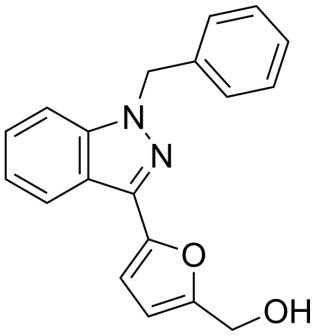
Lificiguat

Cat. No.:	HY-14927
CAS No.:	170632-47-0
Molecular Formula:	$C_{19}H_{16}N_2O_2$
Molecular Weight:	304.34
Target:	Guanylate Cyclase
Pathway:	GPCR/G Protein
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 2 years -20°C 1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 100 mg/mL (328.58 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Mass / Solvent / Concentration	1 mg	5 mg	10 mg
	1 mM	3.2858 mL	16.4290 mL	32.8580 mL
	5 mM	0.6572 mL	3.2858 mL	6.5716 mL
	10 mM	0.3286 mL	1.6429 mL	3.2858 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 (8.21 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 2.5 mg/mL (8.21 mM); Suspended solution; Need ultrasonic
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (8.21 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Lificiguat binds to the β subunit of soluble guanylyl cyclase(sGC) with K_d of 0.6-1.1 μM in the presence of CO.

IC_{50} & Target

Kd: 0.6-1.1 μM (sGC, in the presence of CO)[1]

In Vitro

Soluble guanylate cyclase (sGC) is a heterodimeric heme protein and the primary NO receptor. Lificiguat (YC-1) binds near or directly to the heme-containing domain of the beta subunit. In the absence of CO, Lificiguat (YC-1) binds with K_d=9-21 μM,

depending on construct. In the presence of CO, these values decrease to 0.6-1.1 μM. Lificiguat (YC-1) greatly enhanced CO binding to heterodimeric sGC, as expected (K_d=1 μM). Lificiguat (YC-1) stimulates sGC two- to four-fold in the absence of NO but acts synergistically with CO or NO to achieve several hundred fold activation. Binding of Lificiguat(YC-1) can also overcome inhibitory phosphorylation of sGC[1]. Lificiguat (YC-1) is a soluble guanylyl cyclase (sGC) activator. HCC cell lines HepG2, BEL-7402 and HCCLM3 are incubated for 72 h with Sorafenib and/or Lificiguat (YC-1). Sorafenib or Lificiguat (YC-1) alone inhibits HCC cell proliferation in a dose-dependent manner. Moreover, combination of Sorafenib and Lificiguat (YC-1) significantly suppresses proliferation of HCC cells in a dose-dependent manner. In addition, at the ED_{50} doses for both Sorafenib and Lificiguat (YC-1), combination index values (CI)=0.93 in HepG2, 0.95 in BEL-7402 and 0.72 in HCCLM3 respectively, suggesting that Sorafenib and Lificiguat (YC-1) synergistically inhibit proliferation of HCC cells[2].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

In Vivo

Lificiguat (YC-1) (30 or 60 mg/kg, i.p.) inhibits MDA-MB-468 tumor growth in a dose-dependent manner. The effect of the prodrug formulation of Lificiguat (YC-1), YC-1-S, in MDA-MB-468 tumor-bearing mice is also investigated. In vivo pharmacokinetic analysis reveal that YC-1-S is quickly converted into its active form. Mice are administered 20, 40 or 80 mg/kg YC-1-S p.o. YC-1-S also displays dose-dependent inhibition of MDA-MB468 tumor growth. Both Lificiguat (YC-1) and YC-1-S dose-dependently reduce tumor weight. Moreover, the mean body weight of mice is not affected by Lificiguat (YC-1) or YC-1-S compare with vehicle-treated groups[3]. Lificiguat (YC-1) is a potent NO-GC activator reported to improve rodent learning behavior when examined with the Morris water maze (MWM) and avoidance tests. Lificiguat (YC-1) enhances long-term potentiation (LTP) in hippocampal Schafer collateral-CA1 synapse via the NO-cGMP-PKG-dependent pathway and potentiated LTP induction in the amygdala, increases the activation of ERK, and potentiated the expression of brain-derived neurotrophic factor (BDNF) cAMP response element-binding protein (CREB) in response to fear memory test[4].

