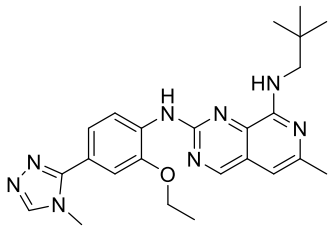
Product data sheet

MedKoo Cat#: 206988 Name: BOS172722 CAS#: 1578245-44-9 Chemical Formula: $C_{24}H_{30}N_8O$ Exact Mass: 446.2543 Molecular Weight: 446.56	
Product supplied as:	Powder
Purity (by HPLC):	≥ 98%
Shipping conditions	Ambient temperature
Storage conditions:	Powder: -20°C 3 years; 4°C 2 years.
	In solvent: -80°C 3 months; -20°C 2 weeks.

1. Product description:
BOS172722 is a potent and selective MPS1 inhibitor with IC50 = 11 nM. BOS172722 showed very good bioavailability in all three species despite very modest solubility at physiological pH. Monopolar spindle 1 (MPS1) occupies a central role in mitosis and is one of the main components of the spindle assembly checkpoint. The MPS1 kinase is an attractive cancer target.

2. CoA, QC data, SDS, and handling instruction
SDS and handling instruction, CoA with copies of QC data (NMR, HPLC and MS analytical spectra) can be downloaded from the product web page under "QC And Documents" section. Note: copies of analytical spectra may not be available if the product is being supplied by MedKoo partners. Whether the product was made by MedKoo or provided by its partners, the quality is 100% guaranteed.

3. Solubility data

Solvent	Max Conc. mg/mL	Max Conc. mM
DMSO	5	11.19
1M HCl	65	145.56

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	**1 mg**	**5 mg**	**10 mg**
1 mM	2.24 mL	11.20 mL	22.39 mL
5 mM	0.45 mL	2.24 mL	4.48 mL
10 mM	0.22 mL	1.12 mL	2.24 mL
50 mM	0.04 mL	0.22 mL	0.45 mL

5. Molarity Calculator, Reconstitution Calculator, Dilution Calculator
Please refer the product web page under section of "Calculator"

6. Recommended literature which reported protocols for in vitro and in vivo study
In vitro study

Woodward HL, Innocenti P, Cheung KJ, Hayes A, Roberts J, Henley AT, Faisal A, Mak GW, Box G, Westwood IM, Cronin N, Carter M, Valenti M, De Haven Brandon A, O'Fee L, Saville H, Schmitt J, Burke R, Broccatelli F, van Montfort RLM, Raynaud FI, Eccles SA, Linardopoulos S, Blagg J, Hoelder S. Introduction of a Methyl Group Curbs Metabolism of Pyrido[3,4- d]pyrimidine Monopolar Spindle 1 (MPS1) Inhibitors and Enables the Discovery of the Phase 1 Clinical Candidate N2-(2-Ethoxy-4-(4-methyl-4 H-1,2,4-triazol-3-yl)phenyl)-6-methyl- N8-neopentylpyrido[3,4- d]pyrimidine-2,8-diamine (BOS172722). J Med Chem. 2018 Sep 27;61(18):8226-8240. doi: 10.1021/acs.jmedchem.8b00690. Epub 2018 Sep 10. PMID: 30199249; PMCID: PMC6166229.

In vivo study

Anderhub SJ, Mak GW, Gurden MD, Faisal A, Drosopoulos K, Walsh K, Woodward HL, Innocenti P, Westwood IM, Naud S, Hayes A, Theofani E, Filosto S, Saville H, Burke R, van Montfort RLM, Raynaud FI, Blagg J, Hoelder S, Eccles SA, Linardopoulos S. High Proliferation Rate and a Compromised Spindle Assembly Checkpoint Confers Sensitivity to the MPS1 Inhibitor BOS172722 in Triple-Negative Breast Cancers. Mol Cancer Ther. 2019 Oct;18(10):1696-1707. doi: 10.1158/1535-7163.MCT-18-1203. PMID: 31575759.

7. Bioactivity

Product data sheet

Biological target:

Inhibitor of monopolar spindle 1 (MPS1) checkpoint.

In vitro activity

Optimizing HLM stability proved challenging since it was not possible to identify a consistent site of metabolism and lowering lipophilicity proved unsuccessful. Key to overcoming this problem was the finding that introduction of a methyl group at the 6-position of the pyrido[3,4- d]pyrimidine core significantly improved HLM stability. Met ID studies suggested that the methyl group suppressed metabolism at the distant aniline portion of the molecule, likely by blocking the preferred pharmacophore through which P450 recognized the compound. This work ultimately led to the discovery of BOS172722 as a Phase 1 clinical candidate.

Reference: Woodward HL, Innocenti P, Cheung KJ, Hayes A, Roberts J, Henley AT, Faisal A, Mak GW, Box G, Westwood IM, Cronin N, Carter M, Valenti M, De Haven Brandon A, O'Fee L, Saville H, Schmitt J, Burke R, Broccatelli F, van Montfort RLM, Raynaud FI, Eccles SA, Linardopoulos S, Blagg J, Hoelder S. Introduction of a Methyl Group Curbs Metabolism of Pyrido[3,4-d]pyrimidine Monopolar Spindle 1 (MPS1) Inhibitors and Enables the Discovery of the Phase 1 Clinical Candidate N2-(2-Ethoxy-4-(4-methyl-4 H-1,2,4-triazol-3-yl)phenyl)-6-methyl- N8-neopentylpyrido[3,4- d]pyrimidine-2,8-diamine (BOS172722). J Med Chem. 2018 Sep 27;61(18):8226-8240. doi: 10.1021/acs.jmedchem.8b00690. Epub 2018 Sep 10. PMID: 30199249; PMCID: PMC6166229.

In vivo activity

In in vivo pharmacodynamic experiments, BOS172722 potently inhibits the spindle assembly checkpoint induced by paclitaxel in human tumor xenograft models of TNBC, as measured by inhibition of the phosphorylation of histone H3 and the phosphorylation of the MPS1 substrate, KNL1. This mechanistic synergy results in significant in vivo efficacy, with robust tumor regressions observed for the combination of BOS172722 and paclitaxel versus either agent alone in long-term efficacy studies in multiple human tumor xenograft TNBC models, including a patient-derived xenograft and a systemic metastasis model. The current target indication for BOS172722 is TNBC, based on their high sensitivity to MPS1 inhibition, the well-defined clinical patient population with high unmet need, and the synergy observed with paclitaxel.

Reference: Anderhub SJ, Mak GW, Gurden MD, Faisal A, Drosopoulos K, Walsh K, Woodward HL, Innocenti P, Westwood IM, Naud S, Hayes A, Theofani E, Filosto S, Saville H, Burke R, van Montfort RLM, Raynaud FI, Blagg J, Hoelder S, Eccles SA, Linardopoulos S. High Proliferation Rate and a Compromised Spindle Assembly Checkpoint Confers Sensitivity to the MPS1 Inhibitor BOS172722 in Triple-Negative Breast Cancers. Mol Cancer Ther. 2019 Oct;18(10):1696-1707. doi: 10.1158/1535-7163.MCT-18-1203. PMID: 31575759.