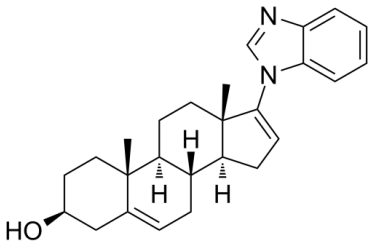
Data Sheet

Product Name:	Galeterone
Cat. No.:	CS-0334
CAS No.:	851983-85-2
Molecular Formula:	C26H32N2O
Molecular Weight:	388.55
Target:	Cytochrome P450
Pathway:	Metabolic Enzyme/Protease
Solubility:	DMSO : 25 mg/mL (64.34 mM; Need ultrasonic)



BIOLOGICAL ACTIVITY:

Galeterone (TOK-001) is a multifunctional antiandrogen and **CYP17** inhibitor (**IC_{50}**=47 nM) in castration resistant prostate cancer (CRPC). IC50 & Target: IC50: 47 nM (CYP17)[1] **In Vitro:** Galeterone (TOK-001) affords strong CYP17 lyase inhibition, with IC_{50} of 47 nM [1]. Galeterone (TOK-001) is both a CYP17A1 inhibitor and androgen receptor antagonist and the similarity of these binding modes is likely the reason for this dual mechanism of action.This CYP17A1 binds abiraterone and Galeterone (TOK-001) with absorbance decreases at 402 nm and increases at 424 nm, consistent with nitrogen binding to the heme iron (type II interaction) with K_d of <100 nM[2]. When LNCaP cells are cultured in medium supplemented with charcoal-stripped serum (CSS, T<1 nM) followed by treatment with increasing concentrations of Galeterone (TOK-001), the steady-state levels of AR protein are markedly decreased (up to 84%, 15 μM Galeterone (TOK-001)). In LAPC-4 cells, abiraterone alcohol reduced AR expression to a greater extent than Galeterone (TOK-001) at concentrations greater than or equal to 1 μM. When LNCaP cells are treated with 20 μM TOK-001 for 24 h, AR mRNA levels are reduced by 38%[3]. **In Vivo:** Mice inoculated with LAPC-4 tumors are treated subcutaneously with 0.15 mmol/kg of Galeterone (TOK-001) twice daily. Mice treated with TOK-001 have smaller average tumor volume on day 31 when compared to control (p= 0.0001). Galeterone (TOK-001) treatment also significantly reduces the growth rate of tumor growth compared to control (p<0.0001). Upon excision, final tumor weights are also significantly reduced in animals treated with Galeterone (TOK-001) compared to animals treated with control, and castration (p<0.05)[1].

PROTOCOL (Extracted from published papers and Only for reference)

Cell Assay: TOK-001 is dissolved with DMSO and diluted with appropriate media[3].[3]LNCaP cells are seeded in 24-well plates at 70% confluence a day before transfections. Cells then are transfected with plasmid DNA (0.5 μg/well) carrying pIR-AR 5′UTR-Luc (5′UTR; test) or pIRES-Luc (IRES, control) for 6 h in serum-free and antibiotic-free conditions. Transcription of both luciferase reporter genes is under the control of the CMV promoter. Lipofectamine 2000 reagent is used in all transfections according to the manufacturer's instructions. Cells are then treated with doses of Galeterone (TOK-001) (0, 10, and 20 μM) in 5% FBS/T-Medium. Luciferase reporter gene activities are measured using Luciferase Assay System from Promega at 36 h post treatment using a BMG Labtech microplate reader. Relative luciferase units are normalized to total protein and then normalized to vector control (pIR-AR 5′UTR-Luc) and the result is presented as luciferase activity. For cell proliferation studies, LNCaP cells in 96-well plate are seeded 24 h prior to drug treatment and then treated with control (mock), Galeterone (TOK-001) (10 μM), or abiraterone alcohol (10 μM) in 5% FBS/T-medium for 72 h. Cell proliferation is determined using MTS[3]. **Animal Administration:** TOK-001 is dissolved in DMSO and then diluted with saline or PBS[1].[1]Mice[1]

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($p<0.05$).

References:

[1]. Bruno RD, et al. Synthesis and biological evaluations of putative metabolically stable analogs of VN/124-1 (TOK-001): head to head anti-tumor efficacy evaluation of VN/124-1 (TOK-001) and abiraterone in LAPC-4 human prostate cancer xenograft model.Steroid

[2]. DeVore NM, et al. Structures of cytochrome P450 17A1 with prostate cancer drugs abiraterone and TOK-001.Nature. 2012 Jan 22;482(7383):116-9.

[3]. Soifer HS, et al. Direct regulation of androgen receptor activity by potent CYP17 inhibitors in prostate cancer cells.J Biol Chem. 2012 Feb 3;287(6):3777-87. Epub 2011 Dec 15.

CAIndexNames:

Androsta-5,16-dien-3-ol, 17-(1H-benzimidazol-1-yl)-, (3.beta.)-

SMILES:

C[C@@]12C(N3C=NC4=CC=CC=C34)=CC[C@]1([C@@]5(CC=C6[C@@](C)([C@]5(CC2)[H])CC[C@@H](C6)O)[H])[H]

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