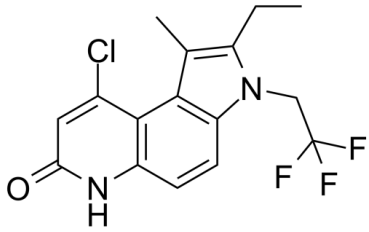
Data Sheet

Product Name:	LGD-3303
Cat. No.:	CS-0028120
CAS No.:	917891-35-1
Molecular Formula:	C16H14ClF3N2O
Molecular Weight:	342.74
Target:	Androgen Receptor
Pathway:	Others
Solubility:	DMSO : 16.67 mg/mL (48.64 mM; Need ultrasonic); H2O : < 0.1 mg/mL (insoluble)



BIOLOGICAL ACTIVITY:

LGD-3303 is a selective androgen receptor modulator (**SARM**). IC50 & Target: SARM[1] **In Vitro:** LGD-3303 is a nonsteroidal, nonaromatizable androgen receptor ligand that binds to the androgen receptor with high affinity in a radiolabeled to competitive binding assay (K_i=0.9 nM). LGD-3303 binds to the mineralocorticoid, glucocorticoid, and progesterone receptors with greatly reduces affinity in comparison with the androgen receptor (K_i=1261, 581, and 136 nM, respectively). LGD-3303 potently activates transcription through the androgen receptor (EC_{50}=3.6 nM) and has 134% efficacy relative to the steroidal androgen Dihydrotestosterone (DHT)[1]. **In Vivo:** LGD-3303 completely inhibits the loss of muscle weight with an oral dose of 1 mg/kg/day. At higher doses, LGD-3303 significantly increases levator ani muscle weight above eugonadal levels. In contrast, LGD-3303 has greatly reduced potency and efficacy on the other measured endpoints. LGD-3303 does not maintain eugonadal levels of serum LH at doses less than 10 mg/kg/day. LGD-3303 maintains eugonadal prostate weight only at doses of 100 mg/kg/day or greater and never fully returns the mean preputial gland weight to eugonadal levels at any tested dos. In no case does LGD-3303 restore LH, prostate, or preputial gland weights to supraphysiological levels significantly exceeding sham-operated controls. The ventral prostate, in particular, demonstrates a greatly reduced response to LGD-3303. At the muscle normalizing dose (1 mg/kg/day), ventral prostate weight is not significantly increased above the level of ORDX control rats (20% efficacy relative to intact rats). At the highest doses tested, ventral prostate never significantly exceeds eugonadal levels and reaches an apparent plateau with minimal increase in prostate weight as dosing escalated from 30 to 300 mg/kg/day. To investigate this apparent plateau in pharmacological activity, plasma concentrations of LGD-3303 are analyzed from the highest dose groups. Exposure to LGD-3303 (AUC_{0-6}) monotonically increases with dose from 10 to 300 mg/kg/day [2].

PROTOCOL (Extracted from published papers and Only for reference)

Kinase Assay: [1]In vitro binding is determined using recombinant baculovirus expressed human androgen receptor (hAR), human glucocorticoid receptor (hGR), human mineralocorticoid receptor (hMR), or human progesterone receptor (hPR). Tritium-labeled reference ligand is used with varying concentrations of LGD-3303 as a competing ligand. Inhibition constant (Ki) values are calculated by application of the Cheng-Prusoff equation. Reporter assays are performed. Briefly, CV1 cells are cultured in DMEM supplemented with 10% charcoal resin-stripped fetal bovine serum (FBS), and seeded 48 h before transfection in 96-well microtiter plates. Cells are transiently transfected using a nonliposomal formulation, the FuGENE 6 transfection reagent, with luciferase reporter plasmids MMTV-LUC or MTV-ERE5-LUC, a β-galactosidase (β-Gal) expression plasmid coding for the constitutive expression of Escherichia coli β-galactosidase, and hAR, hGR, hMR, hPR, or human estrogen receptor α (pRShERα) expression plasmids. Cells are treated with varying concentrations of LGD-3303 or reference compound for 40 h. The normalized luciferase response is calculated as relative luciferase units/(β-gal O.D415/β-Gal incubation time in minutes). The effective concentration that produces 50% of the maximum response (EC_{50}) is determined, and agonist efficacy is calculated as a percent of normalized luciferase response relative to the maximum response by the reference agonist (i.e., DHT for hAR, dexamethasone for hGR, aldosterone for hMR, progesterone for hPR-B, or 17β-estradiol for

hERα)[1].

Animal Administration: LGD-3303 is administered in a suspension of Tween 80, polyethylene glycol-400, and 0.1% carboxy-methyl cellulose in water (0.005:10:89.995%)[2].[2]Rats[2]

Male Sprague-Dawley rats (7-8 weeks old, 200 g) are used. Rats are sorted by weight, assigned to experimental groups (n=5/group), and surgery is performed. Experimental groups consist of **LGD-3303** (doses ranged from **0.1-300 mg/kg/day**) or vehicle. LGD-3303 is administered by once daily oral gavage in a volume of 4 mL/kg. On the 14th day, blood is collected into lithium heparin tubes by jugular puncture at 0, 0.5, 1, 2, 4, and 6 h postdosing from the animals in the high-dose groups. Blood is centrifuged, and plasma is stored at -20°C for pharmacokinetic analysis. On the 15th day, rats are killed by decapitation, and trunk blood is collected, allowed to clot in serum separator tubes, and centrifuged, and serum is stored at -80°C for future analysis of serum luteinizing hormone (LH) levels. The wet weights of the ventral prostate, levator ani muscle, and preputial gland are measured at necropsy[2].

References:

[1]. Vajda EG, et al. Combination treatment with a selective androgen receptor modulator q(SARM) and a bisphosphonate has additive effects in osteopenic female rats. J Bone Miner Res. 2009 Feb;24(2):231-40.

[2]. Vajda EG, et al. Pharmacokinetics and pharmacodynamics of LGD-3303 [9-chloro-2-ethyl-1-methyl-3-(2,2,2-trifluoroethyl)-3H-pyrrolo-[3,2-f]quinolin-7(6H)-one], an orally available nonsteroidal-selective androgen receptor modulator. J Pharmacol Exp Ther. 2009 Feb;328(2):663-70.

CAIndexNames:

7H-Pyrrolo[3,2-f]quinolin-7-one, 9-chloro-2-ethyl-3,6-dihydro-1-methyl-3-(2,2,2-trifluoroethyl)-

SMILES:

O=C1NC2=C(C3=C(N(CC(F)(F)F)C(CC)=C3C)C=C2)C(Cl)=C1

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