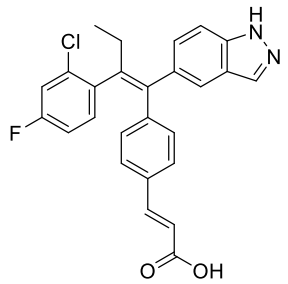
Product data sheet

MedKoo Cat#: 206041 Name: Brilanestrant CAS#: 1365888-06-7 Chemical Formula: $C_{26}H_{20}ClFN_2O_2$ Exact Mass: 446.11973 Molecular Weight: 446.9064	
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:
Brilanestrant, also known as GDC-0810, ARN-810 and RG6046, an orally bioavailable Selective Estrogen Receptor Degrader (SERD) that demonstrates robust activity in tamoxifen-resistant breast cancer xenografts. GDC-0810 functions by binding to the estrogen receptor, inducing a conformational change resulting in the degradation of the receptor. GDC-0810 or ARN-810 demonstrates robust activity in models of tamoxifen-sensitive and tamoxifen-resistant breast cancer, and is currently in clinical trials in women with locally advanced or metastatic estrogen receptor-positive breast cancer.

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	89	199.15
Ethanol	89	199.15

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	**1 mg**	**5 mg**	**10 mg**
1 mM	2.24 mL	11.19 mL	22.38 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

1. Lai A, Kahraman M, Govek S, Nagasawa J, Bonnefous C, Julien J, Douglas K, Sensintaffar J, Lu N, Lee KJ, Aparicio A, Kaufman J, Qian J, Shao G, Prudente R, Moon MJ, Joseph JD, Darimont B, Brigham D, Grillot K, Heyman R, Rix PJ, Hager JH, Smith ND. Identification of GDC-0810 (ARN-810), an Orally Bioavailable Selective Estrogen Receptor Degrader (SERD) that Demonstrates Robust Activity in Tamoxifen-Resistant Breast Cancer Xenografts. J Med Chem. 2015 Jun 25;58(12):4888-904. doi: 10.1021/acs.jmedchem.5b00054. Epub 2015 May 22. PMID: 25879485.

2. Joseph JD, Darimont B, Zhou W, Arrazate A, Young A, Ingalla E, Walter K, Blake RA, Nonomiya J, Guan Z, Kategaya L, Govek SP, Lai AG, Kahraman M, Brigham D, Sensintaffar J, Lu N, Shao G, Qian J, Grillot K, Moon M, Prudente R, Bischoff E, Lee KJ, Bonnefous C, Douglas KL, Julien JD, Nagasawa JY, Aparicio A, Kaufman J, Haley B, Giltnane JM, Wertz IE, Lackner MR, Nannini MA, Sampath D, Schwarz L, Manning HC, Tantawy MN, Arteaga CL, Heyman RA, Rix PJ, Friedman L, Smith ND, Metcalfe C, Hager JH. The selective estrogen receptor downregulator GDC-0810 is efficacious in diverse models of ER+ breast cancer. Elife. 2016 Jul 13;5:e15828. doi: 10.7554/eLife.15828. Erratum in: Elife. 2019 Jan 07;8: PMID: 27410477; PMCID: PMC4961458.

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In vivo study

1. Lai A, Kahraman M, Govek S, Nagasawa J, Bonnefous C, Julien J, Douglas K, Sensintaffar J, Lu N, Lee KJ, Aparicio A, Kaufman J, Qian J, Shao G, Prudente R, Moon MJ, Joseph JD, Darimont B, Brigham D, Grillot K, Heyman R, Rix PJ, Hager JH, Smith ND. Identification of GDC-0810 (ARN-810), an Orally Bioavailable Selective Estrogen Receptor Degrader (SERD) that Demonstrates Robust Activity in Tamoxifen-Resistant Breast Cancer Xenografts. J Med Chem. 2015 Jun 25;58(12):4888-904. doi: 10.1021/acs.jmedchem.5b00054. Epub 2015 May 22. PMID: 25879485.

