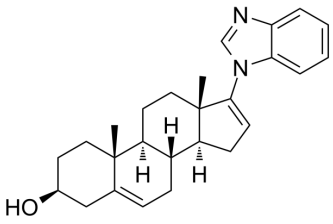
Galeterone

Cat. No.:	HY-70006
CAS No.:	851983-85-2
Molecular Formula:	$C_{26}H_{32}N_2O$
Molecular Weight:	388.55
Target:	Cytochrome P450
Pathway:	Metabolic Enzyme/Protease
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 6 months -20°C 1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : 25 mg/mL (64.34 mM; Need ultrasonic)

Preparing Stock Solutions	Mass / Solvent / Concentration	1 mg	5 mg	10 mg
	1 mM	2.5737 mL	12.8684 mL	25.7367 mL
	5 mM	0.5147 mL	2.5737 mL	5.1473 mL
	10 mM	0.2574 mL	1.2868 mL	2.5737 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (6.43 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (6.43 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (6.43 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Galeterone (TOK-001) is a multifunctional antiandrogen and CYP17 inhibitor (IC_{50}=47 nM) in castration resistant prostate cancer (CRPC).

IC_{50} & 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]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
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]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [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]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice[1] 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 reduced 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). MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Nature. 2012 Jan 22;482(7383):116-9.
- Drug Metab Dispos. 2017 Jun;45(6):635-645.

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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.

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