-BGT226 induces cancer cell death through an apoptosis-independent pathway. NVP-BGT226 induces autophagy as indicated by the aggregation and upregulation of the microtubule-associated protein light chain 3B-II, and p62 degradation. Gene silencing of Beclin1 or cotreatment of the autophagosome inhibitor, 3-methyladenine, inhibits the NVP-BGT226-induced autophagy and leads to the retrieval of colony survival.[2] NVP-BGT226 inhibits growth in common myeloma cell lines and primary myeloma cells (such as NCI-H929, U266, RPMI-8226 and OPM2 MM cell lines) at nanomolar concentrations in a time-dependent and dose-dependent manner. NVP-BGT226 inhibits phosphorylation of protein kinase B (Akt), P70S6k and 4E-BP-1 in a time-dependent and dose-dependent manner. The stimulatory effect of insulin-like growth factor 1, interleukin-6 and conditioned medium of HS-5 stromal cells on myeloma cell growth is completely abrogated by NVP-BGT226. Inhibition of phosphoinositol-3-kinase/mammalian target of rapamycin by NVP-BGT226 is highly effective, and NVP-BGT226 represents a potential new candidate for targeted therapy in multiple myeloma. Combined inhibition of PI3K and mammalian target of rapamycin (mTOR) by NVP-BGT226 has been proven to be very effective in terms of induction of apoptosis and inhibition of proliferation. [3] In another study, after 24 hours, 86.9% MiaPaCa-2 100 nM NVP-BGT226 treated cells arrests at the G0/G1 phase compared to 55.6% of control cells. [4]

In a xenografted animal model, NVP-BGT226 significantly delays tumor growth in a dose-dependent manner, along with suppressed cytoplasmic expression of p-p70 S6 kinase and the presence of autophagosome formation. NVP-BGT226 inhibits tumor growth in a dose-dependent manner in a FaDu cell xenografted mouse model. Oral administration of NVP-BGT226 at 2.5 and 5 mg/kg for 3 weeks causes 34.7% and 76.1% reduction of the tumor growth on day 21, respectively (compared with control). NVP-BGT226 displays comparable inhibition against tumor growth to rapamycin. The final volume of both groups is significantly smaller than those treated with LY294002 (a PI3K inhibitor) or the control. [2]

References

[1] Markman B, et al. Ann Oncol, 2012, 23(9), 2399-2408.

[2] Chang KY, et al. Clin Cancer Res, 2011, 17(22), 7116-7126.

[3] Baumann P, et al. Anticancer Drugs, 2012, 23(1), 131-138.

[4] Glienke W, et al. Tumour Biol, 2012, 33(3), 757-765.

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