2. Joseph JD, Darimont B, Zhou W, Arrazate A, Young A, Ingalla E, Walter K, Blake RA, Nonomiya J, Guan Z, Kategaya L, Govek SP, Lai AG, Kahraman M, Brigham D, Sensintaffar J, Lu N, Shao G, Qian J, Grillot K, Moon M, Prudente R, Bischoff E, Lee KJ, Bonnefous C, Douglas KL, Julien JD, Nagasawa JY, Aparicio A, Kaufman J, Haley B, Giltnane JM, Wertz IE, Lackner MR, Nannini MA, Sampath D, Schwarz L, Manning HC, Tantawy MN, Arteaga CL, Heyman RA, Rix PJ, Friedman L, Smith ND, Metcalfe C, Hager JH. The selective estrogen receptor downregulator GDC-0810 is efficacious in diverse models of ER+ breast cancer. Elife. 2016 Jul 13;5:e15828. doi: 10.7554/eLife.15828. Erratum in: Elife. 2019 Jan 07;8: PMID: 27410477; PMCID: PMC4961458.

7. Bioactivity

Biological target:

Brilanestrant (GDC-0810, ARN-810) is a potent ER-α binder (ER-α, IC50 = 6.1 nM; ER-β, IC50 = 8.8 nM), a full transcriptional antagonist with no agonism and displays good potency and efficacy in ER-α degradation (EC50 = 0.7 nM) and MCF-7 breast cancer cell viability (IC50 = 2.5 nM) assays with good selectivity over other nuclear hormone receptors.

In vitro activity

GDC-0810-mediated ERα depletion is dependent on the 26S proteasome. GDC-0810 antagonizes ERα ligand binding domain mutants in vitro and in vivo. In cell-free E2 competitive binding assays that was used to determine the binding of GDC-0810 to ER.WT, ER.Y537S and ER.D538G ligand binding domains, GDC-0810 retains its ability to potently displace E2 from the ligand binding domain, albeit with a slightly increased IC50 (WT: 2.6 nM vs. ER.Y537S: 5.5 nM and ER.D538G: 5.4 nM). GDC-0810 can compete the PGC1α co-activator peptide off the mutated ligand binding domain, implying that GDC-0810 is capable of driving an 'active' to 'inactive' conformational shift of mutant ER, though with a ~five-seven fold reduction in biochemical potency compared to wild-type ER.

Reference: Elife. 2016 Jul 13;5:e15828. https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/27410477/

In vivo activity

In mice, GDC-0810 exhibits low clearance (11 mL/min/kg) and 61% oral bioavailability. Importantly, GDC-0810 plasma concentrations increase proportionately with the applied dose and achieve an AUC0–24 of 94.1 µg*hr/ml when dosed by oral gavage at 100 mg/kg/day (Supplementary file 2A). To determine the ability of GDC-0810 to inhibit E2 stimulated tumor growth in vivo, the MCF7 tumor bearing nu/nu mice were orthotopically implanted with 0.36 mg/60 day release E2 pellets with GDC-0810, ranging from 1 to 100 mg/kg/day p.o. Fulvestrant was delivered by sub-cutaneous injection, with an initial loading dose of 50 mg/kg on days 1, 3 and 8, and subsequent dosing of 25 mg/kg twice per week to achieve exposures similar to those achieved in the clinic. In the MCF7 xenograft model, GDC-0810 displayed dose dependent efficacy (Figure 4A). The 100 mg/kg/day dose caused tumor regressions; an effect similar to withdrawal of estrogen pellets at the start of dosing. In contrast, fulvestrant, at a clinically relevant dose as well as at a considerably higher dose (200 mg/kg, 3 times per week), yielded only modest tumor growth inhibition (Figure 4A and Figure 4—figure supplement 1A). It is important to note that the restriction of the fulvestrant response to tumor growth inhibition, rather than stasis or tumor regression, was not a function of low exposure, as the plasma concentrations at the 200 mg/kg dose were on average 12–14 µg*hr/mL, approximately 30-fold above the clinical exposure of the fulvestrant 500 mg clinical regimen. Gene expression analysis of harvested MCF7 tumors demonstrated that GDC-0810 (at 100 mg/kg/day, evaluated on day 28) robustly modulated ER target genes, including PGR, c-MYC, AREG and MUC1 (Figure 4B,C; Figure 4—figure supplement 1B). Indeed, the gene expression changes induced by GDC-0810 are similar to, and in some cases even more pronounced than, those induced by withdrawal of the estrogen pellet at the beginning of the study, highlighting that GDC-0810 actively and efficiently attenuates ER signaling (Figure 4B,C; Figure 4—figure supplement 1B).

Reference: Elife. 2016 Jul 13;5:e15828. https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/27410477/

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