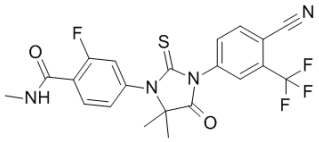
Data Sheet

Product Name:	Enzalutamide
Cat. No.:	CS-0317
CAS No.:	915087-33-1
Molecular Formula:	$C_{21}H_{16}F_4N_4O_2S$
Molecular Weight:	464.44
Target:	Androgen Receptor; Autophagy
Pathway:	Autophagy; Others
Solubility:	10 mM in DMSO



BIOLOGICAL ACTIVITY:

Enzalutamide is an **androgen-receptor (AR)** antagonist with **IC_{50}** of 36 nM in LNCaP cells.
IC50 & Target: IC50: 36 nM (androgen-receptor, in LNCaP cells)[1]
In Vitro: Enzalutamide has greater affinity to AR than Bicalutamide does in a competition assay with 16β-[^{18}F]fluoro-5α-DHT (18-FDHT) in castration-resistant LNCaP/AR cells (AR-overexpressing). While Enzalutamide shows no agonism in LNCaP/AR prostate cells. Enzalutamide antagonizes induction of prostate-specific antigen (PSA) and transmembrane serine protease 2 (TMPRSS2), combination with the synthetic androgen R1881 in parental LNCaP cells. Enzalutamide inhibits the transcriptional activity of a mutant AR protein (W741C, mutation of Trp741 to Cys)[1]. Enzalutamide also prevents nuclear translocation and co-activator recruitment of the ligand-receptor complex[2].
In Vivo: Enzalutamide induces great tumor regression in castrate male mice bearing LNCaP/AR xenografts at a dose of 10 mg/kg[1]. En zalutamide shows dose-independent pharmacokinetics at intravenous and oral doses of 0.5-5 mg/kg[4].

PROTOCOL (Extracted from published papers and Only for reference)

Cell Assay: Enzalutamide is dissolved in DMSO and stored, and then diluted with appropriate medium before use[1]. [1]LNCaP cells (10^7 cells/condition) are grown in RPMI media supplemented with 5% charcoalstripped serum for 22 days, then treated with DMSO or 1 nM R1881, combined with an antiandrogen (DMSO, 1 μM Bicalutamide, 10 μM Bicalutamide, 1 μM RD162, 10 μM RD162, 1 μM MDV3100, or 10 μM MDV3100) for 8 hours. An aliquot of cells are harvested for qRT-PCR of PSA and TMPRSS2 mRNA. The remaining cells are cross-linked using 1% paraformaldehyde for 10 minutes, then glycine is added and samples centrifuged (4°C, 4000 rpm, 5 minutes) to stop further crosslinking. Chromatin immunoprecipitation is performed using a chromatin immunoprecipitation assay kit. Immunoprecipitated DNA is amplified by real-time PCR. Primers are PSA enhancer forward-ATGTTCACATTAGTACACCTTGCC and reverse-TCTCAGATCCAGGCTTGCTTACTGTC and TMPRSS2 enhancer forward-TGGTCCTGGATGATAAAAAAAGTTT and reverse-GACATACGCCCCACAACAGA[1]. **Animal Administration:** Enzalutamide is dissolved in vehicle (10 % DMSO, 45 % polyethylene glycol 400, and 45 % saline) (Rat)[4].[3][4]Mice[3]
Following a 5-day acclimation period, 5- to 9-week-old male CB17SCID mice are castrated and allowed to recover for an additional 5 days before inoculation with tumor cells. LNCaP cells co-expressing exogenous AR and the AR-dependent reporter construct ARR2-Pb-Luc (LNCaP-AR-Lux cells) are used to generate a xenograft model of human prostate cancer. Before implantation, LNCaP-AR-Lux cells are prepared by the addition of trypsin-EDTA, washed with complete medium, collected and resuspended at 20×10^6 cells/mL. Cell suspensions are diluted with Matrigel to 2×10^6 cells/0.2 mL and delivered subcutaneously in the suprascapular region. Tumor growth is monitored to the volume of 100 mm^3 when treatment begins (80 days). The observed rate of tumor take with LNCaP-AR-Lux cells is between 70% and 80%. Body weight and tumor volumes (width^2×length/2) are measured two to three times per week with

a digital caliper, and the average tumor volumes are determined. Test drugs are diluted in Tween 80:PEG 400, and stored at 4°C until administration by oral gavage. Each group of mice (n=7) is treated daily for 28 consecutive days with 1, 10, or 50 mg/kg Enzalutamide, vehicle control, or 50 mg/kg Bicalutamide. At the end of the treatment period or when tumor volume exceeded 1,000 mm^3, animals are euthanized and blood and tissue samples are collected for analysis.

Rat[4]

Male SD rats (n=3) are administered Enzalutamide through the tail vein (intravenous) and by oral gavage at 1 mg/kg and are kept in metabolic cages after dosing. Urine and feces samples are collected over the following time intervals after dosing: 0-2, 2-4, 4-6, 6-10, 10-24, 24-48, and 48-72 h. The metabolic cages are rinsed with distilled water, and residues are added to the urine samples at 72 h. To extract the Enzalutamide present in the feces, samples are shaken vigorously for 12 h with 50 % methanol.

References:

[1]. Tran C, et al. Development of a second-generation antiandrogen for treatment of advanced prostate cancer. Science, 2009, 324 (5928), 787-790.

[2]. Scher HI, et al. Antitumour activity of MDV3100 in castration-resistant prostate cancer: a phase 1-2 study. Lancet, 2010, 375(9724), 1437-1446.

[3]. Guerrero J, et al. Enzalutamide, an androgen receptor signaling inhibitor, induces tumor regression in a mouse model of castration-resistant prostate cancer. Prostate. 2013 Sep;73(12):1291-305.

[4]. Kim TH, et al. Pharmacokinetics of enzalutamide, an anti-prostate cancer drug, in rats. Arch Pharm Res. 2015 Nov;38(11):2076-82.

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