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PROTOCOL

Kinase Assay [1]

CO dissociation constants are measured by titrating CO from a saturated solution into sGC protein and monitoring the appearance of the CO-bound Soret absorption band. The Ms sGC β_1(1-380) and Bt sGC β_1(1-197) samples are prepared in Ar-purged buffer supplemented with excess dithionite. CO binding experiments are performed in a 10 cm pathlength cuvette for Ms sGC-β_1(1-380) and Ms sGC-NT21 using a Cary 50 spectrophotometer with a modified sample holder. Binding data in the presence and absence of 50 μM Lificiguat (YC-1) is plotted using a single site saturation ligand binding model in SigmaPlot[1].

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Cell Assay [2]

Cell proliferation assay is measured using a Cell Counting Kit-8 (CCK-8). Briefly, cells are cultured in 96-well plates at a concentration of 3×10^3/well, incubated for 24 h, and treated with Sorafenib and/or Lificiguat (YC-1). After 72 h treatment, CCK-8 reagent is added to each well. The absorbance is measured at 450 nm after 2.5 h incubation at 37°C using an automated ELISA plate reader. Any synergistic effects resulting from combination of the compounds are measured using Microsoft Excel software to determine the combination index values (CI>1: antagonistic effect, CI=1: additive effect, and CT<1: synergistic effect)[2].

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Animal Administration [3][4]

Mice[3]

Fifty-eight female nu/nu mice (4 weeks-old) are used. MDA-MB-468 breast cancer cells (5×10^6 cells per mouse) are suspended in 0.1 mL of Matrigel solution (50% v/v Matrigel in PBS) and inoculated into the mammary fat pads of nude mice. When the tumor masses reach 100 mm^3, the tumor-bearing mice are randomly divided into groups for treatments with different Lificiguat (YC-1)/YC-1-S doses. The mice are i.p. injected with YC-1 (30 or 60 mg/kg) or administered YC-1-S p.o. Tumor size and mouse body weight are measured once every 3 days, and tumor volume (mm^3) is calculated using the equation: length×$(width)^2$×0.5. At the end of the experiments, mice are killed and tumor nodules are dissected and weighed. Tumor tissues are subjected to Western blotting.

Rats[4]

4-month-old (200-250 g) and 24-month-old (550-600 g) male Wistar-albino rats are used. Lificiguat (YC-1) is prepared immediately prior to use and given intraperitoneally (i.p.) in a volume of 0.1 mL per 100 g body weight. All rats receives 1

mg/kg/day of Lificiguat (YC-1) for 2 weeks. DMSO is administered to 4-month-old and 24-month-old rats (n=10, for each group). Doses are selected to confirm the selected doses on locomotor activity; all results are measured.
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CUSTOMER VALIDATION

- Signal Transduct Target Ther. 2021 Oct 13;6(1):352.
- Adv Healthc Mater. 2022 Dec 5;e2202210.
- Cell Death Dis. 2021 Jan 12;12(1):77.
- Stem Cell Res Ther. 2022 Jul 16;13(1):316.
- Biomed Pharmacother. 2018 Nov;107:1736-1743.

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REFERENCES

[1]. Purohit R, et al. YC-1 binding to the β subunit of soluble guanylyl cyclase overcomes allosteric inhibition by the α subunit. Biochemistry. 2014 Jan 14;53(1):101-14.

[2]. Kong J, et al. YC-1 enhances the anti-tumor activity of sorafenib through inhibition of signal transducer and activator of transcription 3 (STAT3) in hepatocellular carcinoma. Mol Cancer. 2014 Jan 13;13:7.

[3]. Chang LC, et al. YC-1 inhibits proliferation of breast cancer cells by down-regulating EZH2 expression via activation of c-Cbl and ERK. Br J Pharmacol. 2014 Sep;171(17):4010-25.

[4]. Komsuoglu Celikyurt I, et al. Effects of YC-1 on Learning and Memory Functions of Aged Rats. Med Sci Monit Basic Res. 2014 Aug 21;20:130-7.

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