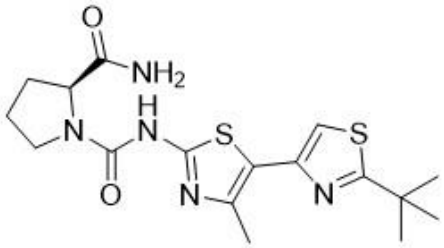
Product data sheet

MedKoo Cat#: 407127 Name: A66 CAS#: 1166227-08-2 Chemical Formula: $C_{17}H_{23}N_5O_2S_2$ Exact Mass: 393.12932 Molecular Weight: 393.52	
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:

A66 is a potent and highly selective p110α inhibitor with IC50 of 32 nM in a cell-free assay, >100 fold selectivity for p110α over other class-I PI3K isoforms. A66 blocks phosphoinositide 3-kinase signalling and tumour growth in certain cell types.

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	44.5	113.08

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	1 mg	5 mg	10 mg
1 mM	2.54 mL	12.71 mL	25.41 mL
5 mM	0.51 mL	2.54 mL	5.08 mL
10 mM	0.25 mL	1.27 mL	2.54 mL
50 mM	0.05 mL	0.25 mL	0.51 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

1. Jamieson S, Flanagan JU, Kolekar S, Buchanan C, Kendall JD, Lee WJ, Rewcastle GW, Denny WA, Singh R, Dickson J, Baguley BC, Shepherd PR. A drug targeting only p110α can block phosphoinositide 3-kinase signalling and tumour growth in certain cell types. Biochem J. 2011 Aug 15;438(1):53-62. doi: 10.1042/BJ20110502. PMID: 21668414; PMCID: PMC3174055.
2. Jacobsen RG, Mazloumi Gavgani F, Mellgren G, Lewis AE. DNA Topoisomerase IIα contributes to the early steps of adipogenesis in 3T3-L1 cells. Cell Signal. 2016 Oct;28(10):1593-603. doi: 10.1016/j.cellsig.2016.07.002. Epub 2016 Jul 9. PMID: 27404349.

In vivo study

1. Jamieson S, Flanagan JU, Kolekar S, Buchanan C, Kendall JD, Lee WJ, Rewcastle GW, Denny WA, Singh R, Dickson J, Baguley BC, Shepherd PR. A drug targeting only p110α can block phosphoinositide 3-kinase signalling and tumour growth in certain cell types. Biochem J. 2011 Aug 15;438(1):53-62. doi: 10.1042/BJ20110502. PMID: 21668414; PMCID: PMC3174055.
2. Seyoum B, Yano M, Pirofski LA. The innate immune response to Streptococcus pneumoniae in the lung depends on serotype and host response. Vaccine. 2011 Oct 19;29(45):8002-11. doi: 10.1016/j.vaccine.2011.08.064. Epub 2011 Aug 22. PMID: 21864623; PMCID: PMC3191269.

7. Bioactivity

Biological target:

A66 is a highly specific and selective p110α inhibitor with an IC50 of 32 nM.

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In vitro activity

It was sought to determine which PI3K isoforms contribute to adipogenesis as well as the regulation of the levels of Topo IIα using the selective inhibitors A66 (p110α), TGX-221 (p110β) and PI3065 (p110δ). Addition of A66 reduced the storage of triglycerides dose-dependently reaching the same levels obtained by LY294002 addition at the highest concentration of A66 (10 μM) (Fig. 2B–C). The levels of Topo IIα were also affected by the addition of these PI3K inhibitors with most effect seen at higher doses of A66 (1 and 10 μM). Considering that Topoisomerases II are targets in cancer chemotherapy, the results highlight that treatment of cancer with Topo II inhibitors may alter metabolic processes in the adipose tissue.

Reference: Vaccine. 2011 Oct 19;29(45):8002-11. https://pubmed.ncbi.nlm.nih.gov/27404349/

In vivo activity

To investigate whether the inhibitory effects of A66 S on activation of Akt/PKB signalling translated into the ability to block cell growth in vivo, xenograft studies were performed alongside the well-established pan-PI3K inhibitor BEZ-235 in U87MG cells, which are PTEN-null, and HCT-116 and SK-OV-3 cells, both of which contain H1047R mutations. First, the optimal dosing strategy was determined for xenograft studies by investigating the drug pharmacokinetics after a dose of 10 mg/kg of body weight by intraperitoneal injection in CD-1 mice. Despite a short half-life of only 0.42 h, the large Cmax (8247 nM) of A66 S that was reached 30 min after dosing ensured that the AUC0-inf (area under the curve from zero time to infinity) (6809 nM·h) was similar to that of BEZ-235 (7333 nM·h), which has a longer half-life of 2.73 h (Table 3). Furthermore, the effect of the A66 S form on SK-OV-3 tumour tissue was tested in vivo using a single dose of 100 mg/kg of body weight to determine whether a long-lasting effect of the drug could be achieved on target tissues (Figure 6). These studies show that A66 S causes a profound reduction in the phosphorylation of Akt/PKB and p70 S6 kinase, but not of ERK (extracellular-signal-regulated kinase), at both 1 and 6 h after dosing (Figure 6). This is consistent with A66 S having a full inhibitory effect on PI3K signalling in the tumours during this time. In the present study, levels of A66 S in plasma were determined to be 21.1±1.2 μM and 9.1±1.1 μM at 1 and 6 h after drug injection, whereas levels of A66 S in the tumour were 22.7±2.1 μM and 16.0±1.3 μM at the same time points. Thus, the retention of drug in the tumour is likely to explain the persistence of the inhibitory effect.

Reference: Biochem J. 2011 Aug 15; 438(Pt 1): 53–62. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3174055/